ORIGINAL RESEARCH

Clinical outcome of advanced and metastatic renal cell carcinoma treated with targeted therapy: is there a difference between young and old patients?

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Background: To assess whether the clinical outcome of advanced and metastatic renal cell carcinoma (mRCC) treated with targeted therapy differs between young and old patients.

Patients and methods: A total of 327 patients with advanced renal cell carcinoma and mRCC who received targeted therapy in two Chinese clinical centers were analyzed retrospectively. The patients were stratified into three groups: young (aged <45 years), middle-aged (aged 45–64 years), and old (aged ≥65 years). Overall survival (OS) and progression-free survival (PFS) curves were drawn using the Kaplan–Meier method, and Cox's proportional hazard regression model was used to compare OS and PFS within age groups.

Results: There were no significant differences among young, middle-aged, and old groups in terms of OS (P=0.087), whereas PFS in the old group was significantly better than in the young and middle-aged groups (P=0.043). Both OS and PFS in the younger groups (aged <65 years) were significantly worse than in the old group (age ≥65 years; median OS, 28.1 vs 28.7 months [P=0.029]; median PFS, 11.4 vs 14 months [P=0.015]). No difference in OS or PFS was found between the young and middle-aged groups. After adjusting for sex, body mass index, smoking status, hypertension, diabetes mellitus, Eastern Cooperative Oncology Group score, history of cytokines, and Fuhrman grade, old age was an independent favorable prognostic factor for OS and PFS compared with younger age (<65 years) (OS, hazard ratio, 0.552 [95% confidence interval, 0.329–0.828; P=0.006]; PFS, hazard ratio, 0.584 [95% confidence interval, 0.401–0.850; P=0.005]).

Conclusion: Younger patients with advanced renal cell carcinoma and mRCC receiving targeted therapy have a poorer prognosis compared with old patients. These results remain to be examined in prospective cohorts.

Keywords: kidney cancer, metastasis, targeted therapy, prognosis, age

Introduction

Almost 20%–30% of patients present with metastasis at diagnosis of renal cell carcinoma (RCC), which is the third most prevalent urological malignancy.[1] In addition, relapse and metastasis occur in ~20% of RCC patients who have received surgical intervention.[2] Before the era of targeted therapy, cytokines were the most commonly used agents once RCC patients showed distant metastasis; however, the effect was not satisfactory.[3] Because targeted therapy has been approved for the treatment of metastatic RCC (mRCC), many patients have benefited from this dramatic paradigm shift and have shown improved clinical outcomes.

RCC incidence is strongly related to age. An average of 75% of cases are diagnosed in those aged ≥60 years, with a mean age of 63 years.[4] At present, uncertainties still exist regarding the discrepancy of clinical characteristics between young and old RCC patients, as well as the prognostic effect of age on RCC. Several studies have pointed out that older age is correlated with higher TNM (tumor node metastasis) staging and pathological grade of RCC, suggesting an adverse association with prognosis.[5–7] Jun et al have reported that the incidence of high-grade RCC decreases as age increases.[8] Similarly, another study has found that young RCC patients are more likely to present with unfavorable histological features and to develop metastasis.[9] There are also reports that there is no difference in prognosis between young and old RCC patients.[10,11]

Given the diversity of pathological features among the different ages and the various comorbidities that old patients might experience, the difference in clinical outcomes between young and old RCC patients receiving targeted therapy remains a complex picture. To the best of our knowledge, research focusing on response to targeted therapy among RCC patients of different ages is currently lacking. Hutson and colleagues have reported that median progression-free survival (PFS) and overall survival (OS) are comparable in younger and older (≥70 years) mRCC patients receiving sunitinib, suggesting that elderly patients may achieve additional clinical benefit.[12] Similar results were found from the data of another group of patients treated with sorafenib.[13] However, these two studies were conducted in white patients, and no studies have investigated whether there are different responses between young and old patients in the People's Republic of China. Here, we report a retrospective analysis in which the clinical outcomes of advanced RCC and mRCC treated with targeted therapy among different ages in two clinical centers in the People's Republic of China were compared.

Patients and methods
Study subjects
This was a retrospective analysis of 327 consecutive patients with pathologically confirmed advanced RCC and mRCC between 2006 and February 2014 at the Department of Urology at Fudan University Shanghai Cancer Center and the Affiliated Hospital of Qingdao University. All information about age, sex, history of hypertension or diabetes mellitus, body mass index (BMI), smoking status, histology and staging, history of cytokines therapy, Eastern Cooperative Oncology Group performance status, and International Metastatic Renal-Cell

Carcinoma Database Consortium prognostic model was obtained from electronic records and medical charts. Protocols were approved by the Institutional Research Review Boards of the two clinical centers. All patients provided written informed consent before participation in the study.

The patients included those who received sorafenib or sunitinib as first-line targeted agents, which have been approved by the China Food and Drug Administration and are routinely used for mRCC treatment in the People's Republic of China. Efficacy endpoints included PFS and OS. PFS was defined as the time from receiving targeted therapy until disease progression (detected by radiology) or death (if death happened before progression). Adverse effects were recorded regularly.

Exposure definition
BMI is the patient's weight (in kilograms) divided by the height in square meters before treatment with targeted agents, and the threshold of overweight was 25 kg/m^2 or higher; smoking status (yes/no) represents current smokers or those who had ever smoked more than 100 cigarettes/year; hypertension was defined as 140 and 90 mm Hg for systolic and diastolic blood pressure, respectively, on three consecutive occasions; and criteria of diabetes included 7.0 mmol/L or higher fasting serum glucose level or self-report of diabetes based on a physician's diagnosis.

Statistical methods
The patients were divided into three groups: young (aged <45 years), middle-aged (aged 45–64 years), and old (aged ≥65 years). Categorical variables were expressed as frequencies and percentages, and χ^2 tests were used to compare the difference. OS and PFS curves were drawn using the Kaplan–Meier method and were compared by log-rank test. Cox's proportional hazard regression model was used to evaluate the relationships among OS, PFS, and previously identified clinical variables such as age, sex, BMI, history of hypertension or diabetes, smoking status, stage, Fuhrman grade, pathologic type, and International Metastatic Renal-Cell Carcinoma Database Consortium model. Statistical significance was based on two-sided P values lower than 0.05. SPSS version 20.0 software (IBM Corporation, Somers, NY, USA) was used for statistical analyses.

Results
The study included 327 advanced RCC and mRCC patients whose demographic and clinical characteristics, stratified by age group, are shown in Table 1. Among all the patients,

Table 1 Demographic and clinical characteristics stratified by age in advanced and metastatic renal cell carcinoma patients

Variables	Total (n=327), n (%)	Young (<45 years) (n=52), n (%)	Middle-aged (45–64 years) (n=192), n (%)	Old (≥65 years) (n=83), n (%)	*P*-value
Sex					**0.003**
Male	242 (74.0)	30 (57.7)	142 (74.0)	70 (84.3)	
Female	85 (26.0)	22 (42.3)	50 (26.0)	13 (15.7)	
Body mass index, kg/m²					0.783
<25	233 (71.3)	38 (73.1)	134 (69.8)	61 (73.5)	
≥25	94 (28.7)	14 (26.9)	58 (30.2)	22 (26.5)	
Smoking status					0.208
Yes	110 (33.6)	13 (25.0)	64 (33.3)	33 (39.8)	
No	217 (66.4)	39 (75.0)	128 (66.7)	50 (60.2)	
Hypertension					0.284
Yes	120 (36.7)	16 (30.8)	68 (35.4)	36 (43.4)	
No	207 (63.3)	36 (69.2)	124 (64.6)	47 (56.6)	
Diabetes					0.622
Yes	60 (18.3)	12 (23.1)	34 (17.7)	14 (16.9)	
No	267 (81.7)	40 (76.9)	158 (82.3)	69 (83.1)	
History of cytokines therapy					0.850
Yes	89 (27.2)	15 (28.8)	50 (26.0)	24 (28.9)	
No	238 (72.8)	37 (71.2)	142 (74.0)	59 (71.1)	
Eastern Cooperative Oncology Group score					**0.009**
0	274 (83.8)	52 (100.0)	157 (81.8)	65 (78.3)	
1	47 (14.4)	0 (0)	32 (16.7)	15 (18.1)	
2	6 (1.8)	0 (0)	3 (1.5)	3 (3.6)	
International Metastatic Renal-Cell Carcinoma Database Consortium category					0.683
Favorable	87 (26.6)	12 (23.1)	56 (29.2)	19 (22.9)	
Intermediate	222 (67.9)	38 (73.1)	126 (65.6)	58 (69.9)	
Poor	18 (5.5)	2 (3.8)	10 (5.2)	6 (7.2)	
Pathologic type					0.149
Clear cell RCC	293 (89.6)	42 (80.8)	171 (89.1)	80 (96.4)	
Papillary RCC	16 (4.9)	4 (7.7)	11 (5.7)	1 (1.2)	
Chromophobe RCC	3 (0.9)	1 (1.9)	2 (1.0)	0 (0)	
Other	15 (4.6)	5 (9.6)	8 (4.2)	2 (2.4)	
Stage					0.539
III	5 (1.5)	0 (0)	3 (1.6)	2 (2.4)	
IV	322 (98.5)	52 (100)	189 (98.4)	81 (97.6)	
Fuhrman grade					0.471
1	7 (2.1)	1 (1.9)	4 (2.1)	2 (2.4)	
2	61 (18.7)	7 (13.5)	31 (16.1)	23 (27.7)	
3	101 (30.9)	17 (32.7)	59 (30.7)	25 (30.1)	
4	86 (26.3)	14 (26.9)	56 (29.2)	16 (19.3)	
Missing	72 (22.0)	13 (25.0)	42 (21.9)	17 (20.5)	
Metastatic site					
Lung	211 (64.5)	24 (46.2)	131 (68.2)	56 (67.5)	**0.010**
Bone	81 (24.8)	9 (17.3)	51 (26.6)	21 (25.3)	0.387
Liver	26 (8.0)	7 (13.5)	12 (6.3)	7 (8.4)	0.230
Other	68 (20.8)	12 (23.1)	33 (17.2)	23 (27.7)	0.129
First-line targeted agents					0.186
Sorafenib	187 (57.2)	26 (50.0)	107 (55.7)	54 (65.0)	
Sunitinib	140 (42.8)	26 (50.0)	85 (44.3)	29 (35.0)	
Second-line targeted agents	48 (14.7)	14 (26.9)	25 (13.0)	9 (10.8)	
Sorafenib	9 (2.8)	3 (5.8)	4 (2.1)	2 (2.4)	0.345
Sunitinib	11 (3.4)	4 (7.7)	5 (2.6)	2 (2.4)	0.168
Axitinib	9 (2.8)	1 (1.9)	7 (3.6)	1 (1.2)	0.485
Everolimus	19 (5.8)	6 (11.5)	9 (4.7)	4 (4.8)	0.157
Adverse effects					
Fatigue	216 (66.1)	30 (57.7)	133 (69.3)	53 (63.9)	0.261
Hand–foot syndrome	187 (57.2)	33 (63.5)	115 (59.9)	39 (47.0)	0.085

(Continued)

Table 1 (*Continued*)

Variables	Total (n=327), n (%)	Young (<45 years) (n=52), n (%)	Middle-aged (45–64 years) (n=192), n (%)	Old (≥65 years) (n=83), n (%)	*P*-value
Diarrhea	142 (43.4)	19 (36.5)	85 (44.3)	38 (45.8)	0.536
Nausea	125 (38.2)	20 (38.5)	71 (37.0)	34 (41.0)	0.822
Rash	116 (35.5)	19 (36.5)	65 (33.9)	32 (38.6)	0.745
Hypertension	82 (25.1)	11 (21.2)	46 (24.0)	25 (30.1)	0.432
Alopecia	78 (23.9)	15 (28.8)	43 (22.4)	20 (24.1)	0.625
Anemia	46 (14.1)	6 (11.5)	25 (13.0)	15 (18.1)	0.461

Note: *P*-values less than 0.05 are shown in bold.
Abbreviation: RCC, renal cell carcinoma.

59 cases were pathologically confirmed by percutaneous renal biopsy, 137 cases received palliative nephrectomy, and 131 cases manifested metastases after surgical resection of renal tumors, of which two patients received partial nephrectomy and 129 patients received radical nephrectomy. Sorafenib and sunitinib were taken as the first-line targeted agents. Once the first-line therapy failed, either switching among first-line drugs or other second-line targeted agents, including axitinib and everolimus, were used in 48 patients.

The most common adverse effects were fatigue, hand–foot syndrome, diarrhea, nausea, and rash, which indicated no significant difference in incidence among groups (Table 1). There were seven patients (no young patients, three middle-aged patients, and four old patients) permanently discontinuing targeted therapy as a result of intolerable adverse effects during the follow-up of 3–80 months (median, 28.4 months).

First, we compared the difference in OS and PFS among the young, middle-aged, and old groups. As shown in Figure 1A, there were no significant differences among the young, middle-aged, and old groups in terms of OS

(*P*=0.087), whereas PFS in the old group was significantly better than that in the young and middle-aged groups (*P*=0.043) (Figure 1B). We combined the young and young and middle-aged groups (named "younger group") and found that both OS and PFS in the younger group were significantly worse than the corresponding values in the old group (median OS, 28.1 vs 28.7 months [*P* = 0.029]; median PFS, 11.4 vs 14 months [*P* = 0.015]) (Figure 2A and B). Next, we compared OS and PFS in young and middle-aged patients and found no difference between these two groups (Figure 3A and B). In addition, the difference of demographic and clinicopathological characteristics between these two groups is listed in the supplementary Table.

We then assessed the effect of old age on OS and PFS, using Cox's proportional hazard regression model, as summarized in Table 2. After adjusting for sex, BMI, smoking status, hypertension, diabetes, Eastern Cooperative Oncology Group score, history of cytokines, and Fuhrman grade, old age (≥65 years) was an independent favorable prognostic factor for both OS and PFS compared with younger age (<65 years) (OS: hazard ratio, 0.552 [95% confidence
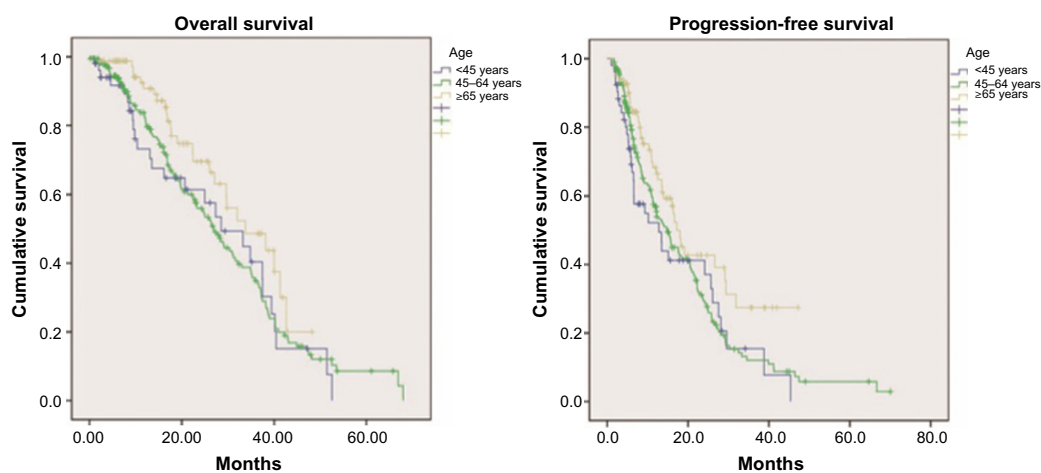

Figure 1 Kaplan–Meier curves of overall survival and progression-free survival among the young, middle-aged and old groups.
Note: There were no significant differences among young, middle-aged, and old groups in terms of overall survival (*P*=0.087), whereas progression-free survival in the old group was significantly better than in the young and middle-aged groups (*P*=0.043).
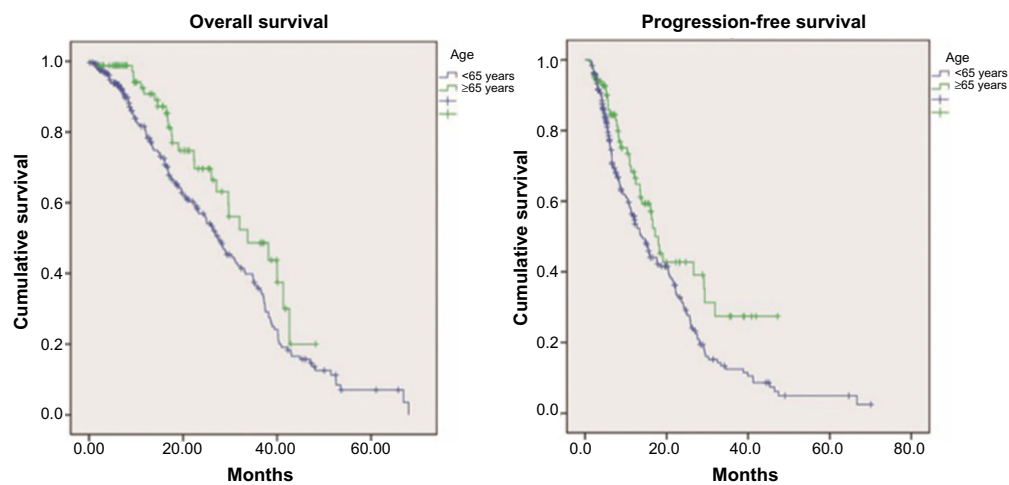
Figure 2 Kaplan–Meier curves of overall survival and progression-free survival in old and younger groups.
Note: Both overall survival (*P*=0.029) and progression-free survival (*P*=0.015) in the younger group were significantly worse than in the old group.

interval, 0.329–0.828; *P*=0.006]; PFS: hazard ratio, 0.584 [95% confidence interval, 0.401–0.850; *P*=0.005]).

Discussion

In this retrospective study, conducted in two clinical centers in Eastern China, we revealed a favorable prognosis in old patients with advanced RCC and mRCC who received targeted therapy. OS and PFS in old patients (aged ≥65 years) were significantly better than that in younger patients (aged <65 years), whereas there was no notable difference in OS and PFS between young (aged <45 years) and middle-aged (aged 45–64 years) patients.

Targeted therapy has changed the intervention strategy for mRCC since 2005, when targeted agents were approved by the US Food and Drug Administration. Given the incidence of RCC peaks among old people,[6,14] it is important

to evaluate these patients thoroughly and to choose proper treatment. However, little information about the efficacy and safety of targeted agents in old mRCC patients was supplied in clinical trials because relatively fewer old patients were enrolled for various reasons, such as greater prevalence of comorbidity and poorer baseline organ function. Therefore, paucity of clinical evidence and concerns about toxicity and intolerance in old patients might restrict the scope of targeted therapy. To date, only two studies were conducted to compare the clinical outcomes of targeted agents between old and young RCC patients. Eisen and colleagues have analyzed the data from a phase 3 clinical trial and found that outcomes of older and younger patients with advanced RCC treated with sorafenib were similar and had predictable and manageable adverse events.[13] OS was not documented by the authors, who only assessed the difference in PFS
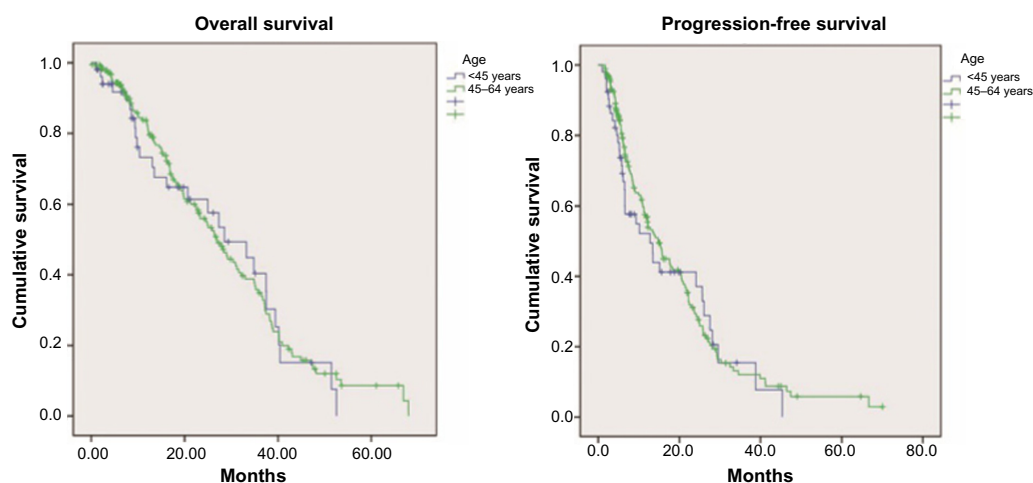

Figure 3 Kaplan–Meier curves of overall survival and progression-free survival in young and middle-aged groups.
Note: There were no significant differences between young and middle-aged groups regarding overall survival and progression-free survival.

Table 2 Hazard ratio for overall survival and progression-free survival in advanced and metastatic renal cell carcinoma patients receiving targeted therapy

Variables	n	Overall survival						Progression-free survival					
		Crude hazard ratio	95% confidence interval	P-value	Adjusted hazard ratio*	95% confidence interval	P-value	Crude hazard ratio	95% confidence interval	P-value	Adjusted hazard ratio*	95% confidence interval	P-value
Age													
Younger (<65 y)	244	—			—			—			—		
Old (≥65 y)	83	**0.627**	**0.411–0.956**	**0.03**	0.517	0.326–0.822	**0.005**	**0.647**	**0.454–0.922**	**0.016**	**0.592**	**0.406–0.863**	**0.006**
Body mass index, kg/m²													
<25	233	—			—			—			—		
≥25	94	1.187	0.835–1.687	0.339	1.676	1.095–2.568	0.018	1.019	0.742–1.399	0.907	1.231	0.857–1.766	0.26
Smoking status													
No	217	—			—			—			—		
Yes	110	1.084	0.783–1.500	0.627	0.889	0.621–1.273	0.521	1.196	0.893–1.602	0.231	0.956	0.698–1.312	0.782
Hypertension													
No	207	—			—			—			—		
Yes	120	1.363	0.996–1.865	0.053	1.703	1.160–2.501	0.007	**1.474**	**1.111–1.956**	**0.007**	**1.607**	**1.149–2.247**	**0.006**
Diabetes													
No	267	—			—			—			—		
Yes	60	1.14	0.766–1.695	0.519	0.991	0.650–1.513	0.968	1.071	0.743–1.545	0.713	0.989	0.676–1.446	0.953
History of cytokines therapy													
No	238	—			—			—			—		
Yes	89	0.806	0.564–1.153	0.238	0.765	0.521–1.124	0.172	0.868	0.629–1.199	0.392	0.846	0.607–1.179	0.324
Eastern Cooperative Oncology Group score													
0	274	—		**<0.001**	—		**<0.001**	—		**<0.001**	—		**<0.001**
1	47	0.682	0.437–1.066	0.093	0.631	0.390–1.020	0.060	0.805	0.543–1.193	0.279	0.789	0.521–1.193	0.261
2	6	**13.664**	**5.796–32.211**	**<0.001**	25.461	9.900–65.480	**<0.001**	**5.191**	**2.271–11.869**	**<0.001**	**5.89**	**2.452–14.151**	**<0.001**
Stage													
III	5	—			—			—			—		
IV	322	1.817	0.579–5.707	0.306	0.636	0.185–2.183	0.472	2.225	0.707–7.005	0.172	1.142	0.342–3.809	0.829
Fuhrman grade													
1 + 2	68	—			—			—			—		
3 + 4	187	**3.849**	**2.271–6.524**	**<0.001**	4.227	2.462–7.259	**<0.001**	**2.410**	**1.622–3.579**	**<0.001**	**2.461**	**1.637–3.697**	**<0.001**
Pathologic type													
Clear cell renal cell carcinoma	293	—			—			—			—		
Non-clear cell renal cell carcinoma	34	1.226	0.729–2.063	0.442	1.329	0.757–2.331	0.322	1.150	0.706–1.874	0.575	1.102	0.660–1.840	0.710
International Metastatic Renal–Cell Carcinoma Database Consortium category													
Favorable	87	—		0.471	—		0.335	—		0.372	—		0.180
Intermediate	222	1.236	0.881–1.732	0.220	1.304	0.917–1.853	0.139	1.237	0.908–1.687	0.177	1.333	0.967–1.838	0.080
Poor	18	1.133	0.511–2.516	0.758	1.234	0.533–2.857	0.623	1.327	0.657–2.683	0.430	1.502	0.725–3.111	0.273

Notes: *Adjusted for sex, body mass index, smoking status, hypertension, diabetes, Eastern Cooperative Oncology Group score, history of cytokines therapy, stage, Fuhrman grade, pathologic type, and International Metastatic Renal-Cell Carcinoma Database Consortium category. P-values less than 0.05 are shown in bold.

between old and young patients. During our preparation for this study, another retrospective data analysis from six trials revealed a slightly better, but not significant, median PFS (11.0 vs 9.9 months) and median OS (25.6 vs 23.6 months) in older, as opposed to younger, mRCC patients receiving first-line sunitinib treatment. Adverse effects occurred more often in older than in younger patients.[12] Likewise, our study found that older patients with advanced RCC and mRCC in the People's Republic of China could benefit from targeted therapy, with even better clinical outcomes. Both OS and PFS were notably prolonged, whereas adverse events did not clearly increase. Intriguingly, the favorable outcomes were observed only in patients aged 65 years or older compared with younger patients. There was no significant difference between young and middle-aged patients with respect to OS, PFS, and adverse effects.

Together with the two aforementioned studies, our results raise the possibility that antiangiogenic agents may be more effective for old patients with advanced RCC and mRCC. Although the studies had conflicting results, the clinicopathological features of RCC were age-dependently different. Observations from several studies have shown that early-stage RCC decreases with increasing age, and that young patients are more likely to present with relatively favorable histology, suggesting that RCC in younger patients does not behave biologically in a more aggressive manner.[8,10,14,15] It is known that RCC is characterized by abundant vasculature, and age-related discrepancy in cancer vasculature has been observed through tumor biopsy. Meehan et al have investigated the influence of age on structural and molecular traits, focusing on RCC vasculature, and have found that microvascular density is dramatically higher in old clear cell RCC patients (aged ≥65 years) than in their younger counterparts.[16] Experimental results from mouse xenograft models have indicated that old mice respond better than young ones to antiangiogenic treatment.[17] Therefore, we speculate that old patients have a favorable prognosis with targeted therapy that might be ascribed to different tumor vasculature, of which higher microvascular density represents an important feature.

Several studies have found better OS and PFS in East Asian mRCC patients, using targeted agents, compared with corresponding international studies.[18–21] Similar results were observed in the present study for both OS and PFS. Although the underlying mechanism regarding the discrepancy of response to targeted agents among different ethnic backgrounds is still a subject of research, race-dependent variation in clinicopathological characteristics and molecular

targets is known. For example, RCC patients from white, African-American, Hispanic, and Asian backgrounds have different symptoms, disease course, and clinical outcomes after standard treatment.[22] Gene polymorphism may also explain the disparity of response and tolerability in RCC patients receiving targeted therapy.[23] However, further studies of the exact mechanism are still warranted.

Several limitations in the present study are worth mentioning. First and foremost, the patients included in this study received different first-line targeted therapy. Some of them took different second-line agents after first-line therapy failed, whereas others did not. In addition, some had a history of cytokine therapy. The disparity in therapeutic strategy might have a confounding effect on the results. Second, several well-known factors affecting the outcome of RCC such as lactic dehydrogenase and time from diagnosis to treatment were not considered, which might also have resulted in an unbalanced baseline. Third, histopathological types differed among the three groups, although clear cell RCC accounted for more than 80% of cases. It is hard to illustrate the extent to which different histopathological types contributed to the different responses to targeted agents. Finally, our data were subject to the inherent bias of the retrospective nature of the study and the relatively small sample size. Nevertheless, this is believed to be the first study conducted in the Chinese population to provide additional data on the relationship between age and targeted therapy.

In conclusion, old age is a favorable prognostic factor for advanced RCC and mRCC patients receiving targeted therapy. Prolonged OS and PFS were observed in old patients (aged ≥65 years) compared with younger ones (aged <65 years), whereas there was no significant difference between young (aged <45 years) and middle-aged (aged 45–64 years) patients. Adverse effects were comparable among patients with different age levels. Further prospective studies based on a large population are warranted.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Demographic and clinical characteristics between younger and old groups in advanced and metastatic renal cell carcinoma patients

Variables	Young (<45 years) (n=244) n (%)	Old (≥65 years) (n=83) n (%)	*P*-value
Gender			**0.013**
Male	172 (70.5)	70 (84.3)	
Female	72 (29.5)	13 (15.7)	
BMI (kg/m²)			0.602
<25	172 (70.5)	61 (73.5)	
≥25	72 (29.5)	22 (26.5)	
Smoking status			0.172
Yes	77 (31.6)	33 (39.8)	
No	167 (68.4)	50 (60.2)	
Hypertension			0.144
Yes	84 (34.4)	36 (43.4)	
No	160 (65.6)	47 (56.6)	
Diabetes			0.687
Yes	46 (18.9)	14 (16.9)	
No	198 (81.1)	69 (83.1)	
History of cytokines therapy			0.687
Yes	65 (26.6)	24 (28.9)	
No	179 (73.4)	59 (71.1)	
Eastern Cooperative Oncology Group score			0.185
0	209 (85.7)	65 (78.3)	
1	32 (13.1)	15 (18.1)	
2	3 (1.2)	3 (3.6)	
International Metastatic Renal-Cell Carcinoma Database Consortium category			0.537
Favorable	68 (27.9)	19 (22.9)	
Intermediate	164 (67.2)	58 (69.9)	
Poor	12 (4.9)	6 (7.2)	
Pathologic type			0.120
Clear cell RCC	213 (87.4)	80 (96.4)	
Papillary RCC	15 (6.1)	1 (1.2)	
Chromophobe RCC	3 (1.2)	0 (0)	
Other	13 (5.3)	2 (2.4)	
Stage			0.449
III	3 (1.2)	2 (2.4)	
IV	241 (98.8)	81 (97.6)	
Fuhrman grade			0.128
1	5 (2.1)	2 (2.4)	
2	38 (15.6)	23 (27.7)	
3	76 (31.1)	25 (30.1)	
4	70 (28.7)	16 (19.3)	
Missing	55 (22.5)	17 (20.5)	
Metastatic site			
Lung	155 (63.5)	56 (67.5)	0.516
Bone	60 (24.6)	21 (25.3)	0.897
Liver	19 (7.8)	7 (8.4)	0.851
Other	45 (18.4)	23 (27.7)	0.072
First line targeted agents			0.093
Sorafenib	133 (54.5)	54 (65.0)	
Sunitinib	111 (45.5)	29 (35.0)	

(*Continued*)

Table S1 (*Continued*)

Variables	Young (<45 years) (n=244) n (%)	Old (≥65 years) (n=83) n (%)	*P*-value
Second line targeted agents	39 (16.0)	9 (10.8)	
Sorafenib	7 (2.9)	2 (2.4)	0.825
Sunitinib	9 (3.7)	2 (2.4)	0.577
Axitinib	8 (3.3)	1 (1.2)	0.318
Everolimus	15 (6.1)	4 (4.8)	0.655
Adverse effects			
Fatigue	163 (66.8)	53 (63.9)	0.624
Hand-foot syndrome	148 (60.6)	39 (47.0)	**0.030**
Diarrhea	104 (42.6)	38 (45.8)	0.616
Nausea	91 (37.3)	34 (41.0)	0.552
Rash	84 (34.4)	32 (38.6)	0.497
Hypertension	57 (23.4)	25 (30.1)	0.220
Alopecia	58 (23.8)	20 (24.1)	0.952
Anemia	31 (12.7)	15 (18.1)	0.224

Note: *P*-values less than 0.05 are shown in bold.
Abbreviations: BMI, body mass index; RCC, renal cell carcinoma.