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Urologic Oncology: Seminars and Original Investigations 37 (2019) 294.e1–294.e8

UROLOGIC ONCOLOGY

Original Article

Tyrosine kinase inhibitors in the first-line treatment for metastatic nonclear cell renal carcinoma: A retrospective analysis of a national database

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Received 13 June 2018; received in revised form 7 October 2018; accepted 17 December 2018

Abstract

Background: Nonclear cell renal cell carcinoma (nccRCC) is a heterogeneous group of primary kidney tumors. The aim of the present retrospective study was to analyze outcomes of patients with nccRCC treated with tyrosine-kinase inhibitors (TKIs) based on a national registry.

Methods: The registry contained evaluable data of 93 nccRCC patients treated with first-line TKIs, including 87 patients with papillary renal cell carcinoma (RCC) and 6 patients with chromophobe RCC. The control cohort consisted of 1,788 patients with clear-cell RCC treated with first-line TKIs. Multivariable Cox proportional hazard model was used to evaluate the effect of potential prognostic factors on the survival measures.

Results: Median progression-free survival was 11.8 and 6.5 months in the clear cell renal cell carcinoma and nccRCC patients, respectively ($P = 0.018$), and median overall survival was 33.2 and 22.0 months, respectively ($P = 0.007$). In the multivariate analysis, independent factors associated with inferior progression-free survival included high tumor grade, worse Memorial Sloan Kettering Cancer Center risk group, absence of nephrectomy, and sunitinib (as opposed to pazopanib) as first-line targeted therapy. Independent predictors of inferior overall survival included nonclear cell histology, tumor grade, worse Memorial Sloan Kettering Cancer Center risk group, absence of nephrectomy, older age, and sunitinib as first-line targeted therapy.

Conclusions: The present retrospective, registry-based study confirms that patients with nccRCC treated with TKIs have worse clinical outcomes compared to clear cell renal cell carcinoma patients with similar baseline characteristics.

Keywords: Nonclear cell renal carcinoma; Targeted therapy; Sunitinib; Pazopanib

1. Introduction

Nonclear cell renal cell carcinoma (nccRCC) is a heterogeneous group of primary kidney tumors. Papillary

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https://doi.org/10.1016/j.urolonc.2018.12.017
1078-1439/

carcinoma type I or II is the most frequent subtype comprising 10%−15% cases of adult renal cell carcinoma (RCC)) patients, followed by chromophobe carcinoma (approximately 5% of cases). Other subtypes are very rare and include unclassified carcinoma, translocation carcinoma, medullary carcinoma, collecting duct carcinoma (also called Bellini duct carcinoma), and adult Wilms tumors. An updated World Health Organization classification introduced in 2016 also includes newly defined entities such as hereditary leiomyomatosis and RCC syndrome-associated RCC, succinate dehydrogenase-deficient RCC, tubulocystic RCC, acquired cystic RCC, and clear cell papillary RCC [1].

The treatment of metastatic RCC (mRCC) has advanced significantly over the past 10 years. Tyrosine kinase inhibitors (TKI) or antibodies targeting the vascular endothelial growth factor signaling pathway, inhibitors of the mammalian target of rapamycin (mTOR), and checkpoint inhibitors including antiprogrammed death-1 antibodies are at present the mainstay of systemic therapy [2−6]. Current international guidelines are based mainly on phase III studies that, with some exceptions, excluded nccRCC patients [7]. Only in the phase III study comparing the efficacy of temsirolimus vs. interferon-α enrolment of patients with nccRCC was allowed, and approximately 20% of patients in that trial had nccRCC [6].

In the absence of data from randomized studies, treatment recommendations for patients with nccRCC rely on data from phase II trials, analyses from expanded-access programs, and retrospective studies [8−21]. In general, these data indicate that the outcomes of nccRCC patients are inferior to those in patients with clear-cell mRCC [22,23]. The aim of the present retrospective study was to analyze outcomes from the RENIS registry for nccRCC patients treated with TKIs in comparison with outcomes observed in ccRCC in the real-world clinical practice.

2. Methods

2.1. Patients

Patients with nonclear cell mRCC and sunitinib or pazopanib as first-line treatment for metastatic disease initiated between 2006 and 2015 were included in the present analysis. Due to the reimbursement restrictions on targeted treatment of mRCC, the analysis only included patients with good or intermediate prognosis according to the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model [24]. Patients with ccRCC treated with first-line sunitinib and pazopanib during the same period were included in the control cohort for comparative analysis. Although response assessment interval and methods are not specified in the registry entry criteria, reimbursement specifications call for restaging using computed tomography every 3 to 4 months and response assessment Response Evaluation Criteria in Solid Tumors.

2.2. Data source

The data were sourced from RENIS (http://renis.registry.cz/), a national registry collecting anonymized data of mRCC patients treated with a targeted therapy. The registry is updated twice a year and collects baseline characteristics of the patients, disease characteristics at diagnosis, data on anticancer treatment, outcomes and adverse events. The RENIS registry contains data on approximately 95% of mRCC patients treated in the Czech Republic with targeted treatment outside of clinical trials. Prescribing restrictions defined by healthcare payers limit the use of this treatment to comprehensive cancer centers [25,26]. The RENIS registry and the use of registry data for analysis were approved by the Multicenter Ethics Committee of the University Hospital and the Masaryk Memorial Cancer Institute in Brno, Czech Republic.

2.3. Statistical analysis

Descriptive statistics and frequency tables were used to characterize the sample data set. Statistical significance of differences categorical parameters was assessed using the Fisher's exact test. For continuous variables Mann−Whitney test was used. Overall survival (OS) was defined as the time from the first targeted treatment initiation to the death of any cause. Progression-free survival (PFS) was defined as the time from the first targeted treatment initiation to the first documented progression or death of any cause. Patients without an event were censored at the last visit. PFS and OS were estimated using the Kaplan−Meier method and all point estimates include 95% confidence intervals (95% CI). Statistical significance of differences in survival between the subgroups was assessed using the log-rank test. Multivariable Cox proportional hazard model was used to evaluate the effect of potential prognostic factors on the survival measures. Hazard ratios were complemented with 95% confidence intervals and supported with significance levels. Overall response rate (ORR) was defined as the sum of complete response rate and partial response rate and disease control rate as ORR plus stable disease rate. All statistical tests were performed at the significance level of $\alpha = 0.05$.

3. Results

3.1. Patient population and baseline characteristics

The RENIS registry contained data of 3,602 mRCC patients. In total 181 patients had nccRCC, including 154 patients with papillary type I or type II carcinoma, 18 patients with chromophobe carcinoma, 7 patients with collecting duct carcinoma, and 2 patients with oncocytic carcinoma. Ninety-three of the nccRCC patients including 87 patients with papillary RCC and 6 patients with chromophobe RCC received first-line treatment with TKIs and had

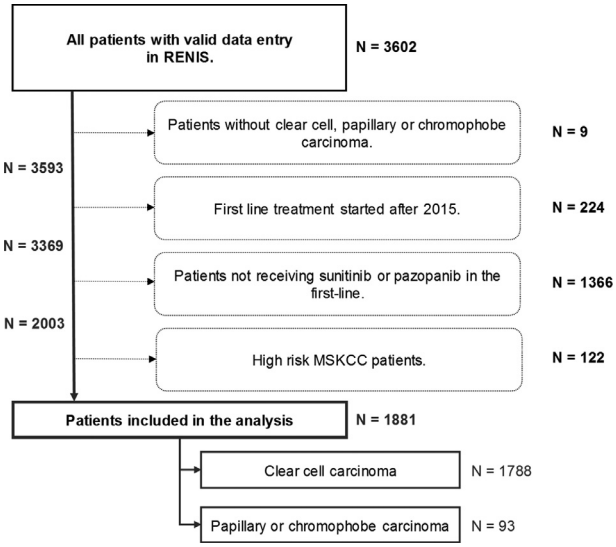

Fig. 1. CONSORT diagram of selection of patient data from the RENIS database.

valid data for the present outcome analysis (Fig. 1). There were no patients with presurgical TKI treatment in the studied nccRCC cohort. The control cohort consisted of 1,788 patients with clear-cell RCC (ccRCC) treated with first-line TKIs. Both cohorts were contemporaneous when analyzed by year of treatment initiation (data not shown). The median follow-up in patients who were alive at the time of evaluation ($n = 1{,}007$; 53.5%) was 21.6 months. Table 1 presents the principal patient characteristics. At treatment initiation, a higher proportion of patients with nccRCC compared to ccRCC had metastases in the liver, lymph nodes, and peritoneum, while the proportion of patients with lung and bone metastases was lower in the nccRCC cohort (Supplementary Table 1).

3.2. Treatment outcomes

Median duration of the first line targeted treatment was 7.1 months in ccRCC patients and 4.5 months in nccRCC patients ($P = 0.027$). Response rates were inferior in patients with nccRCC, with ORR of 27.5% and 15.7% ($P = 0.016$), and DCR of 62.1%, and 49.4% ($P = 0.027$) for ccRCC and nccRCC, respectively. Second and higher lines of treatment were prescribed with similar frequency in both ccRCC and nccRCC patients (Supplementary Table 2). The proportion of patients with treatment discontinuation for toxicity was similar—10.7 vs. 9.6% for clear-cell and nccRCC cohorts, respectively. The type, frequency, and severity of reported adverse events were also similar (data not shown).

Median PFS was 11.8 and 6.5 months ($P = 0.018$), and median OS was 33.2 and 22.0 months ($P = 0.007$) in ccRCC and nccRCC patients, respectively (Fig. 2). ccRCC patients with good and intermediate prognosis had median PFS of 18.1 and 9.4 months, respectively, and nccRCC patients had PFS of 10.3 and 6.3 months, respectively. Median OS was 46.6 and 26.8 months for these prognostic categories in ccRCC patients compared to 22.5 and 22 months, respectively, in nccRCC patients (Table 2).

In a Cox multivariate analysis, independent factors associated with poor PFS included high-tumor grade, worse MSKCC risk group, absence of nephrectomy, and sunitinib as first-line targeted therapy (as opposed to pazopanib). The independent factors for worse OS included nonclear cell histology, tumor grade, worse MSKCC risk group, absence of nephrectomy, older age, and sunitinib as first-line targeted therapy (Table 3).

4. Discussion

The present retrospective study confirms that patients with nccRCC treated with TKIs have inferior clinical outcomes compared to ccRCC patients with similar baseline characteristics.

Before there is new evidence from the ongoing randomized trials with newer agents, targeted therapy with TKIs and mTOR inhibitors will remain the mainstay of treatment for nccRCC based on results from small prospective trials as well as observational and retrospective studies.

Data from 2 prospective phase II studies that compared the efficacy of sunitinib and everolimus in patients with nccRCC are available. In the randomized ASPEN study, sunitinib or everolimus were administered as first-line treatment in patients with nccRCC ($n = 108$). Median PFS for sunitinib and everolimus was 8.3 and 5.6 months, with median OS of 31.5 and 13.2 months, respectively. In contrast to the patients with papillary carcinoma who constituted the majority of the study population, patients with chromophobe nccRCC had superior PFS when treated with everolimus compared to sunitinib (11.4 vs. 5.5 months), possibly due to mutations in the phosphoinositol-3 kinase-mTOR and tuberous sclerosis 2 pathways [20,27].

Another prospective study, Everolimus vs. sunitinib prospective evaluation in metastatic nonclear cell renal cell carcinoma (ESPN), compared the efficacy of first-line treatment with sunitinib and everolimus in nccRCC patients and included a crossover strategy [21]. The study, which also enrolled 18% of patients with sarcomatoid ccRCC, was closed prematurely as the interim analysis did not support the expected superiority of everolimus over sunitinib. Median PFS and OS in the sunitinib and everolimus arms were 6.1 and 16.2 months vs. 4.1 and 14.9 months, respectively [21].

Single arm studies with sunitinib have been carried out in the nccRCC patients, reporting median OS ranging from 12.4 to 25.6 months [14,15,19]. Similar results have been obtained in nccRCC patients treated with sunitinib within the expanded access program [9].

Data on the efficacy and safety of pazopanib in the nccRCC population are more limited, but indicate outcomes

Table 1
Baseline patient characteristics

Characteristic	Clear cell carcinoma ($n = 1788$)	Papillary or chromophobe carcinoma ($n = 93$)	P value
Sex, *n* (%)			
Males	1258 (70.4)	68 (73.1)	0.641
Females	530 (29.6)	25 (26.9)	
Age at diagnosis [years]—median (range)	62 (25-85)	63 (33-82)	0.067
Stage at diagnosis, *n* (%)			
Stage I	272 (15.2)	20 (21.5)	0.275
Stage II	230 (12.9)	14 (15.1)	
Stage III	349 (19.5)	20 (21.5)	
Stage IV	722 (40.4)	32 (34.4)	
Unknown	215 (12.0)	7 (7.5)	
Primary tumor grade, *n* (%)			
G1 well differentiated	135 (7.6)	7 (7.5)	0.984
G2 moderately differentiated	643 (36.0)	35 (37.6)	
G3-4 poorly differentiated / nondifferentiated	687 (38.4)	34 (36.6)	
GX differentiation degree cannot be assessed	288 (16.1)	15 (16.1)	
Unknown	35 (2.0)	2 (2.2)	
MSKCC score			
good prognosis	563 (31.5)	27 (29.0)	0.649
intermediate prognosis	1225 (68.5)	66 (71.0)	
ECOG PS 2 and higher	73 (4.1)	4 (4.3)	0.790
Calcium > 2.5 mmol/l	98 (5.5)	2 (2.2)	0.233
Hemoglobin < lower limit of normal	488 (27.3)	28 (30.1)	0.552
Time from diagnosis to first target treatment < 1 year	906 (50.7)	45 (48.4)	0.672
LDH more than 1.5× upper limit of norm	111 (6.2)	4 (4.3)	0.655
Prior radiotherapy	210 (11.7)	10 (10.8)	0.870
Prior nephrectomy, *n* (%)	1488 (83.2)	78 (83.9)	0.999
Prior adjuvant cytokines, *n* (%)	80 (4.5)	6 (6.5)	0.315
Type of first targeted treatment, *n* (%)			
sunitinib	1422 (79.5)	78 (83.9)	0.356
pazopanib	366 (20.5)	15 (16.1)	
Age at first target treatment initiation (years) median (5–95th percentile range)	65 (25–88)	66 (37-81)	0.219
ECOG PS at first target treatment initiation, *n* (%)			
PS 0	668 (37.4)	38 (40.9)	0.380
PS 1	1047 (58.6)	51 (54.8)	
PS 2	68 (3.8)	3 (3.2)	
PS 3	5 (0.3)	1 (1.1)	
Dose of sunitinib at treatment initiation, *n* (%)*			
12.5 mg	2 (0.1)	0 (0.0)	
25.0 mg	134 (9.4)	6 (7.7)	
37.5 mg	219 (15.4)	16 (20.5)	
50.0 mg	1067 (75.0)	56 (71.8)	
Sunitinib dose reduction due to adverse event, *n* (%)*	237 (16.7)	12 (15.4)	

ECOG-PS, Eastern Cooperative Oncology Group performance status; G, grade; PS, performance status; LDH, lactate dehydrogenase; MSKCC, Memorial Sloan Kettering Cancer Center

* % calculated for sunitinib-treated patients only.

comparable to sunitinib [10–12,18].The largest cohort ($n = 37$) was retrospectively analyzed by Buti et al. and included mostly patients with papillary nccRCC (51%) and chromophobe carcinoma (24%). DCR was 81% with median PFS and OS of 15.9 and 17.3 months, respectively [11].

There are no clear recommendations for the cytoreductive nephrectomy in patients with asymptomatic, metastatic nccRCC. According to current practice in the Czech Republic, supported by published data, cytoreductive nephrectomy is usually discussed in a multidisciplinary team and usually considered in good or intermediate risk groups according to MSKCC 2002, in the absence of contraindications [28,29]. In the present study, absence of nephrectomy was an independent prognostic factor, consistent with the previous retrospective studies [28,29]. However, recently it has been shown in CARMENA, a prospective, randomized study, that sunitinib was not inferior to nephrectomy followed by sunitinib in clear-cell

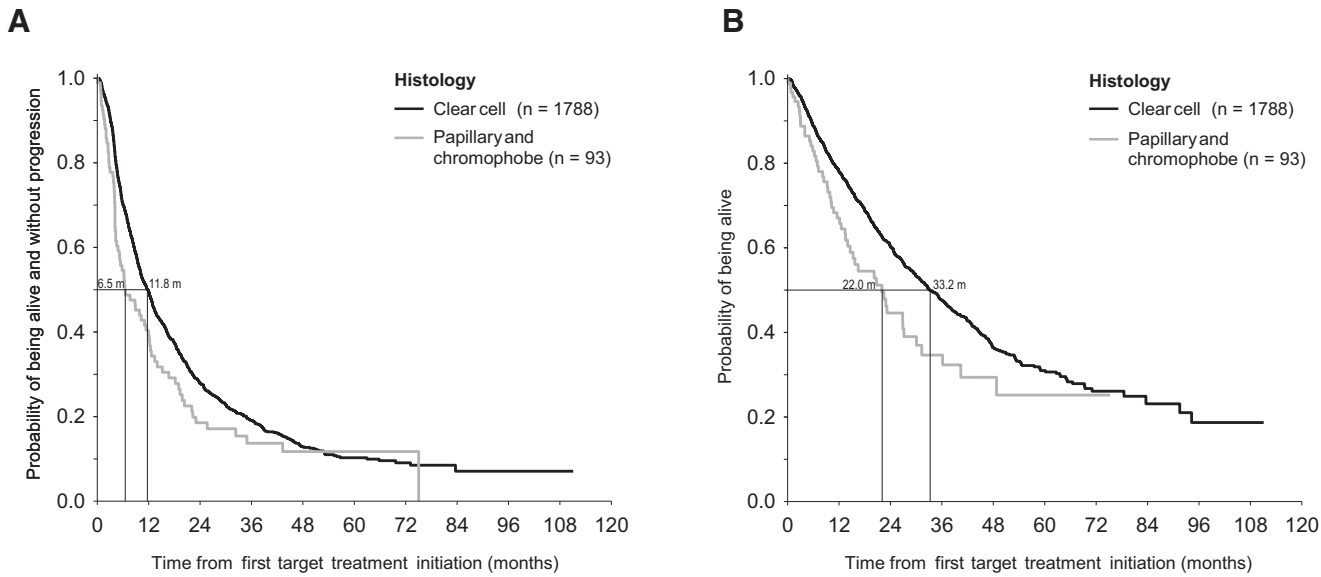

Fig. 2. Progression-free (A) and overall survival (B) from first target treatment initiation.

mRCC [30]. Nevertheless, in contrast to the CARMENA study which enrolled no good prognosis patients and included 43% of poor prognosis patients, our retrospective cohort consisted of good and intermediate prognosis patients exclusively.

The present data from the RENIS registry are in agreement with previous reports as well as with the findings of the retrospective study by Kroeger et al. that proved recently the validity of the International mRCC Disease Consortium prognostic model in the setting of nccRCC. In this study, the largest so far on the subject, patients with nccRCC ($n = 255$) had median times to treatment failure and OS 4.2 and 12.8 months, respectively [22].

The paucity of data from large prospective trials is a major issue facing both the nccRCC patients and their physicians. Further molecular analyses are needed to allow improved targeting of treatment. One promising target is the *MET* signaling pathway, frequently altered in sporadic papillary carcinoma [27,31]. Foretinib, an inhibitor the *MET, VEGF, AXL,* and *TIE-2* pathways, and savolitinib, a

Table 2
Treatment outcomes

	Clear cell carcinoma ($n = 1788$)	Papillary or chromophobe carcinoma ($n = 93$)	*P* value
Median PFS (95% CI)	11.8 months (11.0–12.7)	6.5 months (2.5–10.5)	
6-month PFS (%; 95% CI)	70.0 (67.9–72.2)	54.5 (44.1–65.0)	**0.018**
1-year PFS (%; 95% CI)	49.5 (47.1–51.9)	39.2 (28.9–49.5)	
2-year PFS (%; 95% CI)	27.8 (25.5–30.1)	18.6 (10.0–27.1)	
Median OS (95% CI)	33.2 months (30.3–36.1)	22.0 months (14.6–29.4)	
6-month OS (%; 95% CI)	88.7 (87.2–90.2)	82.9 (75.0–90.8)	**0.007**
1-year OS (%; 95% CI)	78.1 (76.1–80.1)	67.0 (57.0–77.1)	
2-year OS (%; 95% CI)	60.3 (57.8–62.9)	44.6 (33.0–56.1)	
Best first target treatment response—patients with terminated treatment, *n* (%)			
CR	75 (5.0)	1 (1.2)	0.063
PR	337 (22.5)	11 (13.3)	
SD	517 (34.5)	28 (33.7)	
PD	366 (24.4)	31 (37.3)	
Not evaluated	202 (13.5)	12 (14.5)	
ORR (CR+PR)	412 (27.5)	13 (15.7)	**0.016**
DCR (CR+PR+SD)	929 (62.1)	41 (49.4)	**0.027**

Leg.: CI, confidence interval; CR complete response; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Bold font signifies statistical significance.

Table 3
Progression-free survival and overall survival results according to histology subtype subgroup: a multivariable Cox-proportional hazards model

Variable	Category	*n*	Progression-free survival		Overall survival	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Histology	Clear cell	1547	1.00	-	1.00	-
	Papillary or chromophobe	85	1.27 (0.99–1.62)	0.060	1.39 (1.03–1.86)	**0.031**
Sex	Females	476	1.00	-	1.00	-
	Males	1156	1.07 (0.94–1.21)	0.302	0.96 (0.82–1.11)	0.556
Stage at diagnosis	Stage I-III	891	1.00	-	1.00	-
	Stage IV	741	1.01 (0.89–1.15)	0.863	1.08 (0.92–1.27)	0.344
Primary tumour grade	G1	133	1.00	-	1.00	-
	G2	622	1.64 (1.31–2.07)	**<0.001**	1.43 (1.07–1.93)	**0.017**
	G3-4	672	1.27 (0.97–1.66)	0.087	1.70 (1.26–2.28)	**<0.001**
MSKCC	Good	476	1.00	-	1.00	-
	Intermediate	1156	1.38 (1.20–1.60)	**<0.001**	1.60 (1.33–1.92)	**<0.001**
Prior nephrectomy	No	290	1.00	-	1.00	-
	Yes	1342	0.68 (0.58–0.80)	**<0.001**	0.64 (0.53–0.77)	**<0.001**
Age at the treatment initiation	≤ 65 years	859	1.00	-	1.00	-
	> 65 years	773	1.01 (0.90–1.14)	0.811	1.16 (1.01–1.34)	**0.039**
First-line targeted treatment	Sunitinib	1309	1.00	-	1.00	-
	Pazopanib	323	0.80 (0.69–0.93)	**0.004**	0.79 (0.65–0.96)	**0.019**

*Grade was not specified for 205 patients.
G, grade; HR, hazard ratio; MSKCC, Memorial Sloan Kettering Cancer Center.
Bold font signifies statistical significance.

highly selective *MET* inhibitor, have generated promising results in a phase II study [32,33]. Clinical studies with checkpoint inhibitors in nccRCC patients are also underway. The progress is also hampered by the fact that nccRCC is a heterogeneous group of tumors with variable biology, including the papillary type II carcinoma and collecting duct carcinoma associated with poor prognosis as well as chromophobe carcinoma with relatively indolent course and different response to targeted therapies [21,22]. So far, there are no indications that systemic adjuvant therapy is effective in preventing recurrence of nccRCC after nephrectomy [34].

The present study is limited by the retrospective nature. In addition, the treatment response has not been confirmed by a central radiology review. The cohort included mostly patients with papillary carcinoma, and patients with chromophobe carcinoma represented a small minority. Outcomes for patients treated with other first-line agents, eg temsirolimus, and for different histological types of nccRCC could not have been analyzed due to low patient numbers. The population of nccRCC in the registry is much smaller than would be expected based on the frequency of the histology in the population of mRCC patients. Additionally, in chromophobe tumors grade per the Fuhrman systems does not correlate with prognosis and these tumors should not be graded using the International Society of Urological Pathology grading system [35,36]. Nevertheless, these systems are used in current publications and clinical trials [34]. There were only 6.5% patients with chromophobe tumors in our cohort. Therefore the impact of this uncertainty is negligible.

MSKCC staging system has been used instead of the newer International mRCC Database Consortium criteria due to availability of data in the registry [24,37]. However, we have shown previously on similar dataset that MSKCC and criteria perform similarly in our patients [38].

RENIS is a drug-based registry, and relatively strict restrictions of prescriptions of targeted therapies in metastatic nccRCC might have led to a selection bias which resulted in targeted therapy being offered to fewer metastatic nccRCC patients. The limitations of retrospective studies as well as the risk of overinterpretation of the results are best illustrated by the unexpected observation in multivariate analysis of better outcomes with pazopanib compared with sunitinib that contradicts the results of prospective clinical trials [4,39]. This finding may also be explained by a selection bias. First, pazopanib was introduced several years after sunitinib and worse outcome in patients treated with sunitinib may reflect more limited options for second line therapies and less experience with the management of mRCC patients treated with targeted agents in the earlier years. Second, in contrast to randomized trials different patients might have been selected for sunitinib and pazopanib, and sunitinib might have been selected more often for patients with disease characterized by aggressive tumor biology. Thus, the results of this retrospective analysis should not be interpreted as indicating the superiority of one TKI over another or lead to change in practice pattern. Moreover, based on the results of CheckMate 214 trial TKIs may soon be replaced by the combination of checkpoint inhibitors as front-line standard of care for intermediate and poor risk patients leaving first-line

TKIs only for good prognosis patients [40]. Only the results of future clinical trials will indicate the efficacy of checkpoint inhibitors in metastatic nccRCC.

5. Conclusion

The present study indicates, in agreement with previous reports, that patients with metastatic nccRCC have significantly lower ORR as well as shorter PFS and OS *n* compared to patients with ccRCC. Prospective randomized studies with sufficient numbers of patients and stratification based on molecular characteristics are needed to define optimal systemic treatment for nccRCC.

Financial disclosures

Tomas Buchler received honoraria for advisory boards and/or lectures from Novartis, Pfizer, and Roche. Bohuslav Melichar received honoraria for advisory boards and/or lectures from Novartis, Pfizer, Glaxo Smith Kline, Roche, Astellas, Bristol Myers Squibb and Bayer. Alexandr Poprach received honoraria for lectures from Novartis, Bristol-Myers Squibb, Roche and Bayer. Radek Lakomy and Katerina Kopeckova received honoraria for lectures from Novartis. Katerina Kubackova received honoraria for lectures from Pfizer and travel grants from Pfizer and Bayer. Milada Zemanova received honoraria for advisory boards and/or lectures from Novartis and Glaxo Smith Kline and travel grants from Bayer and Novartis. Other authors have declared no conflict of interest.

Funding/Support and role of the sponsor

Supported by grant VES 2015 15-34678A from the Ministry of Health, Czech Republic. The RENIS registry is funded in part by pharmaceutical companies producing targeted agents for renal cancer (Pfizer, Bayer, Glaxo Smith Kline, Roche, and Novartis).

Acknowledgments

We would like to thank the following heads of the comprehensive cancer centers for the permission to use data of patients from their respective regional networks: Dr Martina Chodacka, Chomutov Hospital and Masaryk Hospital in Usti nad Labem; Dr Vaclav Janovsky, Ceske Budejovice Hospital; Dr Otakar Bednarik, University Hospital, Brno; Dr Jana Prausova, Motol University Hospital, Prague; Dr David Feltl, University Hospital, Ostrava; Professor Jindrich Finek, University Hospital, Pilsen; Professor Jiri Petera, University Hospital, Hradec Kralove; Dr Lubomir Slavicek, Jihlava Hospital; Dr Jana Katolicka, St Anna University Hospital, Brno; Professor Rostislav Vyzula, Masaryk Memorial Institute of Oncology, Brno; Dr Jiri Bartos, County Hospital, Liberec; Dr Martin Safanda, Na Homolce Hospital, Prague; Dr Renata Soumarova, Novy Jicin Hospital; Professor Jitka Abrahamova, Thomayer Hospital, Prague; Professor Lubos Petruzelka, General University Hospital, Prague; Dr Milan Kohoutek, T Bata Memorial Hospital, Zlin. We are also indebted to all physicians who provided data for the RENIS registry.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2018.12.017.

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