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Prognosis of Japanese patients with previously untreated metastatic renal cell carcinoma in the era of molecular-targeted therapy

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Key words

Metastasis, molecular-targeted therapy, prognosis, renal cell carcinoma, risk classification

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[Correction added on 30 April 2015, after first online publication: "Vascular endothelial growth factor-tyrosine kinase inhibitor" (VEGF-TKI) has been replaced with "vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI)" throughout the article.]

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A multicenter cooperative study was conducted to clarify the prognosis of Japanese patients with metastatic renal cell carcinoma in the era of molecular-targeted therapy and the clinical usefulness of the Japanese metastatic renal cancer (JMRC) prognostic classification. Of 389 consecutive patients for whom treatment was started between 2008 and 2010 at 23 hospitals in Japan, 357 patients who received vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) or cytokine as initial systemic therapy were the subject of the present study. Patients were classified into three prognostic groups according to the JMRC prognostic classification. The endpoints were progression-free survival (PFS) and overall survival (OS) after the start of the initial treatment. The median PFS and OS for the entire cohort of 357 patients were 9.1 and 27.2 months, respectively. VEGFR-TKI were selected for patients with multiple organ metastases, those with liver metastasis, and those with bone metastasis. The median PFS and OS were 11.0 and 23.2 months and 5.4 and 38.2 months in the VEGFR-TKI group and the cytokines group, respectively. The JMRC prognostic classification was useful as a prognostic model for PFS and OS (c-indexes: 0.613 and 0.630 in patients who initially received VEGFR-TKI and 0.647 and 0.642 in patients who received cytokines, respectively). The present study showed for the first time the prognosis of Japanese patients with metastatic renal cell carcinoma in the era of molecular-targeted therapy. The JMRC prognostic classification may be clinically useful as a prognostic model.

The introduction of molecule targeted therapy has markedly changed the treatment of metastatic renal cell carcinoma (RCC). According to the clinical guidelines, sunitinib, pazopanib and temsirolimus have been used as the initial treatment for RCC. Sorafenib, axitinib and everolimus have been administered to patients who do not respond to initial therapeutic drugs.[1] The Memorial Sloan Kettering Cancer Center (MSKCC) risk classification, which was established in the cytokine era, is routinely used in the selection of these drugs.[2] Several studies report that survival was longer than in the cytokine era in Europe and the USA.[3] These molecule-targeting drugs have also been commonly used in Japan since 2008. Therefore, the current prognosis of Japanese patients may be better than that in the cytokine era.

However, cytokines including Interferon-alpha (IFN-α) and Iterleukin-2 (IL-2), the use of which has markedly decreased in Europe and the USA, are still used as the initial treatment in Japan because two clinical studies involving a large number of patients indicated that overall survival (OS) was markedly longer in cytokine-treated patients than in the European and American series.[4,5] However, marked differences were noted in patient backgrounds and the social insurance systems. Therefore, controversy surrounds whether the above result should be accepted. Furthermore, progression-free survival (PFS), which may be used as an index of the direct therapeutic effects of drugs, has not yet been reported in Japanese patients treated with cytokines because of the lack of useful drugs other than cytokines and their continued administration to most patients with progression.[4]

This multicenter cooperative study was conducted to clarify the prognosis of Japanese patients with metastatic RCC in the era of molecular-targeted therapy and PFS/OS in patients treated with molecule-targeting drugs or cytokines as the initial systemic treatment. We also used the MSKCC risk classification and the Japanese metastatic renal cancer (JMRC) prognostic classification[6] as models to predict PFS and OS after these treatments in Japanese patients with metastatic RCC, and examined their clinical usefulness.

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Patients and Methods

Patient population. Data on 389 consecutive patients for whom treatment was started between 2008 and 2010 at 23 hospitals in Japan (Appendix) was analyzed. Of these, 357 patients who received vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) or cytokine as initial systemic therapy were the subject of the present study. Patients who received mammalian target of rapamycin (mTOR) inhibitor as first line systemic therapy were omitted from this study because only one patient received temsirolimus. Patients were included if they had a clinical and pathological diagnosis of RCC, clinical confirmation of the presence of metastasis, no previous treatment of metastatic lesions, and course observation for 3 months or longer, except for early fatal cases. Exclusion criteria were as follows: the presence of other clinical cancers, insufficient clinical data before and after the treatment, and withdrawal from the study by the patient or his/her family. The study was performed after approval by the internal review boards of the participating institutes.

Clinical, pathological and survival data were collected for each patient. The performance status was assigned according to the Eastern Cooperative Oncology Group Performance Status scale. The stage was assigned according to the 2009 TNM classification of the Union Internationale Contre le Cancer (UICC).[7] Patients were classified into three prognostic groups (favorable, intermediate and poor) according to the MSKCC risk classification and JMRC prognostic classification.[2,6] The pathological grade was determined according to the General Rules for Clinical and Pathological Studies on Renal Cell Carcinoma in Japan. Tumor histology was classified into three groups: clear cell carcinoma, clear cell carcinoma with sarcomatoid features and non-clear cell carcinoma. Tumor responses were determined by an investigator assessment according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1.[8]

Statistical analysis. Patient characteristics are shown as a median for continuous variables and the number of patients with a percentage for categorical variables. The endpoints of the present study were PFS and OS. PFS was calculated from the date when systemic therapy was started to the date of clinically-confirmed progression according to the RECIST or was censored at the date of the last follow up, and median and 1-year PFS along with the 95% confidence intervals (95% CI) were reported. OS was calculated from the date when systemic therapy was started to the date of death as a result of any cause or was censored at the date of the last follow up, and median and 2-year OS along with the 95% CI were reported. Survival distributions were estimated using the Kaplan–Meier method, and PFS or OS was compared among three prognostic groups according to the MSKCC risk classification or JMRC prognostic classification using the log-rank test. The prognostic classification for PFS or OS, respectively, was measured by the overall concordance index (c-index) for the survival analysis model.[9] This index is defined as the proportion of usable patient pairs in which the predictions and outcomes are concordant.[10] The c-index obtained from the JMRC prognostic classification was compared with that from the MSKCC risk classification.

In all statistical analyses, $P < 0.05$ was regarded as significant. All statistical analyses were performed using SAS version 9 (SAS Institute, Cary, NC, USA).

Table 1. Baseline patient characteristics

	Number	%
Gender		
Male	271	76
Age, years		
Median (range)	65 (17–87)	
Metastasis at the initial RCC diagnosis		
Yes	210	59
ECOG-PS		
0	216	61
1	89	25
≥2	43	12
Unknown	9	3
Prior nephrectomy		
Yes	296	83
Number of metastatic sites		
1	152	43
≥2	205	57
Sites of metastasis		
Lung	236	66
Lymph nodes	136	38
Bone	110	31
Liver	45	13
Brain	19	5
Histology of 296 nephrectomized specimens		
CCRCC only	241	81
CCRCC with sarcomatoid features	16	5
Non-CCRCC	33	11
Unknown	6	2

CCRCC, clear cell renal cell carcinoma; ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

Results

Patient characteristics. The distribution of baseline characteristics for all 357 patients is presented in Table 1. A total of 30 (8%), 254 (71%) and 59 (17%) patients were classified into the favorable, intermediate and poor risk groups, respectively, according to the MSKCC risk classification; 14 patients (4%) could not be classified. In contrast, 81 (23%), 140 (39%) and 129 (36%) patients were classified into the favorable, intermediate and poor prognostic groups, respectively, by the JMRC prognostic classification; 7 patients (2%) could not be classified. At the time of analysis, 156 patients (44%) were still alive, 190 patients (53%) had died of RCC and 11 patients (3%) had died of other causes. The median follow up was 22 months (range: 1–66 months). The median PFS after the start of systemic therapies was 9.1 months, and the 1-year PFS rate was 42% (95% CI, 36–48%). Furthermore, the median OS was 27.2 months, and the 2-year OS rate was 53% (95% CI, 48–59%).

Comparison of baseline patient characteristics between patients who received vascular endothelial growth factor receptor-tyrosine kinase inhibitor and those who received cytokines. Of the patients evaluated in the present study, 233 patients received VEGFR-TKI: sunitinib (148), sorafenib (66), axitinib (12) and pazopanib (7). A total of 124 patients were treated with cytokines: IFN-α (116), IL-2 (3) and IFN-α+IL-2 (5). Gender, age and the incidence of metastasis at the initial RCC diagnosis were similar between the two treatment groups; however, patients who received cytokines had a higher rate of prior nephrectomy and a lower rate of multiple organ metastases than in patients who received VEGFR-TKI (Table 2). The rate

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Table 2. Baseline characteristics of patients who initially received VEGFR-TKI (VEGFR-TKI group) and cytokines (cytokines group)

Characteristics	VEGFR-TKI group (n = 233)	Cytokines group (n = 124)	P-value
Male/female, %	76/24	76/24	0.973
Median (range) age, years	66 (17–85)	65 (34–87)	0.688
Prior nephrectomy, %	79	90	0.048
Metastasis at initial RCC diagnosis, %	61	56	0.373
No. of metastatic sites			
Single/multiple organ, %	36/64	55/45	<0.001
Sites of metastasis			
Lung, %	58	81	<0.001
Lymph node, %	44	27	0.002
Bone, %	36	21	0.003
Liver, %	16	6	0.011
The date when initial systemic therapy was started			
2008, %	11	48	
2009, %	33	24	
2010, %	55	28	<0.001
MSKCC risk classification			
Favorable, %	7	11	
Intermediate, %	71	71	
Poor, %	19	12	0.128
Unclassified, %	3	6	
JMRC prognostic classification			
Favorable, %	18	32	
Intermediate, %	38	42	
Poor, %	44	22	<0.001
Unclassified, %	1	4	

JMRC, Japanese Metastatic Renal Cancer; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

of lung metastasis was higher in the cytokine group, while those of lymph node metastasis, bone metastasis and liver metastasis were higher in the VEGFR-TKI group. The distribution of three risk groups according to the MSKCC risk classification was similar between the two treatment groups. However, the rate of patients classified into the favorable prognostic group was higher in patients who were treated with cytokines, while that of patients classified into the poor prognostic group was higher in patients who received VEGFR-TKI when the JMRC prognostic classification was applied.

Progression-free survival in patients who initially received vascular endothelial growth factor receptor-tyrosine kinase inhibitors or cytokines. The median PFS after the start of systemic VEGFR-TKI therapy for the cohort of 233 patients was 11.0 months. No significant differences were observed in the median PFS among patients who received sunitinib, sorafenib, axitinib or pazopanib (data not shown). Significant differences were noted in the median PFS among the favorable (n = 16), intermediate (n = 166) and poor (n = 44) risk groups, which were stratified according to the MSKCC risk classification (P = 0.003) (Fig. 1a). The c-index was 0.596 (95% CI: 0.558–0.634) (Table 3). However, significant differences were also observed in the median PFS among the three groups stratified according to the JMRC prognostic classification (P = 0.013) (Fig. 1b). The c-index was 0.613 (95% CI: 0.566–0.660), which was not significantly different from that calculated using the MSKCC risk classification (P = 0.493). The treatment was discontinued in 202 out of the 233 patients who initially received VEGFR-TKI due to progression (n = 134) or adverse events (n = 68). Of these, secondary drugs were administered to 128 (63%) (VEGFR-TKI: 63 patients, mTORI: 50, and others: 15).

The median PFS after systemic cytokine therapy had been started for the cohort of 124 patients was 5.4 months. No significant differences were observed in the median PFS among the three groups stratified according to the MSKCC risk classification (P = 0.304) (Fig. 2a). The c-index was 0.564 (95% CI: 0.519–0.609). However, significant differences were noted in the median PFS among the favorable (n = 40), intermediate (n = 52) and poor (n = 27) prognostic groups, which were stratified according to the JMRC prognostic classification (P = 0.011) (Fig. 2b). The c-index was 0.647 (95% CI: 0.590–0.705). A significant difference was observed in the c-index between the two prognostic models (P = 0.005). The treatment was discontinued in 113 out of the 124 patients who initially received cytokines due to progression (n = 90) or adverse events (n = 23). Of these, secondary drugs were administered to 96 patients (85%) (VEGFR-TKI: 77 patients, and others: 19).

Overall survival in patients who initially received vascular endothelial growth factor receptor-tyrosine kinase inhibitors or cytokines. The median OS after the start of systemic VEGFR-TKI therapy for the cohort of 233 patients was 23.2 months. Significant differences were noted in the median OS among the three groups stratified according to the MSKCC risk classification (P < 0.001) (Fig. 3a, Table 4). The c-index, the threshold of which was established as 3 years after the treatment, was 0.600 (95% CI: 0.562–0.638). Significant differences were also observed in the median OS among the three groups stratified according to the JMRC prognostic classification (P < 0.001) (Fig. 3b). The c-index was 0.630 (95% CI: 0.587–0.672), which was not significantly different from that calculated using the MSKCC risk classification (P = 0.178).

The median OS after the start of systemic cytokine therapy for the cohort of 124 patients was 38.2 months. No significant differences were observed in the median OS among the three groups stratified according to the MSKCC risk classification (P = 0.063) (Fig. 4a, Table 5). The c-index was 0.584 (95% CI: 0.536–0.633). In contrast, significant differences were noted in the median OS among the three groups stratified according to the JMRC prognostic classification (P = 0.001) (Fig. 4b). The c-index was 0.642 (95% CI: 0.578–0.706). No significant difference was observed in the c-index between the two prognostic models (P = 0.056).

Comparison of progression-free survival and overall survival between patients who initially received vascular endothelial growth factor receptor-tyrosine kinase inhibitors and those who received cytokines in three prognostic groups according to the Japanese metastatic renal cancer prognostic classification. Based on the results described, we considered the JMRC prognostic classification to be more useful than the MSKCC risk classification as a prognostic model for PFS and OS. Therefore, we examined the therapeutic effects of VEGFR-TKI and cytokines in the groups stratified according to this classification. As shown in Table 5, no significant differences were observed in PFS or OS between the two treatments in the favorable prognostic group. In the intermediate and poor prognostic groups, the PFS tended to be longer in patients treated with VEGFR-TKI than in those

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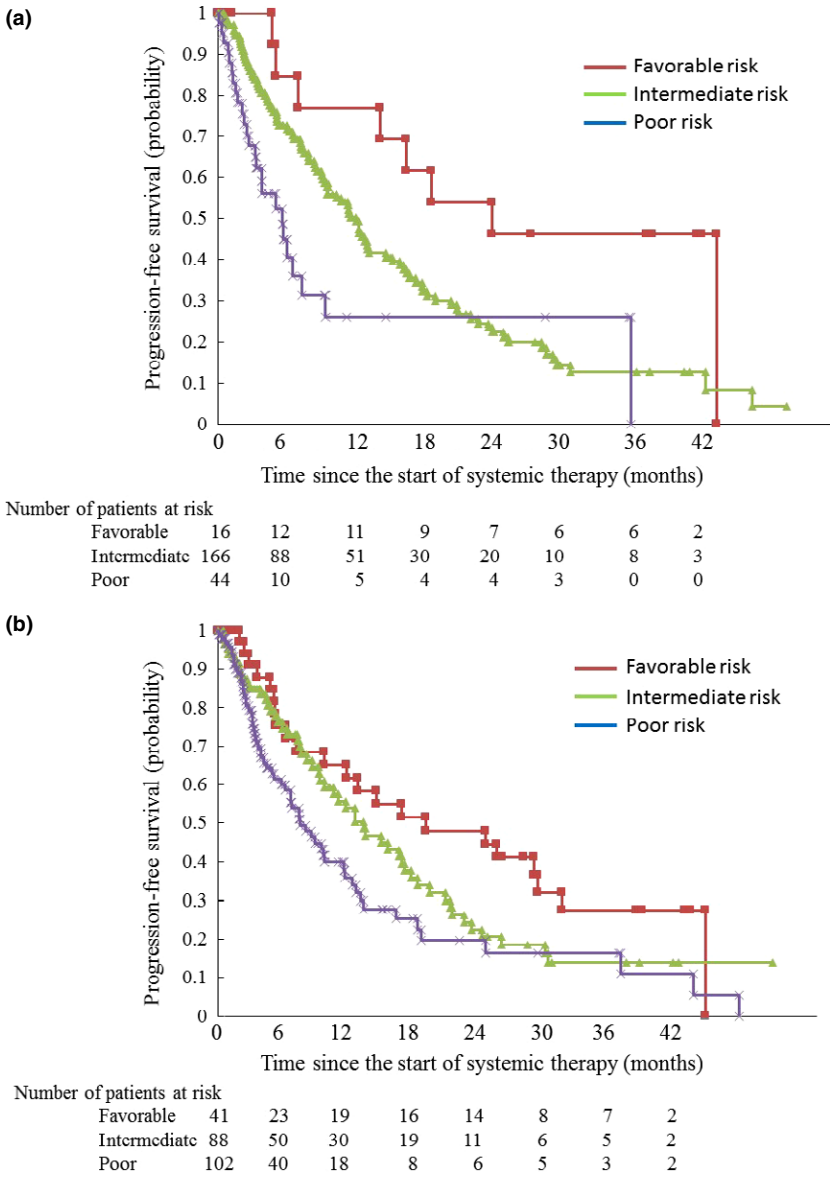


Fig. 1. Progression-free survival of 233 patients who initially received vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) stratified by the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification (a) and by the Japanese metastatic renal cancer (JMRC) prognostic classification (b).

Table 3. Progression-free survival (PFS) in patients who were classified into three prognostic groups according to the MSKCC risk classification or JMRC prognostic classification

Prognostic group	Median, months	HR (5% CI)	c-index (95% CI)	*P*-value†
VEGFR-TKIs group				
MSKCC favorable (*n* = 16)	23.4	1		0.493
MSKCC intermediate (*n* = 166)	11.7	2.131 (1.031–4.408)		
MSKCC poor (*n* = 44)	5.6	3.723 (1.658–8.359)	0.596 (0.558–0.634)	
JMRC favorable (*n* = 41)	18.2	1		
JMRC intermediate (*n* = 88)	12.7	1.427 (0.863–2.357)		
JMRC poor (*n* = 102)	7.2	2.067 (1.253–3.409)	0.613 (0.56–0.660)	
Cytokines group				
MSKCC favorable (*n* = 14)	14.9	1		0.005
MSKCC intermediate (*n* = 88)	5.0	1.499 (0.786–2.857)		
MSKCC poor (*n* = 16)	<3.0	2.348 (0.913–6.039)	0.564 (0.519–0.609)	
JMRC favorable (*n* = 40)	14.9	1		
JMRC intermediate (*n* = 52)	4.8	1.830 (1.104–3.034)		
JMRC poor (*n* = 27)	3.7	2.460 (1.313–4.609)	0.647 (0.590–0.705)	

†Comparison between the c-index obtained from the JMRC prognostic classification and that from the MSKCC risk classification. CI, confidence intervals; HR, Hazard ratio; JMRC, Japanese Metastatic Renal Cancer; MSKCC, Memorial Sloan-Kettering Cancer Center; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

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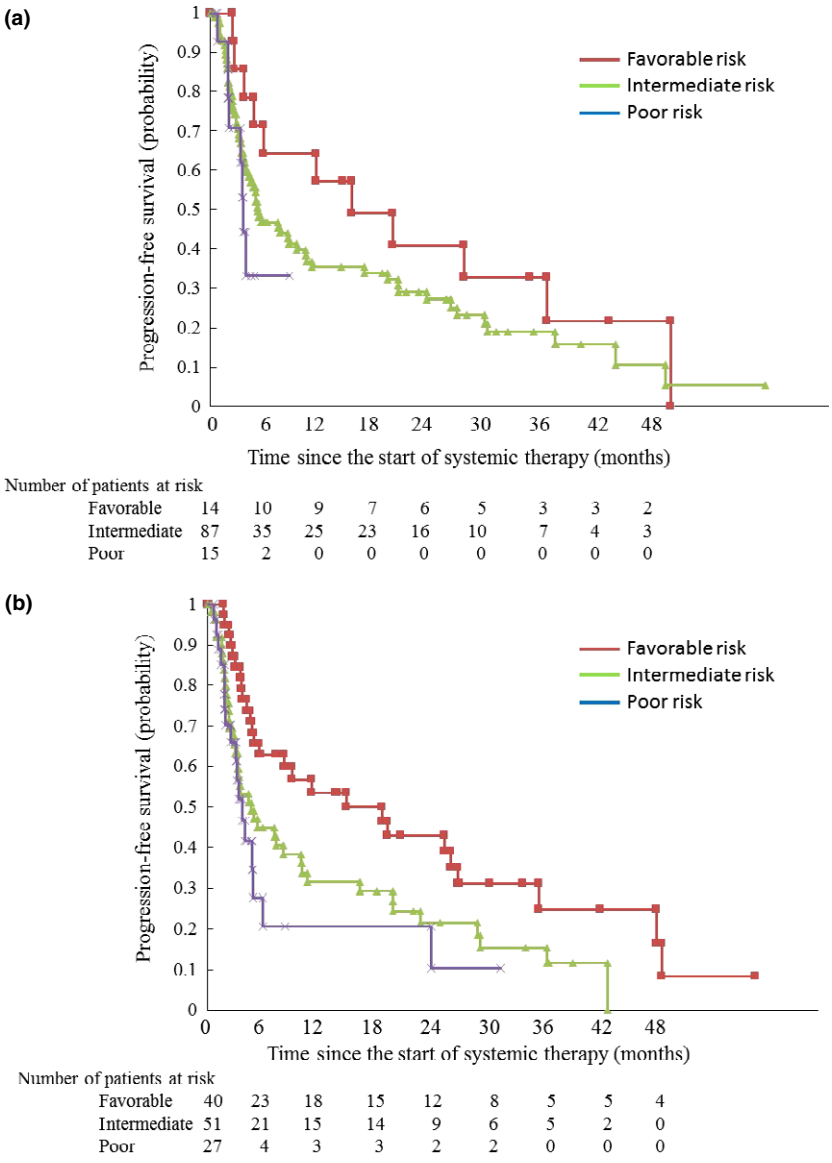


Fig. 2. Progression-free survival of 124 patients who initially received cytokines stratified by the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification (a) and by the Japanese metastatic renal cancer (JMRC) prognostic classification (b).

treated with cytokines. However, no significant difference was found in OS between the two treatments.

Discussion

The present study showed that the median OS was 27.2 months in Japanese patients with metastatic RCC in the era of molecular-targeted therapy. VEGFR-TKI were selected as the initial treatment for approximately two-thirds of the patients, while cytokines were selected for one-third. Regarding patient backgrounds, VEGFR-TKI were selected for patients with multiple organ metastases, those who did not undergo nephrectomy, those with liver metastasis, and those with bone metastasis, in whom the prognosis was considered to be relatively poor. The median PFS in VEGFR-TKI-treated and cytokine-treated patients were 11.0 and 5.4 months, respectively. As a prognostic model for PFS, the JMRC prognostic classification was more useful than the MSKCC risk classification in the cytokines group. However, no significant difference was observed between the two prognostic models in the VEGFR-TKI group. As a prognostic model for OS, no significant difference was noted between the two models in either group.

Previous clinical studies in Europe and the USA suggested that the prognosis of patients with metastatic RCC was improving with the introduction of molecular-targeted therapy. Wahlgran *et al.*[3] reported that median survival was prolonged to 7.5 months in patients with metastatic RCC for whom treatment was started between 2000 and 2005 or between 2006 and 2008. However, the present study demonstrated that median survival in Japanese patients with metastatic RCC after the introduction of molecular-targeted therapy was 27.2 months. As median survival was 21.4 months in the cytokine era,[4] survival may also be prolonged in Japanese patients.

Although VEGFR-TKI, especially sunitinib, have been administered to many Japanese patients and reported to be clinically effective,[11] cytokines are still used as the initial treatment because OS in Japanese patients with metastatic RCC in the cytokine era has been found to be relatively prolonged.[4,6] The efficacy of cytokine therapy was previously reported to be high in post-nephrectomy patients with lung metastasis alone. In the present study, cytokines were also

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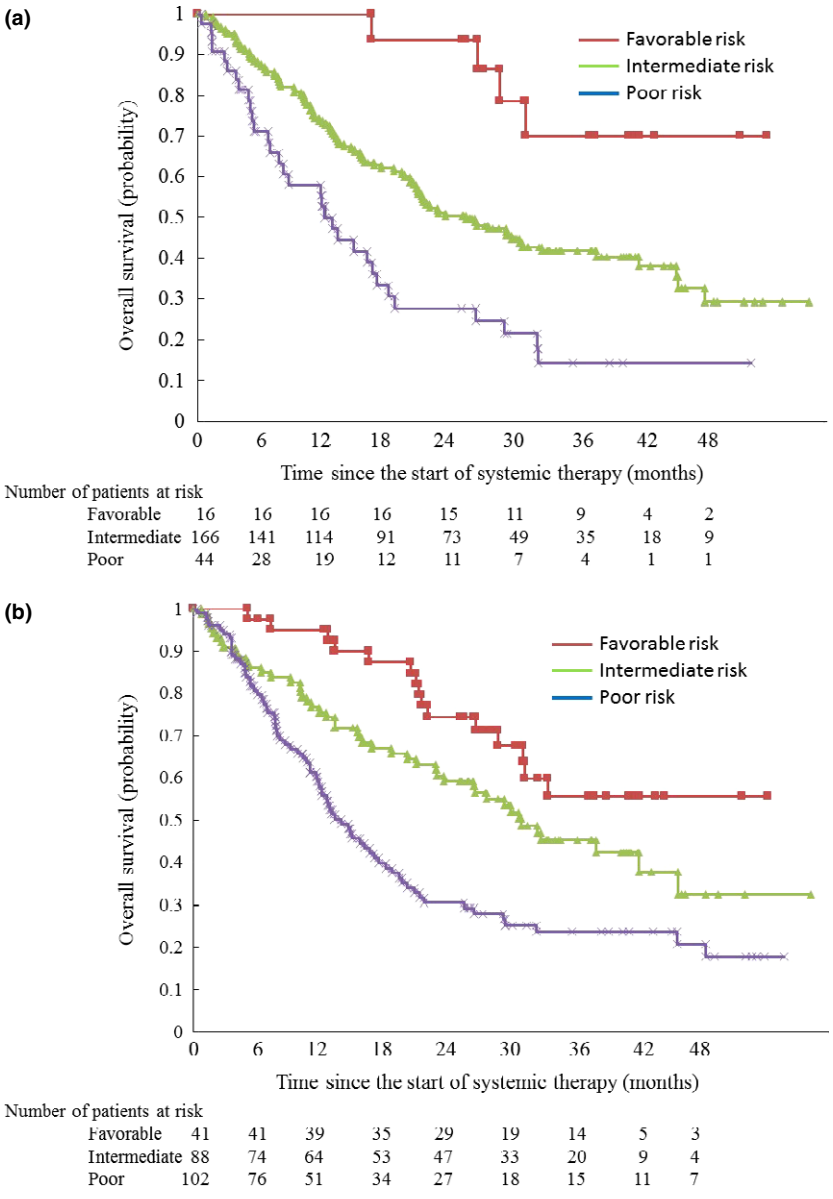


Fig. 3. Overall survival of 233 patients who initially received vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) stratified by the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification (a) and by the Japanese metastatic renal cancer (JMRC) prognostic classification (b).

Table 4. Overall survival (OS) in patients who were classified into three prognostic groups according to the MSKCC risk classification or JMRC prognostic classification

Prognostic group	Median, months	HR (95% CI)	c-index (95% CI)	*P*-value†
VEGFR-TKIs group				
MSKCC favorable (*n* = 16)	Not-reach	1		0.178
MSKCC intermediate (*n* = 166)	25.1	3.398 (1.248–9.254)		
MSKCC poor (*n* = 44)	11.9	7.093 (2.500–20.127)	0.600 (0.562–0.638)	
JMRC favorable (*n* = 41)	Not-reach	1		
JMRC intermediate (*n* = 88)	30.4	1.427 (0.863–2.357)		
JMRC poor (*n* = 102)	13.6	2.067 (1253–3.409)	0.630 (0.587–0.672)	
Cytokines group				
MSKCC favorable (*n* = 14)	47.0	1		0.056
MSKCC intermediate (*n* = 88)	44.3	1.735 (0.969–3.109)		
MSKCC poor (*n* = 16)	18.3	3.304 (1.887–5.785)	0.584 (0.536–0.633)	
JMRC favorable (*n* = 40)	59.0	1		
JMRC intermediate (*n* = 52)	27.9	2.572 (1.347–4.910)		
JMRC poor (*n* = 27)	17.8	3.594 (1.745–7.404)	0.642 (0.578–0.706)	

†Comparison between the c-index obtained from the JMRC prognostic classification and that from the MSKCC risk classification. CI, confidence intervals; HR, Hazard ratio; JMRC, Japanese Metastatic Renal Cancer; MSKCC, Memorial Sloan-Kettering Cancer Center; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

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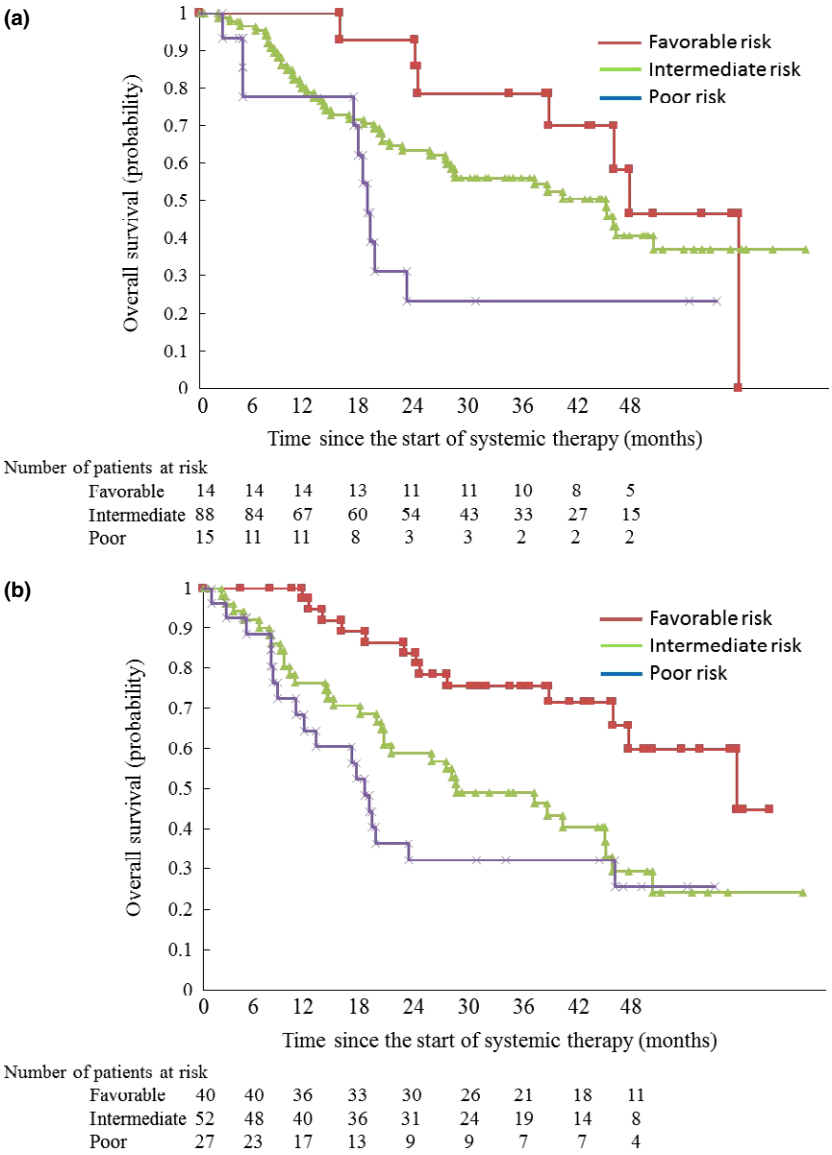


Fig. 4. Overall survival of 124 patients who initially received cytokines stratified by the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification (a) and by the Japanese metastatic renal cancer (JMRC) prognostic classification (b).

administered to these patients. Although cytokine therapy, primarily with IFN-α, has been considered to be effective, no study has reported the PFS in Japanese patients with metastatic RCC. This issue was clarified for the first time in the present study, but the PFS was 5.4 months, which was similar to that previously reported after the start of IFN-α therapy in Europe and the USA.[12–14] Therefore, race-related differences might not exist in the efficacy of cytokines.

In the present study, the median OS was 23.2 months in 233 patients who initially received VEGFR-TKI and 38.2 months in 124 who initially received cytokines. The PFS was 11 months in the former and 5.4 months in the latter. A discrepancy was noted between PFS and OS. Although this may be associated with various factors, they include a difference in the patient background. Therefore, it may be necessary to stratify patients using a prognostic model and examine PFS and OS. MSKCC[2] and mRCC International Database Consortium (IDC) models are now routinely used as such prognostic models.[15] The MSKCC risk classification is a prognostic model established to stratify cytokine-treated patients based on OS, but is also routinely used in patients receiving molecule-targeting drugs. In many guidelines for the treatment of metastatic RCC, drugs are also recommended based on this classification. A review in the cytokine era indicated that there were marked differences in survival and proportion of patients classified by MSKCC risk classification between Japanese patients and patients in Europe and the USA.[4,5] This was attributed to metastatic foci, which may influence the prognosis of patients,[16] not being evaluated in the MSKCC risk classification. In contrast, in the JMRC prognostic classification, a metastatic focus assessment (multiple metastases, bone metastasis alone and liver metastasis alone) was added as a prognostic factor.[6] The c-index was 0.72 when OS was evaluated through internal and external validations in Japanese patients with metastatic RCC in the cytokine era. The questions are whether the JMRC prognostic classification is applicable to metastatic RCC patients in the era of molecular-targeted therapy, and also which of the JMRC prognostic classification and MSKCC risk classification is more useful.

In the present study, an evaluation of PFS in VEGFR-TKI-treated patients revealed that they could be clearly stratified into three prognostic groups using not only the JMRC model but also the MSKCC model. Motzer *et al.*[17] report a nomogram as a prognostic model for PFS in sunitinib-treated patients. The PFS rate was calculated 12 months after the treatment using 11

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Table 5. Comparison of PFS and OS between patients who initially received VEGFR-TKI and those who received cytokines in each prognostic group according to the JMRC prognostic classification

JMRC group	Systemic therapy	Patient number	PFS		OS	
			Median (months)	1Y-PFS (95% CI) (%)	Median (months)	2Y-OS (95% CI) (%)
Favorable	VEGFR-TKI	41	18.2	62 (45–79)	Not-reach	74 (61–88)
	Cytokines	40	14.9	54 (37–70)	59.0	78 (65–92)
Intermediate	VEGFR-TKI	88	12.7	50 (38–63)	30.4	59 (49–70)
	Cytokines	52	4.8	32 (18–45)*	27.9	59 (45–72)
Poor	VEGFR-TKI	102	7.2	34 (22–45)	13.6	30 (21–40)
	Cytokines	27	3.7	21 (1–40)**	17.8	32 (14–51)

*P = 0.060 (VEGFR-TKI *vs* cytokines). **P= 0.080 (VEGFR-TKI *vs* cytokines). CI, confidence intervals; HR, hazard ratio; JMRC, Japanese Metastatic Renal Cancer; OS, overall survival; PFS, progression-free survival; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

pretreatment factors including three parameters for the assessment of metastatic foci, and the c-index was reported to be 0.633 when this nomogram was used. In contrast, the c-index was 0.613 when the JMRC prognostic classification, in which evaluations were performed using only four parameters, was used, and this was not markedly different from the c-index obtained with the nomogram reported by Motzer *et al.*[2] Cytokine-treated patients could be stratified into three groups with the JMRC prognostic classification, but not with the MSKCC risk classification. The c-index was 0.647 when the JMRC model was used, and was significantly higher than that with the MSKCC model. Karakiwiez *et al.*[18] report a nomogram, which was estimated using five pretreatment factors, as a prognostic model for PFS in treatment groups receiving cytokines.[18] The AUC, as a parameter that replaced the c-index, was 70 to 75%, but it cannot be used to compare the results of the PFS assessment between IFN-α and VEGFR-TKI. However, the JMRC prognostic classification facilitates the evaluation of PFS in patients treated with VEGFR-TKI or cytokines, and may be clinically useful.

To predict OS, the results obtained were also similar to those for PFS. Patients in both the VEGFR-TKI and cytokines groups could be stratified into three groups using the JMRC prognostic classification, and the c-indexes were 0.630 and 0.642, respectively. Several models have been proposed as prognostic models for OS.[15,19–22] Heng *et al.*[23] compared the IDC, Cleveland Clinic Foundation (CCF), French, International Kidney Cancer Working Group (IKCWG) and MSKCC models, and reported that their c-indexes were 0.664, 0.662, 0.640, 0.668 and 0.657, respectively; no marked differences were observed between these models. The c-index of the JMRC model in the present study was similar to these results. Further study to compare the predictive ability on OS between the JMRC prognostic classification and the IDC model, which is used in patients receiving molecular-targeting drugs, would be warranted. Furthermore, we might need to establish the new stratification model for Japanese metastatic RCC patients because the c-index of the JMRC prognostic classification was relative low.

We lastly examined PFS and OS of patients who initially received VEGFR-TKI or cytokines in each risk group classified by the JMRC prognostic classification. No significant differences were observed in OS between patients who received VEGFR-TKI and those who received cytokines in any prognostic group. This was attributed to the prolongation of survival in the latter. The median OS in the favorable, intermediate and poor prognostic groups were 59, 27.9 and 17.8 months, respectively. These values were 7 to 8 months longer than the previously reported median OS in the cytokine era.[6] The appearance of molecular-targeted therapy involving VEGFR-TKI has facilitated the switch to effective drugs in the early stage even in patients who initially received cytokines, and this finding may be significant. A secondary treatment was performed in 85% of patients in whom PD or AE required a switch in the treatment administered. This may have contributed to the prolongation of OS despite a relatively short PFS in cytokine-treated patients. Especially in the favorable prognostic group stratified using the JMRC model, initial cytokine therapy may be more advantageous from the perspectives of survival and treatment costs.

A limitation of the present study was that it was a retrospective study. Various biases may have been added. In addition, it was impossible to compare our model with the IDC model, which is commonly used, due to problems regarding data collection. As another limitation, there was no central review because each investigator was responsible for evaluating pathologies, images and treatment responses. However, we clarified the prognosis of Japanese patients with metastatic RCC in the era of molecular-targeted therapy, especially PFS in patients who initially received cytokines, which is significant. Although the results of the present study need to be verified, they indicated that the JMRC prognostic classification may be useful as a prognostic model in Asian patients to whom cytokines are frequently administered even in the era of molecular-targeted therapy.

Disclosure Statement

Nobuo Shinohara and Seiji Naito have received speaker honoraria from GlaxoSmithKline, Novartis and Pfizer. Wataru Obara has received speaker honoraria from Novartis and Pfizer. Masayuki Takahashi has received speaker honoraria from Pfizer.

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Appendix

Study group participants: In addition to the authors, the study group participants included Takao Kamai (Dokkyo Medical University), Noboru Nakaigawa (Yokohama City University), Syou-ichiro Mukai (Miyazaki University), Takashi Kasahara (Niigata University), Yoshito Takahashi (Gifu Prefectural Medical Center), Yoshifumi Kadono (Kanazawa University), Nozomi Tanji (Ehime University), Naoya Masumori (Sapporo Medical University), Atsushi Takahashi (Gryokaku Hospital), Toshiyasu Amano (Nagano Red-Cross Hospital), Toshiro Terachi (Tokai University), Noriaki Tokuda (Saga Prefectural Hospital Koseikan), Takafumi Hatano (JR Tokyo Hospital), Hiroshi Ikeda (Kitakyushu Hospital), Toshiaki Kiuchi (Saiseikai Senri Hospital), Yukio Naya (Teikyo University Chiba Medical Center), Yasuo Yamamoto (Kurashiki Medical Center).

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