

Metastatic papillary renal cell carcinoma in the era of targeted therapy – a retrospective study from three European academic centres

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ABSTRACT

Background: Metastatic papillary renal cell carcinoma (mPRCC) is understudied. The disease is often aggressive and specific treatment options are lacking.

Patients and methods: mPRCC patients ($n=86$) referred to three academic centres in Sweden and Germany in the years 2005–2015 were retrospectively identified from medical records. Statistical analyses included Kaplan–Meier curves and calculation of Cox proportional hazards, generating hazard ratios with 95% confidence intervals. The aim of the study was to evaluate overall survival (OS) of mPRCC patients treated outside of clinical trials in the era of targeted agents (TA) and to identify clinically useful prognostic factors.

Results: Median OS of all mPRCC patients was 11.2 months. TA were used in 77% of the patients and associated with younger age and better Eastern Cooperative Oncology Group performance status (PS). Brain metastases were common (28%). Patients with synchronous or metachronous metastases had similar OS. Variables independently associated with risk of death included age ≥ 60 years, worse PS and ≥ 3 metastatic sites. The MSKCC criteria did not provide additional prognostic information. A subgroup analysis of TA-treated patients revealed an association of lymph node metastasis with risk of death in addition to the other prognostic factors.

Conclusion: OS in mPRCC remained short in the era of targeted agents. Age, PS, and number of metastatic sites provided independent prognostic information.

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Introduction

Renal cell carcinoma (RCC) comprises a broad spectrum of histological subtypes as described 2016 in the World Health Organization (WHO) and in the International Society of Urological Pathology (ISUP) classification [1,2]. Recently, more attention has been paid to the heterogenous group of non-clear cell tumours, consisting of different histological subtypes with papillary (PRCC) being the most common representing 10–15% of all RCC [3]. PRCC can be further divided into type 1 and type 2 [4–8]. In general, an inferior overall survival (OS) has been reported for metastatic papillary RCC (mPRCC) compared to metastatic clear cell RCC [9].

Clinical trials have often excluded patients with non-clear cell subtypes due to small numbers and heterogeneity [10,11]. Consequently, systemic therapies for mRCC have been developed based on clear cell biology, characterized by aberrant vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin (mTOR) signalling, which is distinctly different from that of mPRCC [12]. This has led to the successful introduction of targeted agents (TA) for

clear cell mRCC [10,11,13–16]. In the absence of biological therapies tailored to mPRCC these patients are commonly offered TA [17–20] albeit responding less well than clear cell mRCC. In type 1 mPRCC, MET has emerged as a potential treatment target with kinase inhibitors targeting MET achieving objective responses and disease control [21,22]. Data on check-point inhibitors in mPRCC are so far scarce but initial reports have demonstrated objective responses in some patients [23–25].

Predicting the risk of death and hence selecting the optimal treatment strategy remains a challenge in mPRCC [9,26]. The aim of this retrospective multicentre study was to identify clinically relevant prognostic factors in mPRCC patients treated outside of clinical trials.

Patients and methods

Study population

The study included all patients ($n=86$) with mPRCC referred for oncological treatment at one of three academic centres:

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📎 Supplemental data for this article can be accessed [here](#).

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Table 1. Metastatic papillary RCC patient characteristics.

Patients, <i>n</i>	All 86	Systemic therapy 66	No systemic therapy 20	<i>p</i>
Median age, years (range)	65 (31–85)	62 (31–79)	72 (40–85)	<.001
Sex				
Male, <i>n</i> (%)	64 (74)	48 (73)	16 (80)	
Female, <i>n</i> (%)	22 (26)	18 (27)	4 (20)	
Papillary type				.01
Type 1, <i>n</i> (%)	4 (5)	2 (3)	2 (10)	
Type 2, <i>n</i> (%)	60 (69)	53 (80)	7 (35)	
Mixed	4 (5)	2 (3)	2 (10)	
NOS	18 (21)	9 (14)	9 (45)	
ECOG performance status (PS)				<.001
0, <i>n</i> (%)	45 (52)	43 (65)	2 (10)	
1, <i>n</i> (%)	22 (26)	18 (27)	4 (20)	
≥2, <i>n</i> (%)	19 (22)	5 (8)	14 (70)	
MSKCC risk group				
patients where available, <i>n</i>	84	66	18	
Favourable, <i>n</i> (%)	15 (18)	14 (21)	1 (5)	
Intermediate, <i>n</i> (%)	51 (61)	39 (59)	12 (67)	
Poor, <i>n</i> (%)	18 (21)	13 (20)	5 (28)	
Synchronous metastases, <i>n</i> (%)	42 (49)	35 (53)	7 (35)	
Nephrectomy, <i>n</i> (%)	77 (90)	59 (89)	18 (90)	
Number of metastatic sites				
1–2, <i>n</i> (%)	68 (79)	51 (77)	17 (85)	
≥3, <i>n</i> (%)	18 (21)	15 (23)	3 (15)	
Organs with metastasis				
Lung, <i>n</i> (%)	37 (43)	30 (45)	7 (35)	
Lymph nodes, <i>n</i> (%)	29 (34)	28 (42)	1 (5)	.001
Brain, <i>n</i> (%)	24 (28)	15 (23)	9 (45)	
Liver, <i>n</i> (%)	16 (19)	13 (20)	3 (15)	.052
Bone, <i>n</i> (%)	13 (15)	10 (15)	3 (15)	

the Ludwig–Maximilian’s University Clinic in Munich, Germany ($n=42$), the Karolinska University Hospital in Stockholm, Sweden ($n=31$), and Uppsala University Hospital in Uppsala, Sweden ($n=13$), from January 2005 to December 2015. The patients were retrospectively identified using data from medical records.

Data analysis

Collected variables included age, sex, histology, date of primary diagnosis and metastatic diagnosis, date of death or last follow-up, nephrectomy, treatment with TA, number of metastatic sites at mRCC diagnosis and location of the metastases. Radiology (CT of thorax and abdomen) and clinical monitoring were performed at the discretion of the respective site according to clinical routine. With respect to the diagnostic workup, brain imaging was done routinely in the Munich centre, whereas in the two Swedish centres brain imaging was done only if clinical signs suspicious of brain involvement were present.

Histopathology analyses were done as part of clinical routine on nephrectomy specimens or biopsies. Results from biochemical blood analyses collected for each patient at the time of diagnosis of metastatic disease were used in order to calculate Memorial Sloan Kettering Cancer Centre (MSKCC) risk group. Eastern Cooperative Oncology Group performance status (PS) was obtained from the patient records at the date of the first visit to the oncology department upon the mRCC diagnosis. The MSKCC risk factors were defined as haemoglobin level <120 g/L for women and <130 g/L for men, albumin corrected calcium level >2.5 mmol/L, lactate dehydrogenase level >1.5 × upper limit of normal, PS ≥2

(replacing the original variable Karnofsky <80%) and time from the diagnosis of primary RCC to first metastasis less than one year. In order to apply the MSKCC risk score to all patients, including those not treated with TA, we slightly modified one of the criteria from the original publication by Motzer et al, that is, ‘time to treatment’ using here instead ‘time to first metastasis’ [27]. Hence, each patient was attributed a MSKCC risk group; favourable (zero risk factors), intermediate (one or two risk factors) or poor risk (three or more risk factors). Neutrophil count was only available for some patients, and hence, the IMDC prognostic model could not be applied.

For patients treated with TA, time on drug was defined as the time in months from start until stop of each line of TA, or in the case of death before stop of TA as the time in months from start until death from any cause. OS was defined as the time in months from diagnosis of metastatic disease until death from any cause or last follow-up.

Aim

The aim of the study was to evaluate OS and to identify clinically useful prognosticators in mPRCC.

Statistical analysis

Fisher’s exact test was used for evaluating observed differences between groups and Mann–Whitney U-test was used to compare different sample means. Kaplan–Meier survival plots were generated. Cox proportional hazard regression analyses, with univariable analyses (simple cox) and multivariable analysis (complex cox), were performed to assess associations of

Table 2. Systemic therapy with targeted agents.

Patients, <i>n</i>	66
Number of treatment lines	
1, <i>n</i> (%)	32 (48)
2, <i>n</i> (%)	18 (27)
3, <i>n</i> (%)	11 (17)
>3, <i>n</i> (%)	5 (8)
Median total time on drugs, months (range)	10 (1-74)
First line	
Patients, <i>n</i> (%)	66 (100)
Median time on drug, months (range)	7 (1-74)
Sunitinib, <i>n</i>	45
Sorafenib, <i>n</i>	7
Temsirolimus, <i>n</i>	4
Pazopanib, <i>n</i>	3
Everolimus, <i>n</i>	2
Other, <i>n</i>	5
Second line	
Patients, <i>n</i> (%)	34 (52)
Median time on drug, months (range)	7 (1-26)
Everolimus, <i>n</i>	10
Sorafenib, <i>n</i>	8
Sunitinib, <i>n</i>	7
Axitinib, <i>n</i>	6
Bevaciumab, <i>n</i>	2
Pazopanib, <i>n</i>	1
Third line	
Patients, <i>n</i> (%)	17 (26)
Median time on drug, months (range)	5 (1-15)
Everolimus, <i>n</i>	7
Sorafenib, <i>n</i>	4
Sunitinib, <i>n</i>	2
Axitinib, <i>n</i>	2
Pazopanib, <i>n</i>	1
Nivolumab, <i>n</i>	1

selected clinical variables with OS. A *p* value of <.05 was considered statistically significant. All statistical analyses were performed using *STATISTICA* version 13 (StatSoft Inc, Tulsa, USA).

Ethics

The study was approved by ethical review boards for the use of each institutional database, respectively.

Results

Patient and disease characteristics

Eighty-six patients were included in the study. Patient characteristics are summarized in Table 1. Seventy-two of the patients were followed until death and 14 were still alive at the end of the study (July 2016). Median follow-up (mFU) of alive patients was 33 months (interquartile range 16). Type 2 was the most common subtype (69%), followed by papillary not otherwise specified (NOS; 21%). Four patients had type 1 mPRCC. Forty-nine percent of the patients had synchronous metastases. In patients with metachronous metastatic disease, the median time from primary diagnosis to first metastasis was ten months (range 2–144). Seventy-nine percent had one or two metastatic sites. Lung (43%), lymph nodes (34%), and brain (28%) were the most commonly involved organs at mPRCC diagnosis. All MSKCC risk groups were represented, with 18% favorable, 61% intermediate and 21% poor risk features. Seventy-eight percent of the patients had

a PS of 0 or 1. Median age was 65 years with a male:female ratio of close to 3:1.

Targeted agents

Sixty-six patients (77%) were treated with TA of whom 52% received at least two lines of therapy and 25% three or more lines. TA consisted mainly of VEGFR inhibitors and mTOR inhibitors, with sunitinib as the most frequently used drug in first line and everolimus in second line. A detailed description of the TA used is given in Table 2. MSKCC risk group was not associated with the likelihood of receiving TA (Table 1). Compared to patients not treated with TA, those receiving TA were younger and had better PS (Table 1). Reasons for not receiving TA, as stated in the medical records, were poor performance status and/or comorbidities. One patient remained relapse-free after surgical metastasectomy and did not require TA.

Survival and risk factors for early death

The median overall survival (mOS) of all mPRCC patients was 11.2 months (Figure 1(A)). Clinical variables evaluated for an association with the risk of death included age, sex, nephrectomy, synchronous versus metachronous disease, number of metastatic sites, involved organs (bone, liver, lung, lymph nodes and brain), PS, MSKCC risk group, and TA use (Table 3). Age was associated with the risk of death when analysed as a continuous variable (HR 1.03, CI 1.01–1.05, *p* = .004) as well as a categorical variable, with a cut-off at 60 years discriminating the best (HR 2.03, CI 1.22–3.36, *p* = .006; Figure 1(B)). Metastatic spread to three or more sites (HR 1.80, CI 1.01–3.21, *p* = .046; Figure 1(C)) or brain metastases (HR 1.69, CI 1.02–2.81, *p* = .04; Figure 1(D)) were associated with an increased risk of death. PS had prognostic importance with superior OS for patients with a PS 0 vs PS 1 (HR 0.54, CI 0.31–0.96, *p* = .04) and an increased risk of death for patients with a PS ≥2 vs PS 1 (HR 3.44, CI 1.78–6.64, *p* < .001; Figure 1(E)). mOS of patients treated with TA was 15.8 months compared to 3.4 months for patients not treated with TA (HR 0.34, CI 0.20–0.58, *p* < .001; Figure 1(F)).

All factors significant in univariable analysis were included in the multivariable analysis, which thus included age, number of metastatic sites, brain metastases, PS, and TA use. Age ≥60 years (HR 2.21, CI 1.23–3.97, *p* = .008), PS ≥2 vs 1 (HR 3.01, CI 1.31–6.89, *p* = .009) and ≥3 metastatic sites (HR 2.73, CI 1.45–5.16, *p* = .002) remained independently associated with the risk of death (Table 3). mOS of patients in favourable, intermediate, and poor MSKCC risk groups were 26.9 months, 11.1 months, and 6.4 months, respectively. However, these numerical differences did not reach statistical significance (*p* = .12; Table 3). There were no significant differences in survival depending on nephrectomy (*p* = .13) or between patients with synchronous or metachronous disease (*p* = .41; Table 3). Nephrectomy was performed in 33 of the 42 patients with synchronous metastasis (79%) without significant effect on mOS (12.7 months vs 8.3 months; HR 0.59 CI 0.26–1.33, *p* = .20).

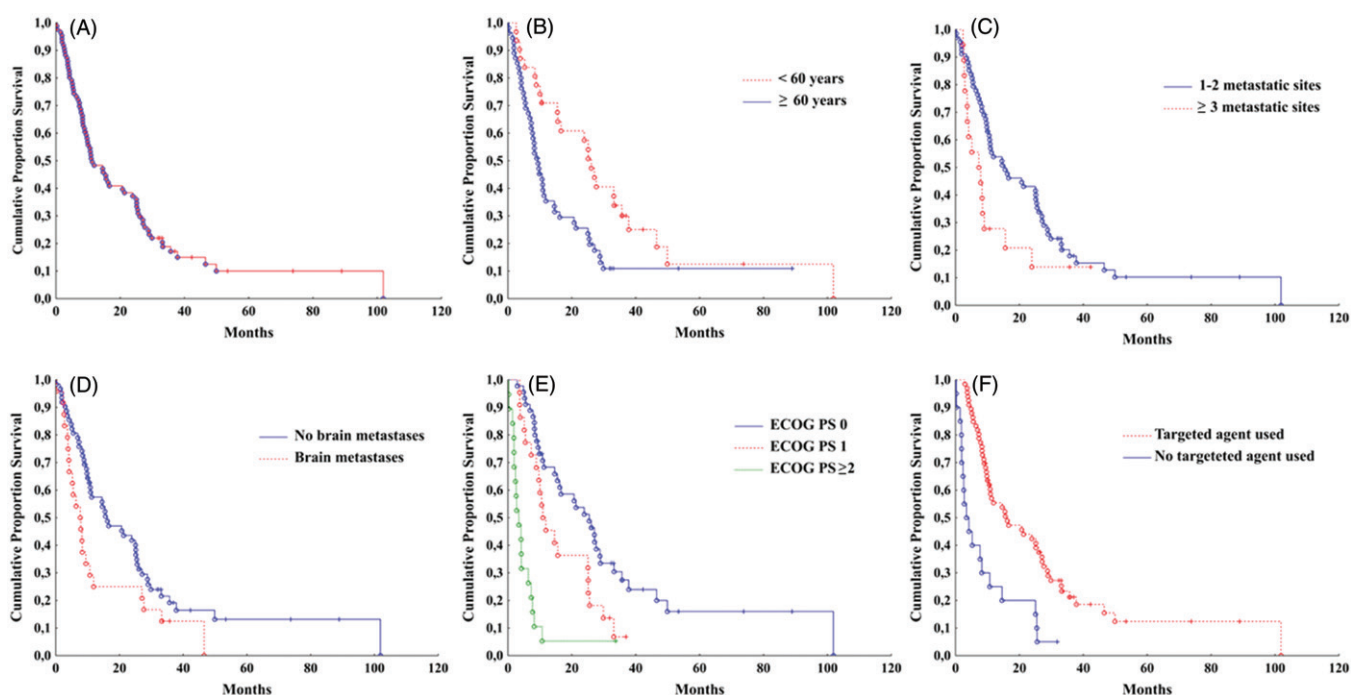


Figure 1. Median overall survival (mOS) and prognostic factors of metastatic papillary renal cell carcinoma patients. (A) mOS of all patients ($n = 86$) 11.2 months. (B) Older patients, above 60 years of age at metastatic diagnosis, do significantly worse than those younger (Hazard ratio (HR) 2.03; 95% Confidence interval (CI) 1.22–3.36, $p = .006$). mOS 25.3 months (<60 years) versus 9.2 months (≥ 60 years). (C) ≥ 3 metastatic sites at metastatic diagnosis are associated with a significantly shorter OS compared to 1–2 metastatic sites (HR 1.80; CI 1.01–3.22, $p = .046$). mOS 15.1 months (1–2 metastatic sites) versus 7.3 months (≥ 3 metastatic sites). (D) Patients with brain metastases at metastatic diagnosis have inferior survival compared to those with no brain metastases (HR 1.69; CI 1.02–2.81, $p = .04$). mOS 15.8 months (no brain metastases) versus 7.7 months (brain metastases present). (E) Patients with an ECOG performance status (PS) of 0 do significantly better than patients with an ECOG PS of 1 (HR 0.54; CI 0.31–0.96, $p = .04$), and patients with an ECOG PS ≥ 2 have a more than a threefold increase in the risk of early death compared to ECOG PS 1 (HR 3.44; CI 1.78–6.64, $p < .001$). mOS 24.7 months (ECOG PS 0) versus 10.9 months (ECOG PS 1) versus 3.1 months (ECOG PS ≥ 2). (F) Systemic therapy with targeted agents (TA) is significantly associated with OS, with patients receiving TA having a decreased risk of early death compared to those who do not receive TA (HR 0.34; CI 0.20–0.58, $p < .001$). mOS 15.8 months (TA used) versus 3.4 months (no TA used).

Table 3. Overall survival, univariate and multivariate cox proportional hazards.

Factor	Category	Median overall survival (months)	Univariable		Multivariable	
			HR (95% CI)	p	HR (95% CI)	p
Age	<60 yrs	25.3	1		1	
	≥ 60 yrs	9.2	2.03 (1.22–3.36)	.006	2.21 (1.23–3.97)	.008
Sex	Female	13.8	1			
	Male	10.8	1.30 (0.75–2.24)	.35		
Nephrectomy	No	8.3	1			
	Yes	12.4	0.56 (0.26–1.19)	.13		
Metastatic disease	Metachronous	11.6	1			
	Synchronous	10.8	1.22 (0.76–1.94)	.41		
Metastatic sites	1–2	15.1	1		1	
	≥ 3	7.3	1.80 (1.01–3.22)	.046	2.73 (1.45–5.16)	.002
Bone metastases	No	12.3	1			
	Yes	7.3	1.38 (0.70–2.71)	.35		
Liver metastases	No	13.6	1			
	Yes	7.3	1.31 (0.71–2.39)	.39		
Lung metastases	No	11.3	1			
	Yes	9.2	1.08 (0.67–1.74)	.75		
Lymph node metastases	No	13.2	1			
	Yes	10.6	1.30 (0.79–2.14)	.30		
Brain metastases	No	15.8	1		1	
	Yes	7.7	1.69 (1.02–2.81)	.04	1.09 (0.56–2.11)	.81
ECOG performance status	0	24.7	0.54 (0.31–0.96)	.04	0.54 (0.29–1.02)	.056
	1	10.9	1		1	
	≥ 2	3.1	3.44 (1.78–6.64)	<.001	3.01 (1.31–6.89)	.009
MSKCC risk group	Favourable	26.9	0.57 (0.28–1.17)	.12		
	Intermediate	11.1	1			
	Poor	6.4	1.59 (0.89–2.83)	.12		
Systemic therapy with targeted agents	No	3.4	1		1	
	Yes	15.8	0.34 (0.20–0.58)	<.001	0.72 (0.37–1.40)	.33

A subgroup analysis of the TA-treated patients (Table S1) confirmed an independent association of age ≥ 60 years (HR 3.10, CI 1.61–5.97, $p < .001$), PS 0 vs 1 (HR 0.27, CI 0.14–0.52, $p < .001$) and ≥ 3 metastatic sites with risk of death (HR 3.44, CI 1.63–7.23, $p = .001$). In addition, lymph node metastasis was independently associated with the risk of death in the TA treated subgroup (HR 2.35, CI 1.26–4.38, $p = .007$). Nephrectomy was performed in most patients treated with TA (89%) and was associated with a decreased risk of death (HR 0.34, CI 0.14–0.82, $p = .02$) in univariable analysis but lost its significance in multivariable analysis (Table S1).

Discussion

Our study demonstrated a mOS of 11 months in mPRCC patients treated in the TA era. This compares unfavourably to the average mRCC patient according to a recent population-based study [28]. Here, we provide evidence that basic clinical factors including age, PS, and metastatic burden allows separation of papillary patients with significantly different outcomes.

During the study period TA was the mainstay of systemic treatment for mPRCC based on phase-II data with sunitinib and everolimus, respectively, producing mOS in the range of 13–21 months in single-arm studies [20,29,30]. Two randomized phase-II trials (ESPN and ASPN) compared sunitinib to everolimus as first-line treatment of non-clear cell mRCC with overall response rates, progression-free survival and OS slightly favouring sunitinib [18,19]. In addition, the RECORD-3 crossover trial favoured sunitinib over everolimus as first-line treatment for non-clear cell mRCC [31]. In our present study, patients treated with TA had a mOS of 16 months. As expected, patients offered TA had better PS. Hence, we found an association of TA use and longer OS in univariable analysis but TA lost its prognostic importance in the multivariable analysis which incorporated PS. Sunitinib was often used in first line typically followed by everolimus in second line, reflecting the current clinical practice and in agreement with the randomized data [31].

Among TA-treated patients, we confirmed the relevance of age, PS and number of metastatic sites for prognostication. Moreover, interestingly, we found lymph node metastasis to be significantly associated with an increased risk of death (Table S1). This could imply a more aggressive biology of tumours able to metastasize within the lymphovascular system or possibly indicate less dependence on VEGFR and/or related tyrosine kinase receptor signalling in lymph node metastases of mPRCC. Notably, lymph node involvement has been associated with inferior outcome in relapsing metastatic clear cell RCC treated with tyrosine kinase inhibitors [32].

Our study included real world patients treated in a clinical routine setting in the years 2005–2015. During most of this time period, MSKCC criteria were the gold standard for prognostic prediction in mRCC [33]. Our findings however indicate that factors other than these criteria may be more important to consider when estimating survival of mPRCC patients. The IMDC criteria were not validated for non-clear

cell mRCC until 2013 [9] and specifically for papillary mRCC in 2017 [33] and hence not available in this retrospective series. However, Kroeger et al, comparing the MSKCC with the IMDC criteria for non-clear cell RCC, reported a very small difference in accuracy between these two models in terms of prognostication [9].

International and multicentre collaboration is necessary to gain new knowledge in rare diseases such as mPRCC. When retrospective, such study design is, however, associated with inherent weaknesses since it restricts any analysis to data available from the clinical routine management of the patients. In our study, we were limited to routine pathology reports, lacking a central pathology review. Hence, misclassification of papillary subtypes in our patient sample is a possibility. Notably, very few patients had type 1 mPRCC precluding any meaningful analyses of survival differences depending on subtype. Moreover, we lacked specific information on any potential sarcomatoid tissue component.

Interestingly, mPRCC patients with metachronous metastases did as poorly as those with synchronous metastases. Moreover, for patients with synchronous metastases nephrectomy did not impact on OS. Hence, our data, though retrospective, tend to support a strategy of avoiding upfront nephrectomy in synchronous mPRCC, instead focusing on improved treatment of the metastases irrespectively of when they occur. This aligns with the recent results for clear cell mRCC reported in the Carmena trial [34].

The metastatic burden should be considered when predicting OS in mPRCC; we found a cutoff of three or more metastatic sites to be useful as prognosticator. A similar association has been demonstrated in clear cell mRCC [35]. In contrast, we found no clear survival impact of specific organ involvement when correcting for factors such as age, PS and number of metastatic sites in multivariable analysis, the exception being lymph node metastasis in patients treated with TA.

Brain metastases (BM) at diagnosis was found in 28% of the patients, which was more common than expected for mRCC [36,37]. Patients with BM typically had PS ≥ 2 (46%) and the prognostic effect of BM was lost in multivariable analysis. Notably, brain imaging routines were different between the Munich cohort (routine brain scans) as opposed to the Swedish cohorts (brain scan only if clinical suspicion). However, this inconsistency could not have led to overestimation but, possibly, to underestimation of the frequency of early BM. Hence, our finding is a conservative figure suggesting that brain imaging should be part of the general diagnostic work-up and follow-up program in mPRCC, allowing for prognostication as well as early consideration of aggressive local therapy of BM.

Increasing age was associated with worse survival with a cut-off at 60 years discriminating the best, independently of PS. Hence, older age did not only reflect frailness. Furthermore, age remained an independent prognostic factor in the patients treated with TA. Perhaps, the tumour biology of mPRCC is different in the elderly [7].

The study has several limitations, the most important being the retrospective design introducing selection bias

particularly with respect to TA treatment. Central pathology was not done, increasing the risk of classification errors. Strengths of the study include the real-world patients setting, the availability of modern treatment options during the study period and the focus on mPRCC specifically.

Conclusion

In conclusion, OS in mPRCC remained short in the era of targeted agents. Age, performance status and number of metastatic sites provided prognostic information. Future clinical trials of novel treatment concept in mPRCC could preferably incorporate the variables identified in the present study for prospective validation as putative prognostic factors.

Disclosure statement

Maria Stenman has received speaker's honoraria from Pfizer.

Michael Staehler is a company consultant for Pfizer, Novartis, GlaxoSmithKline, Roche, Astellas, and Bayer; has received company speaker honoraria from Pfizer, Novartis, GlaxoSmithKline, Roche, Astellas, Bayer, Exelixis and Aveo; has participated in trials for Pfizer, Novartis, GlaxoSmithKline, Roche, Bayer, Aveo, Willex, and Immmatics; has received fellowships and travel grants from Pfizer, Novartis, GlaxoSmithKline, Roche, and Bayer; and has received grants/research support from Pfizer, Novartis, GlaxoSmithKline, Roche, Bayer, Immmatics, Willex and Aveo.

Per Sandström is an employee of Bayer AB, has received research funding from Pfizer and Bayer, speaker's honoraria from Roche, Pfizer, Novartis, Bayer, GSK and BMS, participated in advisory boards for Pfizer, Roche, Bayer, Astellas, GSK and Novartis.

Magnus Lindskog has participated in advisory boards for Pfizer and received speaker's honoraria from Pfizer.

Ulrika Harmenberg has participated in advisory boards for Pfizer, Novartis, Bayer, GlaxoSmithKline and IPSEN and has received a grant from Novartis.

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