ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Assessment of concomitant non-oncologic medication in patients with surgically treated renal cell carcinoma: impact on prognosis, cell-cycle progression and proliferation

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Abstract

Introduction Based on the observation of beneficial effects on cancer metabolism, microenvironment, or VEGF-signaling, several non-anticancer drugs have been discussed as useful in renal cell carcinoma (RCC). In the present study, we investigated the prognostic impact of concomitant medication in RCC and correlated comedication with cell-cycle and proliferation activity in corresponding surgical specimen.

Methods A total of 388 patients who underwent surgery for localized RCC were included. The individual medication was evaluated according to substance classes. Tissue microarrays from corresponding tumor specimen were immunohistochemically (IHC) stained for Cyclin D1 and Ki67 and semi-quantitatively evaluated. Uni- and multivariate analyses were used to compare survival outcomes. For the comparison of IHC expression according to medication subgroups, Kruskal–Wallis analysis was performed.

Results Median follow-up was 57.93 months (95% CI 53.27–69.43) and median OS accounted for 181.12 months (129.72–237.17). Univariate analysis identified pathological standard variables (T-stage > T2, Grading > G2, L1, N1, M1, sarcomatoid subtype, necrosis) as significant determinants of OS. Moreover, statin use ($p = 0.009$) and sartan use ($p = 0.032$) were significantly associated with improved OS. Multivariate analysis identified M1-stage ($p < 0.001$), statin and sartan use ($p = 0.003$ and $p = 0.033$, respectively) as independent prognosticators of survival. Expression of Ki67 was significantly reduced in patients with statin use ($p = 0.013$), while Cyclin D1 expression showed no correlation with comedication.

Conclusions Concomitant intake of statins and sartans identifies as an independent predictor of OS in RCC, and reduced Ki67 expression was significantly associated with statin use. Further evaluation of drug repurposing approaches with these substances in RCC appear warranted.

Keywords HGM-CoA reductase inhibitor · Nephrectomy · Nephron sparing surgery · Renal cell carcinoma · Clear cell · Statin · Localized · Sartan · Angiotensin receptor blockers · Concomitant medication · Ki67 · Cyclin D1 · Proliferation marker · Cell cycle

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Introduction

Approximately, 84,400 new cases of renal cell carcinoma (RCC) are diagnosed per year and it is expected to account for almost 34,700 kidney-cancer-related deaths in the European Union in 2012 (Ferlay et al. 2013). RCC is not responsive to conventional chemo- or radiotherapy. The mainstay of curative therapy in localized RCC are nephron-sparing techniques and radical nephrectomy (Ljungberg et al. 2015). In the setting of metastatic RCC (mRCC) several systemic compounds targeting the vascular-endothelial growth-factor (VEGF) or mammalian-target

of rapamycin (mTOR) pathways have been approved and also novel immunotherapeutic approaches using immune-checkpoint inhibition have become clinical standard in recent years. Nevertheless, the burden of treatment associated side-effects and missing predictive biomarkers for therapy selection remain a relevant clinical problem. Moreover, none of the approved substances has shown consistent benefits in an adjuvant treatment scenario for localized RCC after surgery and a high-risk profile for disease recurrence (Meissner et al. 2018; Sun et al. 2018). Given the high costs for drug development and their clinical implementation, the approach of drug repositioning (DR) of selected non-anticancer drugs appears attractive (Liu et al. 2013). Currently, it is assumed that some non-anticancer drugs can influence tumor metabolism, tumor microenvironment and tumor-associated signal pathways and may have an effect on cancer incidence and outcome in several malignancies (Feldt et al. 2015; Kaffenberger et al. 2015).

Despite available experimental and epidemiological data, individual compounds have not been systematically evaluated with regard to their antineoplastic properties in RCC to date.

Therefore, in the present study, we evaluated the prognostic impact of non-oncologic concomitant medication in patients with surgically treated RCC and further analyzed putative influence on proliferative and cell-cycle activity in corresponding surgical specimen.

Material and methods

Patient characteristics

Patients after surgical treatment (nephrectomy or partial nephrectomy) for RCC between 1993 and 2011, were identified on the basis of the institutional tumor bank. Only patients with histologically confirmed primary clear cell renal carcinoma (ccRCC) were included ($n = 388$). Clinicopathological standard variables, comedication at the time of surgery and follow-up were recorded. The individual medication was evaluated according to substance classes (ACE-inhibitors, anticoagulants, beta-blockers, sulfonylurea, insulin, metformin, calcium channel blockers, sartans, high ceiling diuretics, thiacid diuretics, statins).

Immunohistochemistry

For protein expression analyses, tissue microarrays (TMA) from corresponding specimen were created. The technique of TMA preparation is described in detail elsewhere (Kononen et al. 1998). To determine the proliferative activity in corresponding surgical specimen an immunohistochemical

(IHC) staining for Ki67 was performed and Cyclin D1 was evaluated as a surrogate of cell-cycle activity. TMA slides were incubated with an anti-Ki67 (Mib1) antibody (DAKO, product code: M7240, Glostrup, Denmark) diluted at 1:200 using a commercial diluent (Dako, Glostrup, Denmark) at 37 °C/99 °F for 32 min. For Cyclin D1 staining anti-CycD1 (sp4) antibody (DCS, product code: C1677C01, Hamburg, Germany) diluted at 1:40 using a commercial diluent (Dako, Glostrup, Denmark) at 37 °C/99 °F for 32 min was used. For visualization an iView DAB Detection Kit (ROCHE/Ventana, Tucson, Arizona 85755, USA) was applied. Negative controls were performed by omitting the primary antibody.

Evaluation of TMAs

The semi-quantitative TMA evaluation was performed in a blinded fashion by two independent reviewers (SR, PK). Ki67 and Cyclin D1 expression were both evaluated with regard to nuclear staining. Frequency of positive nuclei per 100 cells was transferred to staining score from 0.0 to 1.0. In addition staining at specific cut offs (Ki67 > 10% and Cyclin D1 > 25%) was evaluated as a categorical variable.

Figure 1 illustrates IHC-staining for Ki67 and Cyclin D1 in RCC.

The study was approved by the institutional ethical review board (no. 078/2012B02). Written informed consent was obtained from all participants.

Statistical analysis

Kaplan–Meier analyses were performed to estimate survival in dependence of exposition to specific medication. Differences between subgroups were evaluated by log-rank tests. Additionally, univariate and multivariate Cox proportional regression analyses were performed to assess the correlation of clinical parameters and comedication with survival. For the comparison of IHC expression according to medication subgroups, Kruskal–Wallis analysis was performed. Statistical significance was regarded as $P < 0.05$. Statistical analyses were performed using MedCalc (Version 12.5, Ostend, Belgium).

Results

The study cohort comprised 388 patients with pathologically confirmed ccRCC after nephrectomy or partial nephrectomy. The median age of the patients was 64.26 years, 66.8% of patients ($n = 259$) were men and 33.2% ($n = 129$) women. A clinical follow-up was available in 373 (96.1%) of these patients. The median follow-up was 57.93 months (95% CI 53.27–69.43) and the median OS accounted for 181.12 months (95% CI 129.72–237.17). A total of 140

Fig. 1 Kaplan–Meier curves for overall survival in dependence of sartan and statin use
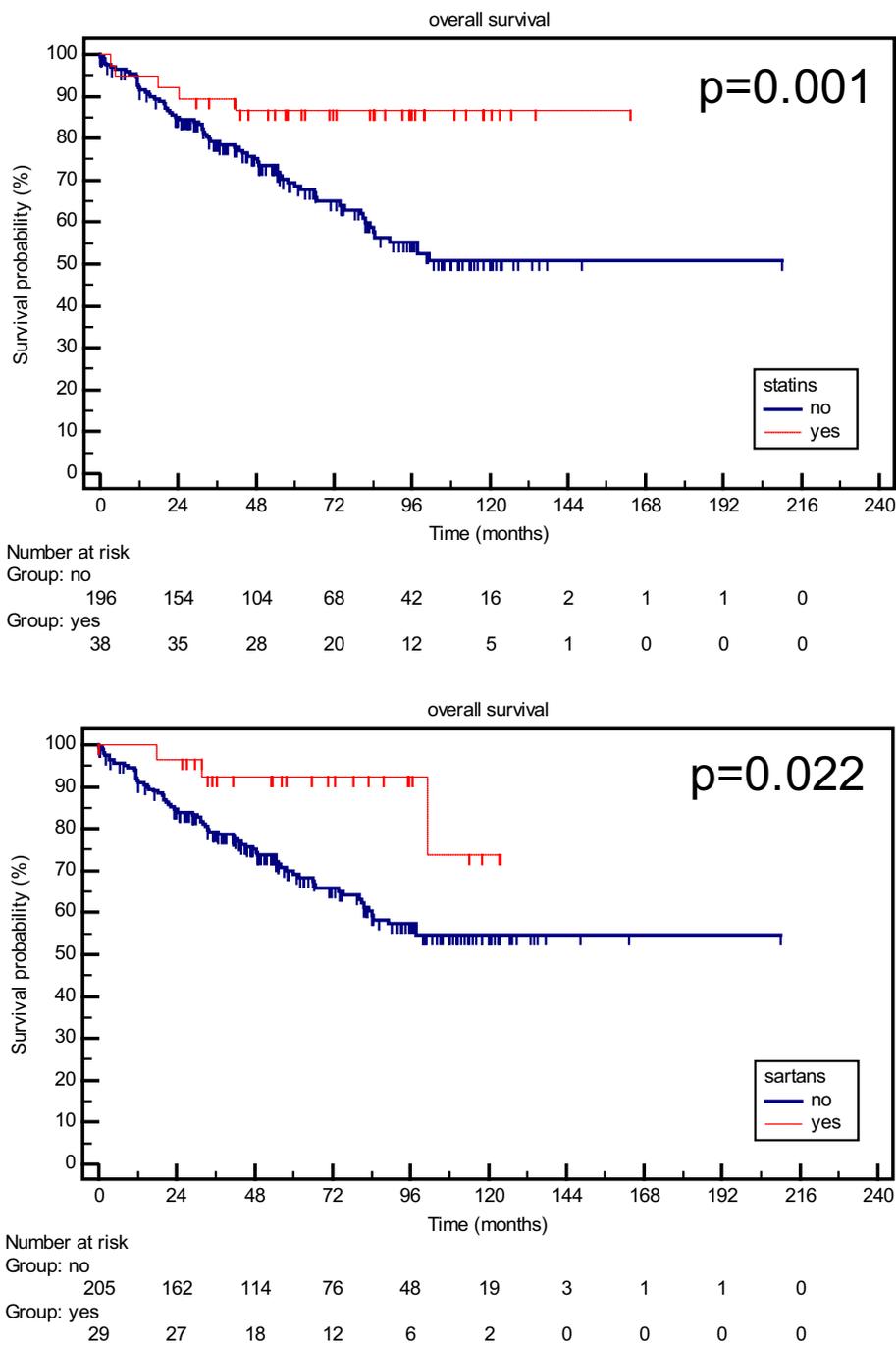
patients (37.5%) died during follow-up. Table 1 shows the detailed patients' clinical and pathological characteristics.

At time of surgery a complete history of medication was available in 246 (63.4%) patients. Up to six different compounds were taken by individual patients, while 34.1% ($n = 84$) patients received no comedication at time of surgery. According to different compounds, beta-blockers ($n = 91$, 37.0%), ACE-Inhibitors ($n = 77$, 31.3%) and Anticoagulants ($n = 62$, 25.2%) were taken in most frequently. Sartans and statins were taken from 31 (12.6%) and 39 (15.9%) patients,

respectively (Table 2). Among the 31 patients with sartan intake, 14 (45.2%) used Candesartan, 5 (16.1%) Losartan, 4 (12.9%) Valsartan, 3 (9.7%) Olmesartan, 3 (9.7%) Irbesartan and 2 (6.4%) Temisartan. In total, 39 patients took statins, 24 (61.5%) Simvastatin, 6 (15.4%) Atorvastatin, 6 (15.4%) Fluvastatin and 3 (7.7%) Pravastatin.

Univariate Cox regression analysis identified T-stage > pT1b ($p < 0.001$), Grading > G2 ($p < 0.001$), lymphovascular invasion (L1, $p < 0.001$), microvascular invasion (V1, $p < 0.001$), positive nodal-status (N1, $p < 0.001$),

Table 1 Clinical and pathological characteristics

Clinical features		
Median/av age in years (range), $n = 388$	64.26/62.77	(17.12–90.32)
Median/av follow-up in months (range), $n = 373$	57.93/71.12	(0–237.18)
Death during follow-up yes/no (%), $n = 373$	140/233	(37.50/62.50)
Median/av tumor diameter in cm (range), $n = 386$	4.8/5.3	(0.3–18.0)
Gender male/female (%)	259/129	(66.80/33.20)

	n	%
Pathological features		
T-stage		
T1a	143	36.90
T1b	86	22.20
T2a	7	1.80
T2b	2	0.50
T3a	118	30.40
T3b	29	7.50
T3c	3	0.80
Nodal stage		
N0	365	94.10
N1	20	5.20
N2	2	0.50
Unknown	1	0.30
Distant metastasis		
M0	330	85.10
M1	57	14.70
Unknown	1	0.30
Grading > G2		
No	308	80.40
Yes	75	19.60
Necrosis		
No	261	67.30
Yes	127	32.70
Sarcomatoid features		
No	364	93.80
Yes	24	6.20
Resection margin status		
R0	361	93.00
R1	26	6.70
Unknown	1	0.30
Lymphovascular invasion		
L0	357	92.00
L1	23	5.90
Unknown	8	2.10
Microvascular invasion		
V0	267	68.80
V1	107	27.60
V2	6	1.50
Unknown	8	2.10

av average, *n* number, % percent, *cm* centimeter

Table 2 Comedication in cohort ($n = 246$)

	n	%
Number of compounds		
0	84	34.10
1	42	17.10
2	38	15.40
3	37	15.00
4	22	8.90
5	18	7.30
6	5	2.00
Type of comedication		
ACE-inhibitors		
No	169	68.70
Yes	77	31.30
Anticoagulants		
No	184	74.80
Yes	62	25.20
Beta-blockers		
No	155	63.00
Yes	91	37.00
Sulfonylurea		
No	238	96.70
Yes	8	3.30
Insulin		
No	239	97.20
Yes	7	2.80
Calcium channel blockers		
No	203	82.50
Yes	43	17.50
Sartans		
No	215	87.40
Yes	31	12.60
High ceiling diuretics		
No	220	89.40
Yes	26	10.60
Statins		
No	207	84.10
Yes	39	15.90
Thiacid diuretics		
No	208	84.60
Yes	38	15.40
Metformin		
No	233	94.70
Yes	13	5.30

n number, % percent

Table 3 Results from univariate and multivariate Cox regression analysis

Covariate	Univariate			Multivariate		
	p value	Exp(*b*)	95% CI of exp(*b*)	*p* value	exp(*b*)	95% CI of exp(*b*)
Clinical features						
Gender; male/female	0.105	0.73	0.50–1.07			
Smoker status (current); yes/no	0.993	1.46	0.93–2.29			
Daily medication; yes/no	0.29	0.69	0.36–1.36			
Comedication						
ACE-Inhibitors	0.741	1.08	0.67–1.75			
Anticoagulants	0.526	1.17	0.72–1.92			
Beta-blockers	0.786	1.07	0.67–1.69			
Sulfonylurea	0.477	0.49	0.07–3.48			
Insulin	0.574	1.49	0.37–6.08			
Calcium channel blockers	0.615	0.85	0.45–1.61			
Sartans	**0.032**	0.28	0.09–0.89	**0.033**	0.27	0.08–0.89
High ceiling diuretics	0.821	1.08	0.56–2.1			
Statins	**0.009**	0.3	0.12–0.73	**0.003**	0.2	0.07–0.56
Thiacid diuretics	0.507	0.8	0.41–1.55			
Metformin	0.616	1.29	0.47–3.54			
Pathological features						
T-Stage > 1b	**< 0.001**	3.49	2.47–4.93	0.553	1.3	0.55–3.11
N-Stage	**< 0.001**	2.71	1.73–4.24	0.48	1.34	0.6–2.97
M-Stage	**< 0.001**	6.43	4.43–9.33	**< 0.001**	3.97	2.19–7.21
Grading > G2	**< 0.001**	3.94	2.72–5.71	0.052	2.12	0.99–4.48
Tumor diameter > 4.8 cm	**< 0.001**	2.16	1.53–3.05	0.662	0.88	**0.**49–1.56
Necrosis	**< 0.001**	2.06	1.48–2.88	0.189	1.41	0.85–2.34
Sarcomatoid features	**< 0.001**	5.53	3.45–8.87	0.18	1.99	0.73–5.42
Resection margin status	0.286	1.4	0.76–2.59			
L1-Stage	**< 0.001**	4.21	2.52–7.0	0.532	1.31	0.56–3.08
V1-Stage	**< 0.001**	2.46	1.85–3.29	0.837	1.08	0.5–2.34
Protein expression analysis						
Cyclin D1 positivity	0.131	0.65	0.38–1.13			
Cyclin D1 > 25%	**0.004**	0.54	0.35–0.82			
Ki67 positivity	**0.039**	1.54	1.02–2.3			
Ki67 > 10%	0.641	1.27	0.46–3.49			

Statistical significance was regarded as $P < 0.05$, significant changes are highlighted in bold

exp(b) hazard ratio, *CI* confidence interval

metastasis (M1, $p < 0.001$), sarcomatoid features ($p < 0.001$), tumor necrosis ($p < 0.001$), and tumor diameter > median tumor size (4.8 cm; $p < 0.001$) as significant determinants of OS.

Among the investigated medication at time of surgery, statins ($p = 0.009$) and sartans ($p = 0.032$) were significantly associated with improved OS (Table 3). Figure 2 illustrates survival in dependence of sartan and statin use. While median survival was not reached in both subgroups, significant differences in 5-year-OS rates were observed (sartans no: 69.45% yes: 92.3% $p = 0.022$; statins no: 69.45% yes 86.50% $p = 0.001$).

Multivariate Cox regression analysis identified M1-stage ($p < 0.001$), statins and sartans ($p = 0.003$ and $p = 0.033$, respectively) as independent prognosticators of OS in patients with ccRCC (Table 3).

Immunohistochemistry analysis

Analysis of Cyclin D1 expression revealed that overall 92% of the tumors showed positive staining for Cyclin D1. Among these, 103 (30.6%) tumors had a Cyclin D1 positive score of > 25% of cells. Evaluation of Ki67 expression showed overall positivity in 70.1%, while staining > 10% was present in only 2.7% of all specimen. Both Ki67 positivity

Fig. 2 Immunohistochemistry-staining for Ki67 (**a** negative, **b** positive staining) and Cyclin D1 (**c** negative, **d** positive staining) in RCC
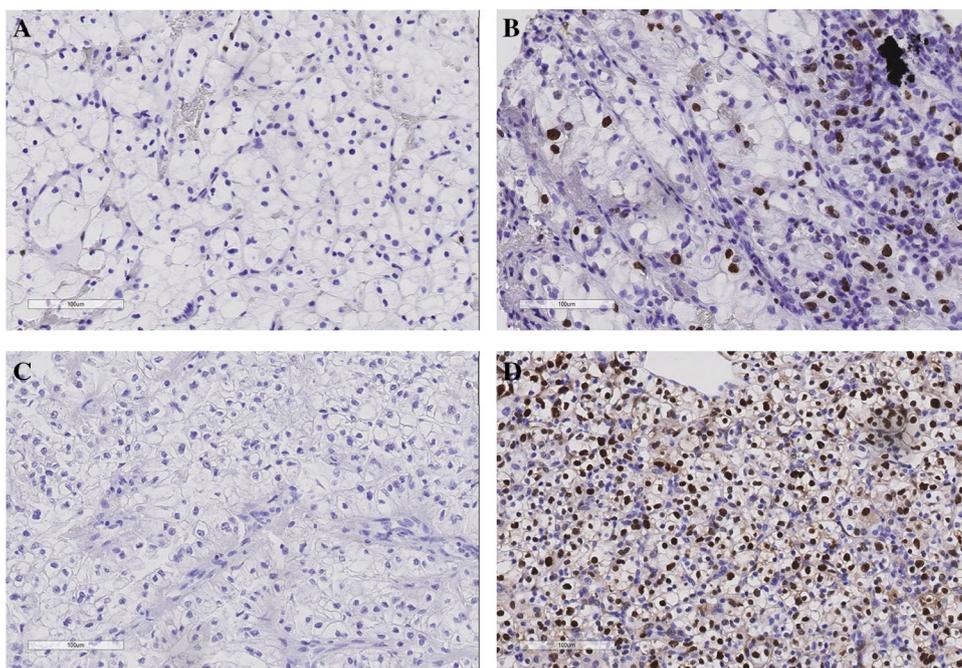
and Cyclin D1 > 25% were significantly predictive of OS ($p = 0.039$ and $p = 0.004$, respectively).

Expression of Ki67 was shown to be significantly lower in patients with Statin use ($p = 0.013$), while Cyclin D1 expression showed no correlation in dependence of statin exposition. Moreover, no significant difference in Ki67 and Cyclin D1 expression was detected in patients with sartan use (Fig. 3).

Discussion

In the present study, we observed a correlation between patient outcome and intake of statins and sartans in localized ccRCC. Statins are a major class of medication for treatment of hypercholesterolemia and widely known to contribute to a notable prevention of cardiovascular disease (Feldt et al. 2015). Statins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the rate-limiting enzyme of the mevalonate pathway (Feldt et al. 2015). In addition to the mainstay of lipid-lowering therapy, the inhibition of mevalonate pathway leads to an inhibition of inflammatory responses and influences the regulation of cell apoptosis and angiogenesis thereby developing an anti-neoplastic activity (Feldt et al. 2015; Nayan et al. 2016). Nielsen et al. showed an association of statin use and a reduced cancer-related mortality for 13 malignancies, e.g. pancreatic cancer and cervical cancer (Nielsen et al. 2012). For patients with RCC, available studies demonstrated conflicting results between statin use and survival outcomes (Hamilton et al. 2014; Kaffenberger et al. 2015; Nayan et al. 2016; Viers et al. 2015).

Nayan et al. reported no significant association between statin use at time of surgery and RCC outcome. In their study 259 of 893 patients used statins, and the propensity score analysis showed no significant correlation with disease-free, cancer-specific or overall survival (Nayan et al. 2016). An analysis by Viers et al. included 2357 patients, of which 630 took statins at the time of radical or partial nephrectomy. The oncologic outcome of patients with surgically treated localized RCC with or without statin usage was not different (Viers et al. 2015). Conversely, Kaffenberger et al. reported that patients with statin medication at the time of nephrectomy had a 52% reduction in cancer-specific mortality and a 38% reduction in all-cause mortality (Kaffenberger et al. 2015).

Ki67 is a well-known proliferation marker and Ki67 index was shown to independently predict cancer progression (Yang et al. 2018). The fact that Ki67 was found to be significantly reduced in statin users in the present evaluation of patients undergoing surgery for RCC may indicate a potential antitumor effect. Analogously, in breast cancer patients with statin usage, a downregulation of the oncogene Cyclin D1 was previously described (Feldt et al. 2015). However, in contrast to these results, Cyclin D1 expression as an indicator of cell cycle activity was not significantly altered in RCC patients with statin or sartan use in the present investigation.

As for statins, in the present study, we also observed a correlation between clinical outcome and intake of sartans in localized ccRCC. The renin angiotensin system (RAS) plays a major role in blood pressure regulation and control of kidney hemodynamics (Araujo et al. 2015; Miyajima
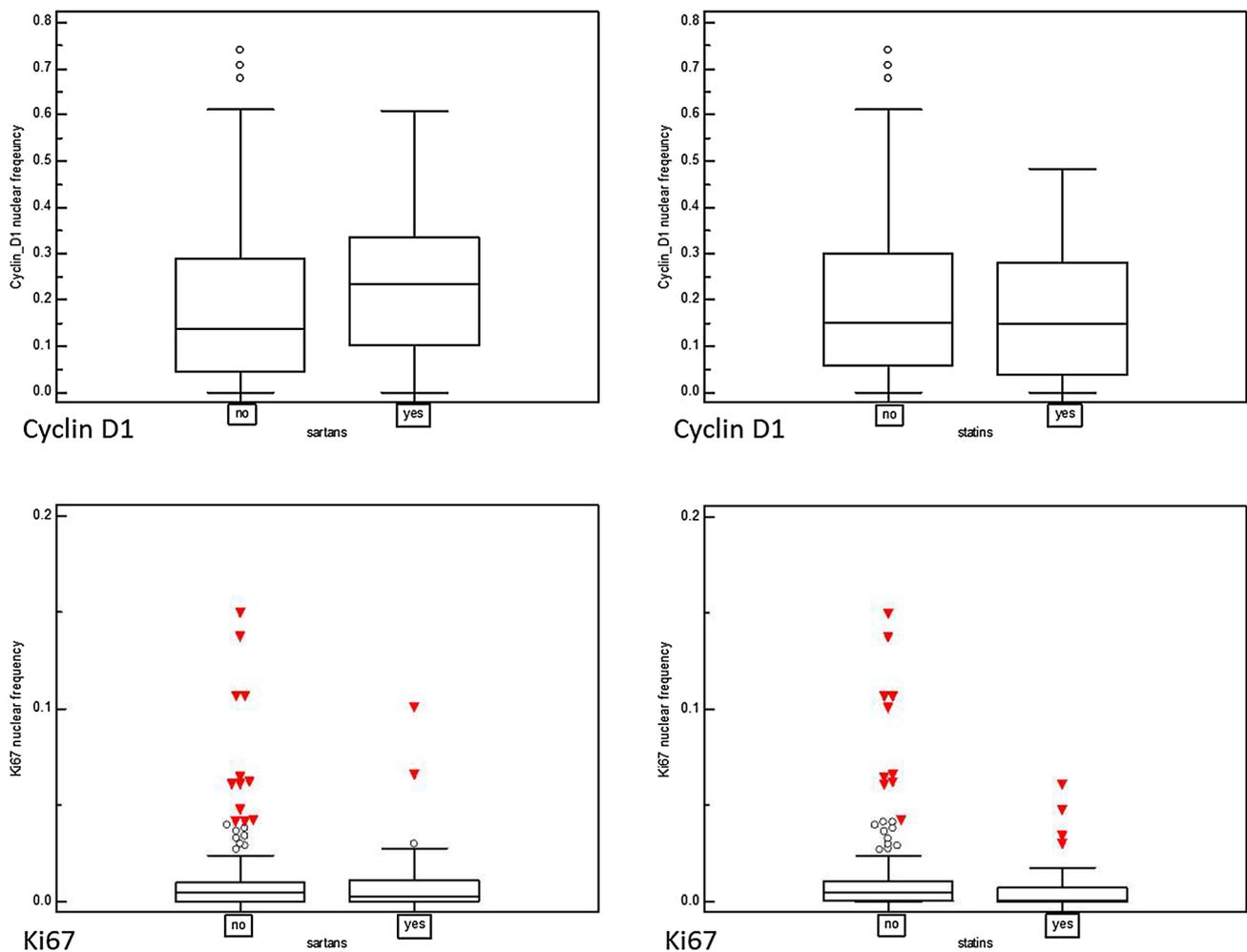
Fig. 3 Cyclin D1 and Ki67 expression in dependence of sartan and statin use (p = from Kruskal–Wallis test)

et al. 2015). Lever et al. reported that long-term Angiotensin II (Ang II) blockade had a protective effect against cancer (Lever et al. 1998). Ang II is an essential part of RAS and its effects are mediated through specific cell surface membrane receptors, called Ang II type 1 receptors (AT1R) and type 2 receptors (AT2R). It is reported that neovascularization can be induced through Ang II via AT1R (Araujo et al. 2015; Miyajima et al. 2015). Araujo et al. showed, that RAS blockade attenuates growth and metastatic potential of RCC in a mouse model (Araujo et al. 2015). Another research group proposed renin–angiotensin blockade as a potential approach for preventive treatment after initial surgical therapy of localized RCC. In their analysis of surgically treated RCC patients, the 5-year disease-specific survival rate was 96.8% among the patients with usage of RAS inhibitors and 89.8% without RAS inhibition, respectively (p = 0.019) (Miyajima et al. 2015). In patients with metastatic RCC treated with pazopanib or sunitinib and usage of angiotensin receptor blockers (ARB), study results revealed no impact on survival in a recent pooled analysis (Sorich et al. 2016).

There is increasing evidence that drug response of anti-cancer, as well as non-anticancer drugs are altered by the individual genetic make-up of the patient, corroborating the concept of personalized medicine and pharmacogenomics (Relling and Evans 2015; Scharfe et al. 2017).

Since both statins (Kitzmiller et al. 2016; Mosshammer et al. 2014; Vassy et al. 2018) and sartans (Needham and Mastaglia 2014; Ramsey et al. 2014) (Cooper-DeHoff and Johnson 2016) are known for their variable pharmacokinetics due to genetic polymorphisms for drug-transporters and metabolizing enzymes, with significant influence on compound efficacy and toxicity, evaluation of personalized approaches in dependence of pharmacogenetic information is appealing. With the ongoing development of computational drug repurposing approaches more opportunities for drug repurposing strategies are available (Luo et al. 2018).

The present study is inherent to limitations of a single-center retrospective approach and the observed correlations need prospective validation to draw causative conclusions. History of medication was restricted by the time of surgery and no information on the total duration of intake of the compounds could be obtained. With regard to the semi-quantitative IHC-score it must be considered that inter-observer variability maybe present.

Conclusions

Concomitant intake of statins and sartans was identified as an independent predictor of OS in surgically treated primary ccRCC, and reduced Ki67 expression was significantly associated with statin use. Based on these observations further evaluation of drug repurposing approaches with these substances in RCC are warranted.

Compliance with ethical standards

Conflict of interest E. N., P. K., K. F., M.Sc., E. S., M.Sw., F. F., J. B., S. K., J. H., A.S., and S. R. have no conflicts of interest to declare.

Research involving human and animal participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval The study was approved by the institutional ethical review board (no. 078/2012B02).

Informed consent Written informed consent was obtained from all participants.

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