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Prediction of early progression of metastatic renal cell carcinoma treated with first-line tyrosine kinase inhibitor

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Abstract

Background: There are various alternative first-line therapeutic options besides tyrosine kinase inhibitors (TKIs) for metastatic renal cell carcinoma (mRCC). To inform therapeutic decision-making for such patients, this study aimed to identify predictive factors for resistance to TKI.

Materials and methods: A total of 239 cases of mRCC patients who received first-line TKI therapy were retrospectively studied. Patients with a radiologic diagnosis of progressive disease within 3 months after initiating therapy were classified as primary refractory cases; the others were classified as non-primary refractory cases. The association between primary refractory cases and age, gender, pathology findings, serum c-reactive protein (CRP) level, metastatic organ status, and 6 parameters defined by the International Metastatic Renal Cell Carcinoma Database Consortium were analyzed.

Results: Of 239 cases, 32 (13.3%) received a radiologic diagnosis of progressive disease within 3 months after initiating therapy. The rates of sarcomatoid differentiation, hypercalcemia, a serum CRP level of 0.3 mg/dL or higher, presence of liver metastasis, anemia, and time from diagnosis to treatment interval of less than a year were significantly higher in the primary refractory group. Multivariate analysis showed that sarcomatoid differentiation, hypercalcemia, a serum CRP level of 0.3 mg/dL or higher, and liver metastasis were independently associated with primary refractory disease. A risk-stratified model based upon the number of patients with these factors indicated rates of primary refractory disease of 4.0%, 10.1%, and 45.0% for patients with 0, 1, and 2 or more factors, respectively.

Conclusions: Sarcomatoid differentiation, hypercalcemia, an elevated serum CRP level, and presence of liver metastasis were associated with primary refractory disease in mRCC patients receiving first-line TKI therapy. These results provide clinicians with useful information when selecting a first-line therapeutic option for mRCC patients.

Keywords: Metastatic renal cell carcinoma; Overall survival; Predictive factor; Tyrosine kinase inhibitor

1. Introduction

Upwards of 20% to 30% of renal cell carcinoma patients have metastases at initial presentation,[1] thus warranting systemic therapy. The introduction of various targeted therapeutic agents over the past decade has led to improved efficacy and a better prognosis as compared with cytokine therapy.[2,3] In addition to the efficacy of single targeted agents, the efficacy of combination regimens consisting of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) for metastatic renal cell carcinoma (mRCC) patients has been demonstrated in randomized controlled trials.[4–7] These regimens have thus become recommended as first-line therapies for mRCC. While the number of therapeutic options is increasing, a clear strategy for determining the best choice for each patient is still lacking.

TKIs (including sunitinib and pazopanib) have become standard first-line therapeutic agents for mRCC. However, some patients have disease refractory to TKI first-line therapy. Several papers have reported mechanisms of resistance to anti-angiogenic agents through an angiogenic escape mechanism such as activation of an alternative pathway and recruitment of supporting cells (eg, pericytes and pro-angiogenic or inflammatory cells) derived from bone marrow.[8] Because the oncologic outcomes of first-line agents are associated with prognosis in patients with mRCC,[9] it is very important to identify patients

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with disease refractory to TKIs, so that a combination regimen rather than a single TKI regimen can be prescribed.

This study investigated the characteristics of mRCC patients with disease that was refractory to first-line TKI therapy and stratified them based upon their risk of being primary refractory to TKIs.

2. Materials and methods

2.1. Patients

The medical records of 239 patients with mRCC who were treated with a TKI as first-line therapy at our institution or other hospitals in Hiroshima Prefecture in Japan from January 2008 to October 2019 were retrospectively studied by reviewing relevant clinical and pathology data. Ethical approval was granted by the Ethics Committee of Hiroshima University (approval notification number: E-45). Patients with a radiologic diagnosis of progressive disease in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1 criteria within 3 months after initiating therapy were classified as primary refractory cases; others were classified as non-primary refractory cases. Clinical and pathology data including age, gender, pathology findings, metastatic status, serum c-reactive protein (CRP) level, choice of first-line agent, prior nephrectomy, and 6 parameters described by the International mRCC Database Consortium were evaluated for all patients, and the distribution of these parameters in each group was compared. Progression-free survival (PFS) and overall survival (OS) rates for each group were analyzed by classification according to the primary effect of first-line agents and stratification based upon the risk of being a primary refractory case.

2.2. Statistical analysis

Differences in the distribution of categorical variables between the 2 groups were analyzed using a chi-squared test. Tumor responses were assessed by an investigator using Response Evaluation Criteria in Solid Tumors criteria. The PFS and OS rates were determined using the Kaplan-Meier method, and differences between the 2 groups were analyzed using log-rank testing. Multivariate analysis of predictive factors for early progression of disease was performed using logistic regression for parameters identified as significant by univariate analysis. All statistical analyses were conducted using StatView 5.0 software (Abacus Concepts, Inc., Berkeley, CA), and a p-value less than 0.05 was considered to be statistically significant.

3. Results

The study cohort consisted of 239 patients (median age 67 years) who received TKI as first-line therapy for mRCC. Thirty-two patients (13.3%) were classified as primary refractory cases, and the remaining 207 patients (86.7%) were classified as non-primary refractory cases; 128 patients (53.6%) died during the observation period. The 50% OS rate was 43.2 months among all patients, 13.8 months in the primary refractory group, and 48.1 months in the non-primary refractory group ($p < 0.0001$). The rate of conversion to second-line therapy after disease progression with first-line TKIs was 65.6% in the primary refractory group and 79.7% in the non-primary refractory group ($p = 0.0760$). The rates of sarcomatoid differentiation, hypercalcemia, serum CRP level > 0.3 mg/dL, liver metastasis, anemia, and time from diagnosis to treatment interval of <1 year were significantly higher in the primary refractory group (Table 1). Multivariate analysis showed that sarcomatoid differentiation, hypercalcemia, serum CRP level of 0.3 mg/dL or higher, and liver metastasis were independently associated with disease that was primary refractory to first-line TKI therapy (Table 2).

Next, we constructed a risk-stratified model of primary refractory mRCC based on the number of patients with these 4 factors. The patients were classified into 3 groups according to the number of predictive factors present: 0, 1, and ≥2. The 50% PFS rate was 13, 15, and 3 months, and the 50% OS rate was 64.7, 35.3, and 11 months among the groups with 0, 1, and ≥2 predictive factors, respectively (Fig. 1). The rate of disease that was primary refractory to first-line TKI therapy was 4.0%, 10.1%, and 45.0% among the groups with 0, 1, and ≥2 predictive factors, respectively.

4. Discussion

In this study, we identified clinical and pathological parameters associated with a risk of disease refractory to first-line TKI therapy among a group of patients with mRCC. We also stratified patients who received first-line TKI therapy on the basis of 4 parameters (sarcomatoid differentiation, hypercalcemia, elevated serum CRP level, and liver metastasis) that were associated with disease that was primary refractory to first-line TKI therapy. To our knowledge, this study is the first to demonstrate risk stratification of mRCC patients for disease that is primary refractory to first-line TKI therapy.

Combination regimens including an ICI have shown better oncological outcomes compared with TKI therapies alone.[6,7] However, some patients treated with an ICI may suffer severe immune-related adverse events, requiring physicians to provide appropriate care to overcome such adverse events. Therefore, especially for patients with a relatively favorable risk profile, TKIs should still be considered as an effective first-line therapy equivalent or superior to combination regimens including ICIs.[7,10] There are several TKI therapeutic agents indicated for the treatment of mRCC, each with differing characteristics, including target molecules, tumor-suppressive effects, and potential adverse events.[11,12] Since many physicians have experience prescribing TKI therapy for mRCC, an appropriate treatment regimen tailored to individual patient needs should reduce the risk of adverse events and improve the chance of survival.[13] Due to these considerations, single TKI therapy should be considered as a first-line option for mRCC patients, with the caveat that patients who may have disease that is primary refractory to first-line TKI therapy should be treated with combination regimens.

An association between the rate of early tumor shrinkage and the OS rate for patients treated with a TKI was previously demonstrated.[14] Consistent with this finding, patients in the primary refractory group in our study had poorer prognosis than the non-primary refractory group. In addition, patients in the primary refractory group had higher rates of anemia, hypercalcemia, time from diagnosis to treatment interval of less than a year, elevated serum CRP level, liver metastasis, and sarcomatoid differentiation compared to patients in the non-primary refractory group. These parameters have been reported as prognostic factors for mRCC. The first 3 factors are parameters described in the International mRCC Database Consortium risk criteria established based upon data for patients treated with targeted therapy.[15] The pretreated serum CRP level and its fluctuations during treatment were reported to reflect therapeutic efficacy and the prognosis of mRCC patients in the era of targeted

Table 1

Patient characteristics.

	Primary refractory (n = 32) (%)	Non-primary refractory (n = 207) (%)	*p*	Total (n = 239) (%)
Age, yr				
≥68	17 (53.1)	101 (48.8)	0.6482	118 (49.4)
<68	15 (46.9)	106 (51.2)		121 (50.6)
Gender				
Male	25 (78.1)	163 (78.7)	0.9366	188 (78.7)
Female	7 (21.9)	44 (21.3)		51 (21.3)
Pathology				
Clear cell	27 (84.4)	189 (91.3)	0.2160	216 (90.4)
Nonclear cell	5 (15.6)	18 (8.7)		23 (9.6)
Sarcomatoid differentiation				
−	20 (62.5)	190 (91.8)	<0.0001	210 (87.9)
+	12 (37.5)	17 (8.2)		29 (12.1)
Anemia				
−	9 (28.1)	115 (55.6)	0.0038	124 (51.9)
+	23 (71.9)	92 (44.4)		115 (48.1)
Hypercalcemia				
−	24 (75.0)	201 (97.1)	<0.0001	225 (94.1)
+	8 (25.0)	6 (2.9)		14 (5.9)
Neutrophilia				
−	24 (75.0)	180 (87.0)	0.0750	204 (85.4)
+	8 (25.0)	27 (13.0)		35 (14.6)
Thrombocytosis				
−	25 (78.1)	182 (87.9)	0.1299	207 (86.6)
+	7 (21.9)	25 (12.1)		32 (13.4)
KPS				
≥80%	29 (90.6)	193 (93.2)	0.5927	222 (92.9)
<80%	3 (9.4)	14 (6.8)		17 (7.1)
Time from diagnosis to treatment				
≥1 yr	3 (9.4)	91 (44.0)	0.0002	94 (39.3)
<1 yr	29 (90.6)	116 (56.0)		145 (60.7)
CRP				
≤0.3 mg/dL	5 (15.6)	112 (54.1)	<0.0001	117 (49.0)
>0.3 mg/dL	27 (84.4)	95 (45.9)		122 (51.0)
IMDC risk				
Favorable	2 (6.3)	48 (23.2)		50 (20.9)
Intermediate	17 (53.1)	126 (60.9)		143 (59.8)
Poor	13 (40.6)	33 (15.9)		46 (19.2)
Metastatic organ				
Lung	21 (65.6)	140 (67.6)	0.8216	161 (67.4)
Lymph nodes	14 (43.8)	39 (18.8)	0.0016	53 (22.2)
Liver	8 (25.0)	17 (8.3)	0.0039	25 (10.5)
Bone	6 (18.8)	58 (28.0)	0.2714	64 (26.8)
Adrenal gland	2 (6.3)	15 (7.3)	0.5392	17 (7.1)
Ipsilateral kidney	4 (12.5)	15 (7.3)	0.3016	19 (7.9)
Brain	2 (6.3)	8 (3.9)	0.5306	10 (4.2)
Pancreas	3 (9.4)	8 (3.9)	0.1662	11 (4.6)
≥2 organs	18 (56.3)	86 (41.5)	0.1184	104 (43.5)
Nephrectomy				
Radical	11 (34.4)	118 (57.0)	0.0168	129 (54.0)
Cytoreductive	15 (46.9)	75 (36.2)		90 (37.7)
None	6 (18.8)	14 (6.8)	0.0227	20 (8.4)
Prior cytokine therapy				
−	30 (93.8)	173 (83.6)	0.1342	203 (84.9)
+	2 (6.3)	34 (16.4)		36 (15.1)
First-line agent				
Sunitinib	25 (78.1)	121 (58.5)	0.0337	146 (61.1)
Pazopanib	1 (3.1)	18 (8.7)		19 (7.9)
Sorafenib	6 (18.8)	68 (32.9)	0.1084	74 (31.0)
Second-line agent				
None	11 (34.4)	40 (19.3)		51 (21.3)
TKI	9 (28.1)	103 (49.8)		112 (46.9)
mTORi	5 (15.6)	44 (21.3)		49 (20.5)
Nivolumab	7 (21.9)	10 (4.8)		17 (7.1)
Continuation of first-line agent	0 (0)	10 (4.8)		10 (4.2)

CRP = c-reactive protein; IMDC = International mRCC Database Consortium; KPS = Karnofsky performance score; mRCC = metastatic renal cell carcinoma; mTORi = mammalian target of rapamycin inhibitor; TKI = tyrosine kinase inhibitor.

Table 2

Predictive factors for early progression.

	OR	95% CI	*p*
Sarcomatoid differentiation	3.528	1.277–9.752	0.0151
Time from diagnosis to treatment < 1 yr	3.048	0.820–11.331	0.0962
Anemia	1.868	0.728–4.790	0.1934
Hypercalcemia	4.526	1.231–16.640	0.0230
C-reactive protein ≥ 0.3 mg/dL	2.999	1.010–8.904	0.0479
Liver metastasis	3.114	1.029–9.424	0.0444

CI = confidential interval; OR = odds ratio.

therapy.[16–18] Metastatic status (liver, bone, multiple organs) has been shown to be a poor prognostic factor in mRCC patients.[19,20] An association between poor prognosis and the existence and percentage of a sarcomatoid component on histology has also been demonstrated.[21] The factors that characterized the primary refractory group in this study are consistent with those previously published reports.

The cohort in this study was stratified based upon of the number of risk factors for disease that was primary refractory to first-line agents (Fig. 2). Patients with multiple risk factors exhibited early progression and poor PFS. Based on this data, combination regimens including an ICI should be considered as a first-line therapy option in such cases. In this study, the percentage of patients in the primary refractory group was 13.3%. This is lower than published rates in phase III clinical trials[22–26] and in an international, multicenter, population-based study.[27] The data used in this study were derived from real-world clinical practice. Therefore, it is possible that the physicians who participated in this study might have preferred a combination regimen for high-risk patients rather than single TKI therapy, thus reducing the proportion of primary refractory patients in this cohort.

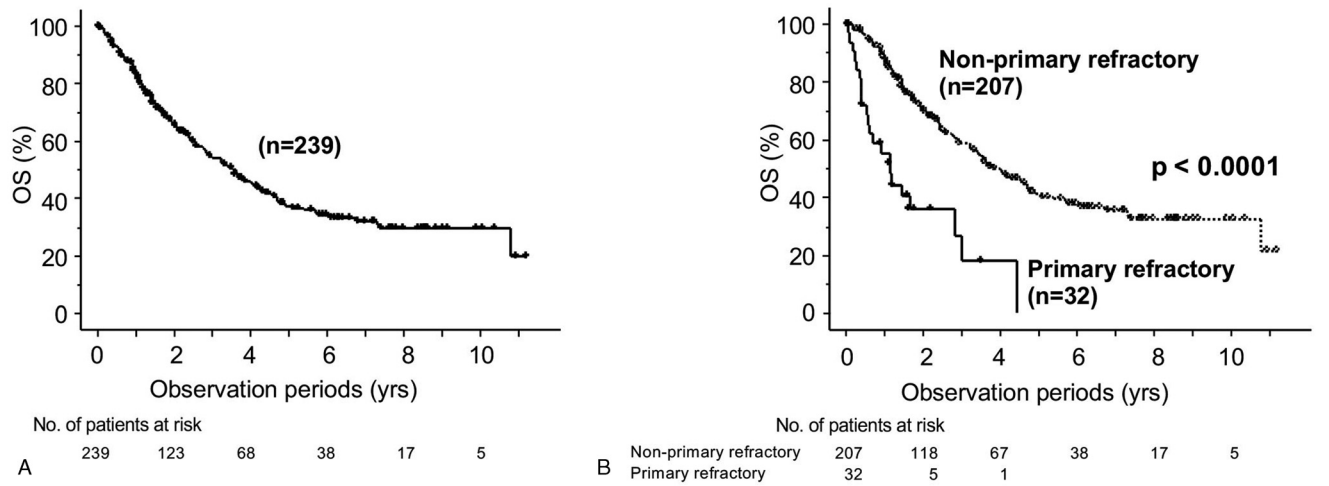

Figure 1. Overall survival of A) all patients and B) groups classified in accordance with the response to first-line therapy. OS = overall survival.

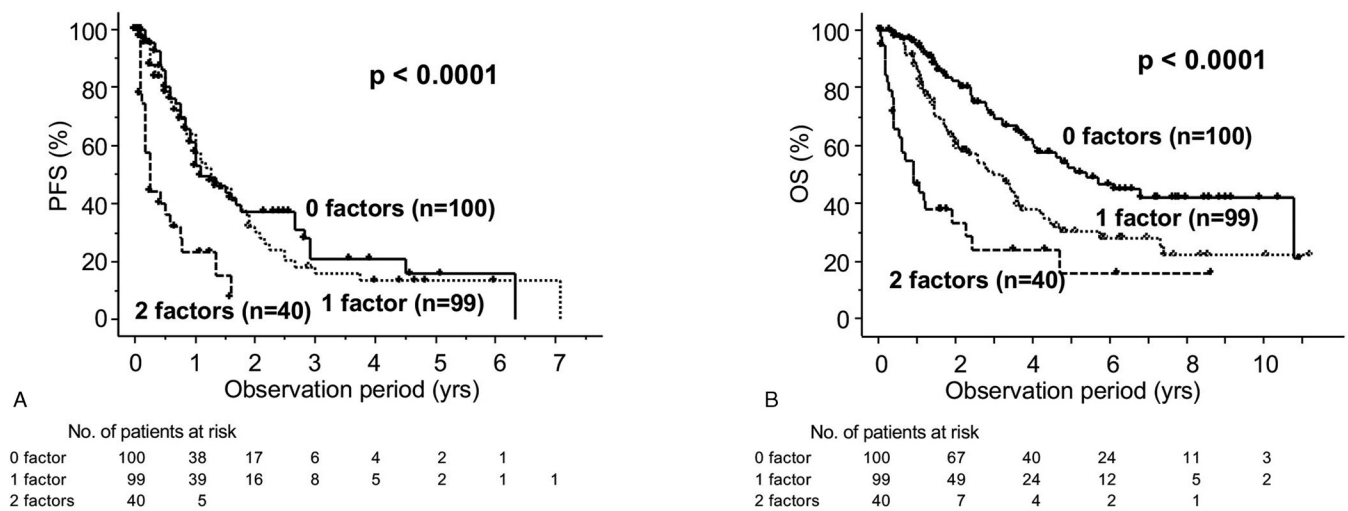

Figure 2. A) Progression-free survival and B) overall survival of patients classified in accordance with the number of risk factors for primary refractory disease. PFS = progression-free survival; OS = overall survival.

This study has 2 limitations. First, this was a retrospective study with a small sample size. A prospective observational study with a larger sample size will be required to validate the risk stratification shown in this cohort of mRCC patients with disease that is primary refractory to first-line TKI therapy. Second, this study only established a predictive risk-stratified model for disease that is primary refractory to first-line TKI therapy, but it did not address the comparative effectiveness of ICI or combination regimens. While many prognostic factors for mRCC have been reported including inflammation-related molecules, blood markers, and metastatic status, predictive factors for the effectiveness of an ICI regimen are still unclear.[28] Prognostic factors for patients treated with a TKI and those treated with an ICI can overlap;[29,30] therefore, it is possible that patients with multiple risk factors might still have a poor prognosis despite treatment with a first-line combination regimen including an ICI. Further study is needed to identify novel biomarkers predicting the effectiveness of each agent, including ICIs and TKIs, in order to establish more precise personalized therapeutic strategies.

In conclusion, we presented a risk-stratified model based on sarcomatoid differentiation, serum CRP level, hypercalcemia, and liver metastasis for patients with mRCC disease that is primary refractory to first-line TKI therapy. With further validation, this model could provide physicians with useful reference information when selecting the most appropriate first-line treatment for mRCC patients. Furthermore, it provides additional evidence regarding predictive factors associated with refractory disease when investigating the use of novel therapeutic strategies for mRCC in an era of multiple treatment options, including ICIs as well as TKIs.

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Statement of ethics

Ethical approval was granted by the Ethics Committee of Hiroshima University (approval notification number: E-45). This study was a retrospective and observation study, therefore, the disclosure of the description about the details and the participation to the study for patients and their families using homepage of our laboratory, instead of written informed consent from patients, was required according to them. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest statement

Jun Teishima has received lecture fees from Pfizer Inc. and Novartis Pharma Inc.

Funding source

None.

Author contributions

Jun Teishima: Design of the study, data analysis, and drafting the manuscript;
Daiki Murata: Data analysis and acquisition;
Shogo Inoue: Data analysis;
Tetsutaro Hayashi, Koji Mita, Yasuhisa Hasegawa, Masao Kato, Mitsuru Kajiwara, Masanobu Shigeta, Satoshi Maruyama, Hiroyuki Moriyama, Seiji Fujiwara: Data acquisition;
Akio Matsubara: Supervision.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68(1):7–30.
[2] Pal SK, Nelson RA, Vogelzang N. Disease-specific survival in de novo metastatic renal cell carcinoma in the cytokine and targeted therapy era. *PLoS One* 2013;8(5):e63341.
[3] Pal SK, Ghate SR, Li N, et al. Real-world survival outcomes and prognostic factors among patients receiving first targeted therapy for advanced renal cell carcinoma: A SEER-Medicare Database Analysis. *Clin Genitourin Cancer* 2017;15(4):e573–e582.
[4] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373 (19):1803–1813.
[5] Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013;369(8):722–731.
[6] Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380 (12):1103–1115.
[7] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380 (12):1116–1127.
[8] Grépin R, Pagès G. Molecular mechanisms of resistance to tumour anti-angiogenic strategies. *J Oncol* 2010;2010:835680.
[9] Seidel C, Busch J, Weikert S, et al. Progression free survival of first line vascular endothelial growth factor-targeted therapy is an important prognostic parameter in patients with metastatic renal cell carcinoma. *Eur J Cancer* 2012;48(7):1023–1030.
[10] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378(14):1277–1290.
[11] Srinivas S, Stein D, Teltsch DY, Tao S, Cisar L, Ramaswamy K. Real-world chart review study of adverse events management in patients taking tyrosine kinase inhibitors to treat metastatic renal cell carcinoma. *J Oncol Pharm Pract* 2018;24(8):574–583.
[12] Dabney R, Devine R, Sein N, George B. New agents in renal cell carcinoma. *Target Oncol* 2014;9(3):183–193.
[13] Atkinson BJ, Kalra S, Wang X, et al. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. *J Urol* 2014;191(3):611–618.
[14] Grünwald V, McKay RR, Krajewski KM, et al. Depth of remission is a prognostic factor for survival in patients with metastatic renal cell carcinoma. *Eur Urol* 2015;67:952–958.
[15] Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. *J Clin Oncol* 2009;27(34):5794–5799.
[16] Teishima J, Kobatake K, Hayashi T, et al. Prognostic significance of C-reactive protein in patients with intermediate-risk metastatic renal cell carcinoma treated with molecular targeted therapy. *Oncol Lett* 2014;8 (2):881–885.
[17] Teishima J, Kobatake K, Kitano H, et al. The impact of change in serum C-reactive protein level on the prediction of effects of molecular targeted therapy in patients with metastatic renal cell carcinoma. *BJU Int* 2016;117(6B):E67–E74.
[18] Teishima J, Kobatake K, Shinmei S, et al. The effect of kinetics of C-reactive protein in the prediction of overall survival in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitor. *Urol Oncol* 2017;35(11):662.e1–662.e7.
[19] Shinohara N, Obara W, Tatsugami K, et al. Prognosis of Japanese patients with previously untreated metastatic renal cell carcinoma in the era of molecular-targeted therapy. *Cancer Sci* 2015;106(5):618–626.
[20] Di Nunno V, Mollica V, Schiavina R, et al. Improving IMDC prognostic prediction through evaluation of initial site of metastasis in patients with

metastatic renal cell carcinoma. *Clin Genitourin Cancer* 2020;18(2): e83–e90.
[21] Korenbaum C, Pierard L, Thiéry A, et al. Treatments, outcomes, and validity of prognostic scores in patients with sarcomatoid renal cell carcinoma: A 20-year single-institution experience. *Clin Genitourin Cancer* 2018;16(3):e577–e586.
[22] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356(2):115–124.
[23] Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356(2):125–134.
[24] Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomised, double-blind phase III trial. *Lancet* 2007;370(9605): 2103–2111.
[25] Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: Final results of CALGB 90206. *J Clin Oncol* 2010;28(13):2137–2143.
[26] Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. *J Clin Oncol* 2010;28(6):1061–1068.
[27] Heng DY, Mackenzie MJ, Vaishampayan UN, et al. Primary anti-vascular endothelial growth factor (VEGF)-refractory metastatic renal cell carcinoma: Clinical characteristics, risk factors, and subsequent therapy. *Ann Oncol* 2012;23(6):1549–1555.
[28] Teishima J, Inoue S, Hayashi T, Matsubara A. Current status of prognostic factors in patients with metastatic renal cell carcinoma. *Int J Urol* 2019;26(6):608–617.
[29] De Giorgi U, Procopio G, Giannarelli D, et al. Association of systemic inflammation index and body mass index with survival in patients with renal cell cancer treated with nivolumab. *Clin Cancer Res* 2019;25 (13):3839–3846.
[30] Teishima J, Murata D, Hasegawa Y, Moriyama H, Mita K, Matsubara A. C-reactive protein can be used to predict the therapeutic effects of nivolumab in patients with metastatic renal cell carcinoma. *Int J Urol* 2019;26(11):1076–1077.

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