

Improved prognosis for elderly patients with metastatic renal cell carcinoma in the era of targeted therapy

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Abstract. The present study investigated the outcomes of targeted therapy for elderly patients with metastatic renal cell carcinoma (mRCC). A total of 277 patients with mRCC who were treated with tyrosine kinase inhibitor as a first-line therapy from January 2008 to May 2018 were retrospectively investigated by reviewing clinicopathological data. Patients 75 years or older were classified into the older-aged group (n=55) while all others were classified into the younger-aged group (n=222). The preoperative clinicopathological characteristics and the overall survival (OS) rate for these two groups were subsequently compared. The median age in the older- and younger-aged groups was 78 and 63 years (P<0.0001), respectively. A total of 7, 42 and 6 cases in the older-aged group and 46, 118 and 58 cases in the younger-aged group were classified into favorable, intermediate, and poor risk groups, respectively. The rate of patients with cardiovascular diseases (29.1%) and malignant diseases other than RCC (20.0%) was significantly higher in the older-aged group compared with the younger-aged group (6.8%; P<0.0001 and 7.2%; P=0.0042, respectively). There was a significant improvement in the OS rate for patients beginning targeted therapy after 2011 compared with those starting therapy prior to 2010. The 50% OS rate in patients starting targeted therapy before 2010 and after 2011 was, respectively,

17.1 and 38.6 months for the older-aged group (P=0.0066), while there was no significant difference for the younger-aged group (P=0.1441; 50% OS; 35.9 vs. 30.5 months). The results of the present study indicated that the prognosis for older patients has improved since the introduction of targeted therapy.

Introduction

While screening using abdominal ultrasonographic examination has been widely used for early-stage renal cell carcinoma (RCC), up to approximately 20-30% of RCC patients have metastases at initial presentation (1). The introduction of targeted agents has enabled physicians to improve prognosis over the past decade compared with that for patients treated with cytokine therapy (2). Furthermore, previous research has demonstrated that the prognosis in the later period of the era of targeted therapy was better than that in the initial period (3).

Aging is associated with an increased risk of developing various malignant neoplasms, including RCC (4). RCC is most frequently detected between the ages of 60 and 70 years, and more than 25% of newly diagnosed RCC patients are older than 75 (5). Greater care should be taken when planning the therapeutic strategy for older patients regardless of systemic therapy or surgical treatment because they have potential comorbidities. It is also very important to clarify the background and prognosis for mRCC patients, who are more elderly. Therefore, we investigated the characteristics before treatment and the outcomes of targeted therapy for older patients with mRCC and compared the results with those for a younger patients.

Patients and methods

Two hundred and seventy-seven patients with metastatic renal cell carcinoma (mRCC) who were treated with

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Table I. Patient characteristics.

Variables	<75 years (n=222) n (%)	≥75 years (n=55) n (%)	P-value	Total (n=277) n (%)
Sex			0.3430	
Male	182 (82.0)	42 (76.4)		224 (80.9)
Female	40 (18.0)	13 (23.6)		53 (19.1)
Pathology			0.4251	
Clear	170 (76.6)	46 (83.6)		216 (78.0)
Non-clear	22 (9.9)	5 (9.1)		27 (9.7)
Unknown	30 (13.5)	4 (7.3)		34 (12.3)
Karnofsky PS			0.4460	
≥80%	203 (91.4)	52 (94.5)		255 (92.1)
<80%	19 (8.6)	3 (5.5)		22 (7.9)
IMDC risk			0.0067	
Favorable	46 (20.7)	7 (12.7)		53 (19.1)
Intermediate	118 (53.2)	42 (76.4)		160 (57.8)
Poor	58 (26.1)	6 (10.9)		64 (23.1)
Metastatic site				
Lung	149 (67.1)	37 (67.3)	0.9825	186 (67.2)
Lymph node	71 (32.0)	12 (21.8)	0.1407	83 (30.0)
Liver	26 (11.7)	9 (16.4)	0.3526	35 (12.6)
Bone	59 (26.6)	13 (23.6)	0.6563	72 (26.0)
Adrenal gland	23 (10.4)	6 (10.9)	0.9053	29 (10.5)
Ipsilateral kidney	17 (7.7)	4 (7.3)	0.9231	21 (7.6)
≥2 organs	107 (48.2)	25 (45.5)	0.7153	132 (47.7)
Prior nephrectomy			0.5194	
Radical	102 (45.9)	30 (54.5)		132 (47.7)
Cytoreductive	76 (34.2)	16 (29.1)		92 (33.2)
None	44 (19.8)	9 (16.4)		53 (19.1)
First-line agent			0.0027	
Sunitinib	148 (66.7)	23 (41.8)		171 (61.7)
Pazopanib	12 (5.4)	4 (7.3)		16 (5.8)
Sorafenib	62 (27.9)	28 (50.9)		90 (32.5)
Prior cytokine therapy			0.1901	
(-)	193 (86.9)	44 (80.0)		237 (85.6)
(+)	29 (13.1)	11 (20.0)		40 (14.4)
Subsequent nivolumab therapy			0.9331	
(-)	201 (90.5)	50 (90.9)		251 (90.6)
(+)	21 (9.5)	5 (9.1)		26 (9.4)

tyrosine kinase inhibitor (TKI) as the first-line therapy at our institute and other hospitals in Hiroshima Prefecture in Japan from January 2008 to May 2018 were retrospectively investigated by reviewing clinicopathological data. Ethical approval was given by the Ethical Committee of Hiroshima University (Hiroshima, Japan) (Allowance notification number: E-45), and after that, it was given by the committee at each collaborative institute. In accordance with the previous study (6) patients aged 75 years or older were classified into the older-aged group, and the others were classified into the younger-aged group. Clinical and pathological data including age, sex, histological finding, metastasis status, comorbidities,

selection of and severe adverse events of first-line agent, prior nephrectomy, Karnofsky performance status, and international mRCC database consortium (IMDC) risk were collected for all patients, and the distribution of these parameters for each group was compared. The overall survival (OS) rate of each group was analyzed by further classification in accordance with their first-line agent and the period in which targeted therapy was started.

Statistical analysis. Differences in the distribution of variables among groups were analyzed using a Chi-square test for categorical variables and a Mann-Whitney U test for

Table II. Comparison of comorbidities.

Variables	<75 years (n=222) n (%)	≥75 years (n=55) n (%)	P-value	Total (n=277) n (%)
Hypertension	46 (20.7)	19 (34.5)	0.0303	65 (23.5)
Ischemic heart disease/heart failure	6 (2.7)	6 (10.9)	0.0074	12 (4.3)
Arrhythmia	6 (2.7)	7 (12.7)	0.0016	13 (4.7)
Vascular disease	3 (1.4)	3 (5.5)	0.0613	6 (2.2)
Cerebrovascular disease	5 (2.5)	3 (5.5)	0.2043	8 (2.9)
Respiratory disease	8 (3.6)	2 (3.6)	0.9907	10 (3.6)
Renal dysfunction	8 (3.6)	5 (9.1)	0.0850	13 (4.7)
Other malignant neoplasm	16 (7.2)	11 (20.0)	0.0042	27 (9.7)

Table III. Discontinuation of first-line agents caused by adverse events.

Variables	<75 years (n=222) n (%)	≥75 years (n=55) n (%)	P-value	Total (n=277) n (%)
Cardiovascular event	5 (2.3)	3 (5.5)	0.2043	8 (2.9)
Respiratory event	1 (0.5)	0 (0)	0.6180	1 (0.4)
Gastrointestinal event	10 (4.5)	3 (5.5)	0.7655	13 (4.7)
Bone marrow suppression	27 (12.2)	6 (10.9)	0.7973	33 (11.9)
Dermatological toxicity	17 (7.7)	4 (7.3)	0.9231	20 (7.2)
Endocrinological event	1 (0.5)	1 (1.8)	0.2835	2 (0.7)
Liver/renal dysfunction	9 (4.1)	2 (3.6)	0.8871	9 (3.3)
Neurological event	2 (0.9)	2 (3.6)	0.1279	4 (1.4)
General fatigue	0 (0)	2 (3.6)	0.0044	2 (0.7)
Patient's desire	9 (4.1)	5 (9.1)	0.1269	5 (1.8)
Total	65 (29.3)	24 (43.6)	0.0412	89 (32.1)

continuous variables. Tumor responses were determined using an investigator assessment based on the response evaluation criteria in solid tumors (RECIST) version 1.1. The OS rate was determined using the Kaplan-Meier method, and differences between groups were analyzed using log-rank testing. All statistical analyses were conducted using Statview 5.0 software (Abacus Concepts, Inc.). $P < 0.05$ was considered statistically significant.

Results

This study cohort consisted of 277 cases of targeted therapy for mRCC. A total of 55 cases (19.9%) were classified into the older-aged group, and the other 222 cases (80.1%) were classified into the younger-aged group. The characteristics of the cases are listed in Table I. The rates of cases categorized as poor risk on the basis of IMDC risk criteria and of those treated with sorafenib were significantly higher in the older-aged group than in the younger-aged group while those treated with sunitinib were significantly lower. Median age in the older- and younger-aged groups was 78 and 63 years. The rate of patients with cardiovascular diseases and malignant diseases including hypertension, ischemic heart disease, heart failure, and arrhythmia besides RCC in the older-aged

group was significantly higher than that in the younger-aged group (Table II). The 50% OS rate for the entire cohort was 33.8 months, and there was no significant difference in the rate regardless of the choice of first-line agent or the existence of prior cytokine therapy (Fig. 1). The rate of cases in which first-line therapy was stopped because of adverse events was significantly higher in the higher-aged group (Table III). There was no significant difference in the OS rate between the higher- and younger-aged groups regardless of the choice of first-line agent (Fig. 2). Table IV compares the characteristics of the patients on the basis of the period in which they started first-line TKI: Either 2008-2010 or 2011-2018. In the latter phase, the rates of patients treated with first-line sunitinib or pazopanib and/or subsequent nivolumab were significantly higher than those in the earlier phase while the rates of patients treated with sorafenib and/or prior cytokine therapy were significantly lower. For all patients, for those treated with sunitinib as a first-line therapy and for those without prior cytokine therapy, there was a significant improvement in the OS rate for patients starting therapy after 2011 compared with the rate for those starting it before 2010 (Fig. 3A-C). The 50% OS rate in patients starting targeted therapy before 2010 and after 2011 was respectively 17.1 and 38.6 months for the older-aged group ($P = 0.0066$), while there was no significant

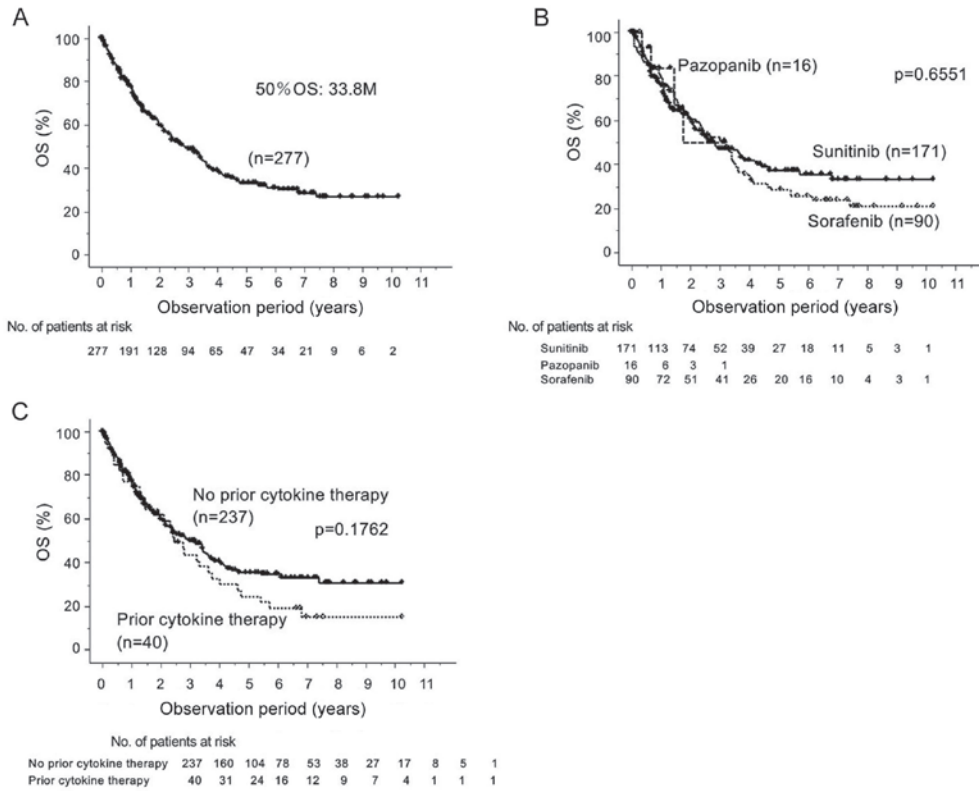


Figure 1. OS rate for (A) all cases, (B) groups divided in accordance with choice of first-line agent, and (C) groups divided in accordance with existence of prior cytokine therapy. OS, overall survival.

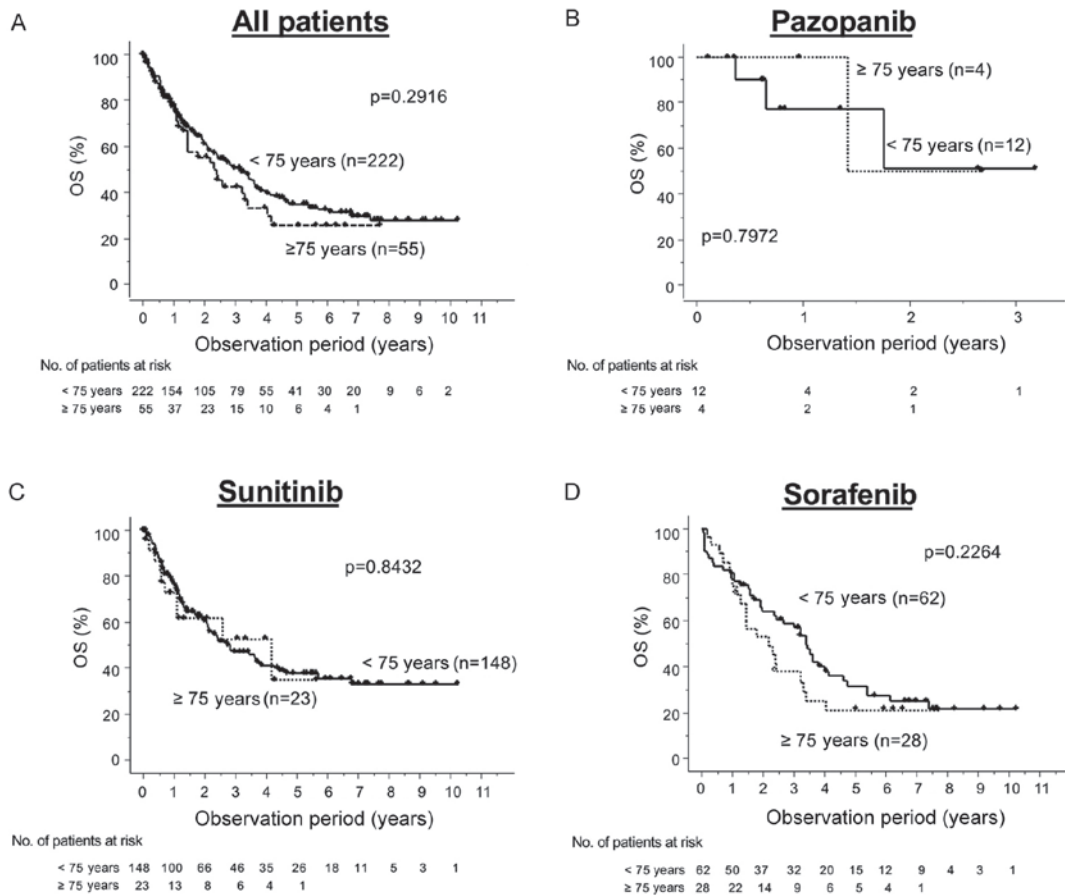


Figure 2. OS rate classified on the basis of patients' age (younger or older) for (A) all cases and for those treated with (B) pazopanib, (C) sunitinib, or (D) sorafenib as first-line agent. OS, overall survival.

Table IV. Characteristics of patients comparing at timing starting first-line TKI.

Variables	2007-2010 (n=97) n (%)	2011-2018 (n=180) n (%)	P-value	Total (n=277) n (%)
Age (years)			0.4755	
≥75	17 (17.5)	38 (21.1)		55 (19.9)
<75	80 (82.5)	142 (78.9)		222 (80.1)
Sex			0.0750	
Male	84 (86.6)	140 (77.8)		224 (80.9)
Female	13 (13.4)	40 (22.2)		53 (19.1)
Pathology			0.0190	
Clear	71 (73.2)	145 (80.6)		216 (78.0)
Non-clear	7 (7.2)	20 (11.1)		27 (9.7)
Unknown	19 (19.6)	15 (8.3)		34 (12.3)
Karnofsky PS			0.5460	
≥80%	88 (90.7)	167 (92.8)		255 (92.1)
<80%	9 (9.3)	13 (7.2)		22 (7.9)
IMDC risk			0.8991	
Favorable	20 (20.6)	33 (18.3)		53 (19.1)
Intermediate	55 (56.7)	105 (58.3)		160 (57.8)
Poor	22 (22.7)	42 (23.3)		64 (23.1)
Metastatic site				
Lung	65 (67.0)	121 (67.2)	0.9714	186 (67.2)
Lymph node	28 (28.9)	55 (30.6)	0.7697	83 (30.0)
Liver	15 (15.5)	20 (11.1)	0.2983	35 (12.6)
Bone	29 (29.9)	43 (23.9)	0.2768	72 (26.0)
Adrenal gland	7 (7.2)	22 (12.2)	0.1943	29 (10.5)
Ipsilateral kidney	6 (6.2)	15 (8.3)	0.5194	21 (7.6)
≥2 organs	49 (50.5)	83 (46.1)	0.4839	132 (47.7)
Prior nephrectomy			0.4416	
Radical	51 (52.6)	81 (45.0)		132 (47.7)
Cytoreductive	28 (28.9)	64 (35.6)		92 (33.2)
None	18 (18.6)	35 (19.4)		53 (19.1)
Ist-line agent			<0.0001	
Sunitinib	44 (45.4)	127 (70.6)		171 (61.7)
Pazopanib	0 (0)	16 (8.9)		16 (5.8)
Sorafenib	53 (54.6)	37 (20.6)		90 (32.5)
Prior cytokine therapy			<0.0001	
(-)	69 (71.1)	168 (93.3)		237 (85.6)
(+)	28 (28.9)	12 (6.7)		40 (14.4)
Subsequent nivolumab therapy			<0.0001	
(-)	97 (100)	154 (85.6)		251 (90.6)
(+)	0 (0)	26 (14.4)		26 (9.4)

TKI, tyrosine kinase inhibitor; IMDC, international mRCC database consortium.

difference in the rate for the younger-aged one (P=0.1441, 50% OS; 35.9 vs. 30.5 months) (Fig. 3E and F).

Discussion

In the present study, we assessed the improvement in the prognosis for patients with mRCC in the earlier and later phases

of the era of targeted therapy for all patients and for patients without prior cytokine therapy. The results showed that the prognosis for older patients improved after the introduction of targeted therapy. To the best of our knowledge, this study is the first to demonstrate an improvement in the prognosis for older patients during the later period of targeted therapy compared with that in the initial one.

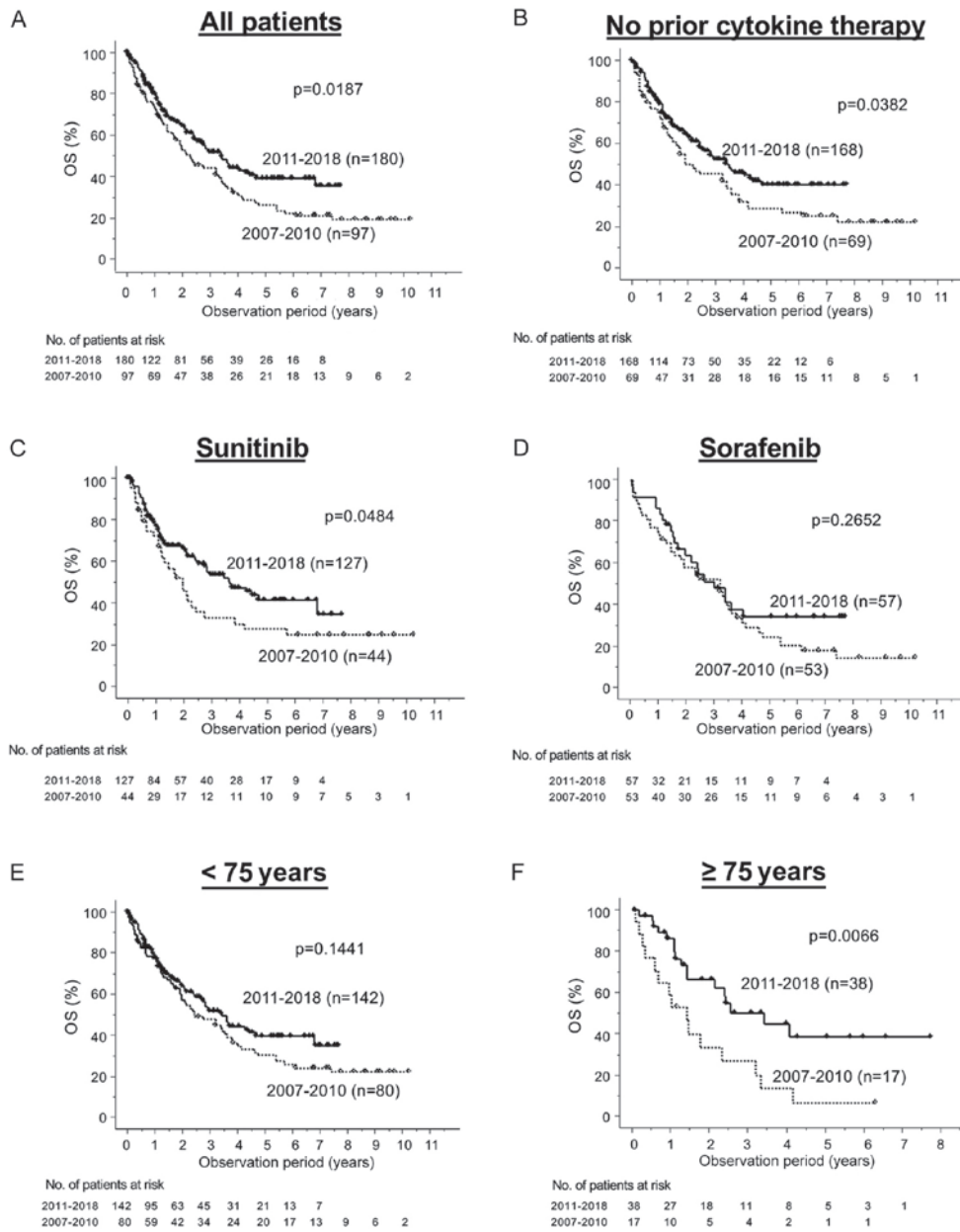


Figure 3. OS rate classified on the basis of when targeted therapy was started (initial period or later period) for (A) all cases, (B) cases without prior cytokine therapy, and cases treated with (C) sunitinib or (D) sorafenib; (E) younger-aged group and (F) Older-aged group. OS, overall survival.

Recently, several randomized control trials have demonstrated the efficacy of immune checkpoint inhibitors (ICIs) and combination regimens including ICIs for mRCC patients (7-10), and as such, many patients with mRCC are being treated with ICI. However, in the CheckMate 025 trials, nivolumab, one of the most common ICIs for mRCC, was reported to be less effective in older patients than in younger ones (7). Moreover, when patients with mRCC receive ICI therapy, immune-related adverse events (irAEs) are inevitable. Physicians need to assess whether patients can overcome such irAEs. These considerations means that TKI is likely to remain one of the standard options for older patients with mRCC.

We can see an improvement in the OS rate in the entire cohort. We can also see some improvement even in the younger-aged group, but it is not statistically significant. Thus, we hypothesize that this improvement represents outcomes

particular to the older-aged group. It is relatively easy to manage younger patients who receive targeted therapy because many of them are generally healthy despite having metastatic RCC. In contrast, many older patients have additional comorbidities (e.g., cardiovascular or respiratory disease), which can prevent them from continuing to receive targeted therapy. Many physicians have now mastered the management of patients who receive targeted therapy in terms of agent choice, agent dose, and adverse events. Therefore, we can see significant improvement in the OS rate, especially for older patients who have more comorbidities.

There are two possible explanations as to why the prognosis for older patients has improved more than that for younger ones. The first is the changes in and increased number of therapeutic options for both first- and second-line therapies. The non-inferiority of pazopanib compared with

sunitinib as a first-line option and the improvement in progression-free survival due to axitinib therapy compared with sorafenib therapy along with the superior OS rate due to nivolumab therapy as second-line options for mRCC have been demonstrated by randomized controlled trials (7,8,11). Moreover, these therapies have been recommended as viable first-line and second-line options in several published guidelines (12,13). On the basis of this evidence, they are now covered by the national health insurance system in Japan. In particular, since pazopanib is reported to be relatively tolerable for patients (14), it seems poised to become a viable option for older patients with severe comorbidities. This increase in the number of treatment options enables physicians to choose the best one for each patient in accordance with their characteristics. However, in this study, pazopanib was administered to only four patients in the higher-aged group, so its effect may be limited to the cohort of this study. As more than half of the patients in the initial period received sorafenib as first-line therapy, the change in the rate of sorafenib as a first-line option might provide some insight into the improvement in the OS rate.

The other possible explanation for the improved prognosis for older patients is optimal management of a therapeutic schedule personalized for each patient. Several previous studies have demonstrated the efficacy and safety of various agents [e.g., sunitinib (6,15-18) and sorafenib (19)] for older patients, and another study reported that an alternative schedule of sunitinib treatment provided a greater improvement in the OS rate compared with the standard schedule (20). Since sunitinib was prescribed on the basis of a personalized schedule in the later period, the data from our present study for patients treated with sunitinib is consistent with those reports (Fig. 3C).

The limitation of the present work is that it is a small retrospective study based on real-world data. Physicians were assumed to have taken into account the comorbidity of patients and the tolerability of each agent when the therapeutic option was chosen. Therefore, some patient-selection bias due to the exclusion of patients with very severe comorbidities from targeted therapy is entirely possible. The older-aged group in this study consisted of 19.9% of the patients, which is a higher rate than in the previous study (21). There might be some differences between countries in terms of the age distribution of patients with mRCC who undergo systemic therapy. In addition, we have no data of clinical classification based on the data of some special molecules identified by gene analysis. A prospective observation study using a greater amount of data is required to further clarify the characteristics and the prognosis for older patients with mRCC.

We have demonstrated that the prognosis for older patients has improved compared with that when targeted therapy was first introduced. Our data clearly indicate the benefit to older patients of the recent rapid introduction of new agents as therapeutic options for mRCC. It is thus expected that the continuing increase of therapeutic options (including ICIs as well as targeted agents) will lead to further improvement in the prognosis for patients with mRCC in the coming years. At the same time, we expect that a more personalized therapeutic strategy will be established for older patients that is based on key molecules identified through gene sequencing in addition

to conventional predictive factors for prognosis and agent efficacy (22,23) as older patients tend to have more comorbidities than younger ones.

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Availability of data and materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' contributions

JT, SI, TH and AM conceived and designed this study. DM, KM, YH, MKat, MKaj, MS, SM, HM and SF acquired the data. JT, SI and TH analyzed the data. JT drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethical Committee of Hiroshima University (Allowance notification no. E-45) (Hiroshima, Japan). The requirement of informed consent was waived by the Institutional Review Board.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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