

A new prognostic classification for overall survival in Asian patients with previously untreated metastatic renal cell carcinoma

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The aims of the present study were to: (i) develop a clinically useful prognostic classification in Asian patients with metastatic renal cell carcinoma (RCC) by combining metastatic features with several pretreatment parameters; and (ii) evaluate the validity of this prognostic classification. Baseline characteristics and outcomes were collected for 361 patients who underwent interferon- α -based therapy between 1995 and 2005. Relationships between overall survival (OS) and potential prognostic factors were assessed using Cox's proportional hazard model. The predictive performance of the model was evaluated using bootstrap resampling procedures and by using an independent dataset obtained from randomly selected institutions. The predictive accuracy was measured using the concordance index (c-index). Four factors were identified as independent prognostic factors: time from initial diagnosis to treatment, anemia, elevated lactate dehydrogenase (LDH), and poor prognostic metastatic group (liver only, bone only, or multiple organ metastases). Each patient was assigned to one of three risk groups: favorable risk (none or one factor; $n = 120$), in which median OS was 51 months; intermediate risk (two factors; $n = 101$), in which median OS was 21 months; and poor risk (three or four factors; $n = 102$), in which median OS was 10 months. The c-index was 0.72 in the original dataset and 0.72 in 500 random bootstrap samples. In the independent dataset for external validation, the c-index was 0.73. Thus, the new prognostic classification is easily applicable for Asian patients with previously untreated metastatic RCC and should be incorporated into patient care, as well as clinical trials performed in Asia. (*Cancer Sci* 2012; 103: 1695–1700)

With the advent of molecular targeted therapy, treatment for metastatic renal cell carcinoma (RCC) has changed markedly. At present, drugs that should be used for molecular targeted therapy are usually selected on the basis of the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification.^(1,2) This results from the fact that clinical trials of molecular targeted drugs, such as sunitinib and temsirolimus, have been performed by selecting subjects on the basis of this risk classification and their usefulness has been clarified.^(3,4) In Japan, the MSKCC risk classification is widely used not only in clinical trials, but also in daily clinical practice.^(5,6) However, whether this risk classification is useful for predicting outcomes in Japanese patients with metastatic RCC is not unclear. Recently, we performed a retrospective study on the MSKCC risk classification in patients with metastatic RCC and reported its applicability to Japanese patients.⁽⁷⁾ However,

when this risk classification was used in Japanese RCC patients, the percentage of patients in the poor risk group was high compared with that in Western series and the survival period of the poor risk group was twice as long in Japanese patients as that in patients in Western countries.^(7,8) This may be because multiple organ metastases are less frequently observed in Japanese patients and the status of metastases is not used as a prognostic variable in the MSKCC risk classification. The importance of the number of organs showing metastasis and metastatic sites on survival in patients with metastatic RCC has been pointed out by several investigators.^(9,10) Thus, the aims of the present study were to develop a clinically available prognostic classification in Asian patients with metastatic RCC, who are still frequently treated with interferon (IFN)- α -based therapy, by combining metastatic features with several pretreatment parameters and to evaluate the validity of this prognostic classification by internal and external validation assessments.

Materials and Methods

Patient population. A total of 361 patients treated with IFN- α -based therapy as their initial treatment in Hokkaido University Hospital and hospitals of the Hokkaido Immunotherapy Research Group (Appendix I) between 1995 and 2005 were the subjects of the present retrospective analysis. Patients were included in the study 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, except for early fatal cases. The exclusion criteria were the presence of other clinical cancer, insufficient clinical data before and after treatment, and withdrawal from the study by the patient and/or his/her family. The study was approved by the Internal Review Boards of the participating institutes.

Clinical, pathological, and survival data were collected for each patient. The performance status was determined on the basis of the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale. Tumor staging was according to the 1997 TNM classification of the Union Internationale Contre le Cancer (UICC).⁽¹¹⁾ Laboratory data included hemoglobin (Hb), serum lactate dehydrogenase (LDH), corrected Ca (cCa), and C-reactive protein (CRP) at the initial diagnosis of metastasis. The LDH values were standardized against the upper limit of

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normal (ULN) in each participating hospital when appropriate. The pathological grade was determined on the basis of the General Rules for Clinical and Pathological Studies on Renal Cell Carcinoma in Japan.⁽¹²⁾ Tumor histology was classified into three groups: clear cell carcinoma, clear cell carcinoma with sarcomatoid features, and non-clear cell carcinoma.

Statistical analysis. Patient characteristics are shown as the median for continuous variables and the number of patients with percentages for categorical variables. The endpoint of the present study was OS, which was calculated from the date when IFN- α -based therapy started to the date of death as a result of any cause (or censored at the date of the last follow-up). Molecular targeted therapeutic drugs were administered during the treatment course in a few patients; in these patients, the day before the initiation of molecular targeted drugs was regarded as the final observation day. Survival distributions were estimated using the Kaplan–Meier method. Median and 2-year OS, along with 95% confidence intervals (CI), are reported. Associations between OS and potential prognostic factors were assessed using the log-rank test and Cox’s proportional hazards model in univariate analysis. If the prognostic factor had $P < 0.05$, then it could be considered as relevant and was included in multivariate analysis. Then, the preselected prognostic factors were included in the multivariate Cox’s proportional hazard model using a stepwise procedure, with a significance level of 0.10 for entering and removing variables. Once the prognostic factors were identified and the final model was formed, a risk group variable was created by counting the number of unfavorable features presented for each patient. The discrimination of the prognosis after 2 years of the prognostic classification was measured using the concordance index (c-index).⁽¹³⁾

For internal validation, we assessed the predictive performance of the final model by using bootstrap resampling procedures.⁽¹⁴⁾ Five hundred bootstrap samples were generated randomly with replacement from the original study population ($n = 371$). The stepwise Cox regression procedure was used for each sample with the same selection criteria as the original modeling. We calculated the frequency of each variable that was included in the resulting models from the 500 bootstrap samples. Furthermore, for each of the samples, we refitted Cox’s regression model by using the variables selected in the final model and we calculated the regression parameters and hazard ratios. The means and 95% CI were computed from the 500 samples and were compared with the model by using the original study population. The c-index analysis was also calculated using the bootstrap resampling procedures. The 95% CI for the c-index was calculated on the basis of 500 bootstrap resamplings. Minimum and maximum resampled estimates of the c-index are also reported.

For external validation, we assessed the predictive activity of the present risk classification by using the 137 metastatic RCC Japanese patients who were independently treated with IFN- α -based therapy in four other institutes. By using the present prognostic classification, the patients were again classified into risk groups, as mentioned above, and median OS along with 95% CI is reported for each risk group. Discrimination of the prognosis after 2 years of the risk classification was evaluated with the c-index, which was compared with the c-index obtained from the original dataset.

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

Results

Patient characteristics and outcome. The distribution of baseline characteristics for the 361 patients is presented in Table 1.

At the time of analysis, 114 patients (32%) were still alive, 240 patients (66%) had died of RCC, and seven patients (2%) had died of other causes. The median follow-up was 21.5 months (range: 1–177 months). Three hundred and forty-five patients received natural IFN- α , whereas the remaining 16 patients were treated with recombinant IFN- α . Eighty-nine patients (25%) underwent metastasectomy during the treatment course. The median OS for the entire cohort of 361 patients was 26 months, with a 2-year OS rate for the entire cohort of 52% (95% CI 47–57%; Fig. 1).

Survival analysis. Relationships between potential prognostic variables and the OS were investigated (Table 2). Median OS was significantly shorter in patients with liver-only or bone-only metastasis than in those with lung-only, lymph node-only, or other organ-only metastasis. The median OS of the former group (liver-only or lung-only) was almost compatible with that of patients with multiple organ metastases. Therefore, we grouped liver-only metastasis and bone-only metastasis together with multiple organ metastases as a possible prognostic variable. Clinical and laboratory features that were significantly associated with poor OS included metastasis at the initial diagnosis of RCC, poor prognostic metastatic group, no prior nephrectomy, time from initial diagnosis to treatment < 1 year, an ECOG-PS > 0 , anemia, hypercalcemia, elevated LDH, and elevated CRP. The significant pretreatment prognostic variables on univariate analysis were selected for the multivariate analysis (Table 3). Because previous nephrectomy was strongly correlated with time from initial diagnosis of RCC to the start of IFN- α -based therapy, the latter was selected for multivariate analysis. Because there were a lot of missing data for serum CRP values, this variable was omitted. Of the significant prognostic variables on univariate analysis, four variables

Table 1. Patient characteristics

Gender (%)	
No. men	262 (73)
No. women	99 (27)
Median (range) age (years)	63 (32–85)
Metastasis at initial diagnosis of RCC (%)	
Yes	205 (57)
No	156 (43)
ECOG-PS (%)	
0	207 (57)
1	88 (24)
≥ 2	56 (16)
Unknown	10 (3)
Prior nephrectomy (%)	293 (81)
No. metastatic sites (%)	
1	214 (59)
2	104 (29)
≥ 3	43 (12)
Sites of metastasis (%)	
Lung	251 (70)
Bone	104 (29)
Lymph nodes	73 (20)
Liver	43 (12)
Histology (%)	
CCRCC only	231 (64)
CCRCC with sarcomatoid	24 (7)
Non CCRCC	40 (11)
Unknown	66 (18)

Unless indicated otherwise, data show the number of patients in each group with percentages given in parentheses. CCRCC, clear cell renal cell carcinoma; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; RCC, renal cell carcinoma.

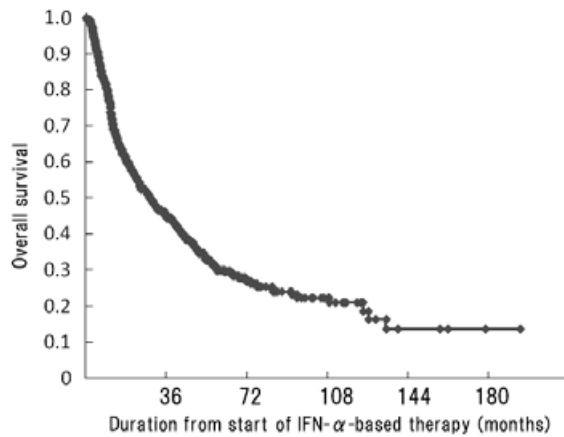


Fig. 1. Overall survival of 361 patients with metastatic renal cell carcinoma. At the time of the last follow-up, 114 patients were alive. IFN- α , interferon- α .

were identified as independent poor prognostic factors: time from initial diagnosis to treatment <1 year, anemia, elevated LDH, and poor prognostic metastatic group.

Prognostic classification model. We established the following new prognostic classification (Japanese Metastatic Renal Cancer [JMRC] prognostic classification) of patients into three groups using these four factors: favorable risk group (no. poor prognostic factors = 0 or 1), intermediate risk group (no. poor prognostic factors = 2), and poor risk group (no. poor prognostic factors = 3 or 4). This prognostic classification was applied to all 361 patients and the survival time was compared among the risk groups (Fig. 2). There were 120 (33%), 101 (28%), and 102 (28%) patients in the favorable, intermediate, and poor risk groups, respectively; 39 patients (11%) could not be classified. The median OS periods were 51, 21, and 10 months in the favorable, intermediate, and poor risk groups, respectively (Table 4). The OS rates at 2 years were 75% (95% CI 66–83%), 47% (95% CI 37–57%), and 25% (95% CI 16–33%) in the favorable, intermediate, and poor risk groups, respectively. The c-index was 0.72 when the JMRC prognostic classification was applied to these 361 patients.

These 361 patients were also classified according to the MSKCC risk classification⁽¹⁾ (Table 5). There were 48 (13%), 166 (46%), and 104 (29%) patients in the favorable, intermediate, and poor risk groups, respectively; 43 patients (12%) could not be classified. The median OS was not reached in the favorable risk group and was 26 and 10 months in the intermediate and poor risk groups, respectively. As shown in Table 5, 70 (42%) and 24 (14%) of 166 patients who were classified as being at intermediate risk by the MSKCC classification were considered to have favorable risk and poor risk by the JMRC classification, respectively. There were significant differences in OS among these three risk groups ($P = 0.002$). Although 28 (27%) of 104 patients who were considered to be at poor risk according to the MSKCC risk classification were classified as being at intermediate risk by the JMRC classification, there was no significant difference in the OS among these patients.

We further applied the JMRC classification to 129 patients with pulmonary-only metastasis. There were 67 (52%) and 48 (37%) patients in the favorable and intermediate risk groups, respectively, and 14 patients could not be classified. The median OS periods were 43 and 18 months in the favorable and intermediate risk groups, respectively.

Table 2. Univariate survival analysis

Factor	n (%)	Median OS (95% CI)	Hazard ratio	P-value
Age (years)				
≥ 65	162 (45)	25 (18–34)	1.180	0.197
<65	199 (55)	27 (21–36)	1	
Metastasis at initial diagnosis of RCC				
Yes	205 (57)	14 (12–20)	2.234	<0.001
No	156 (43)	46 (37–65)	1	
No. metastatic sites				
≥ 2	147 (41)	14 (11–22)	1.451	0.004
1	214 (59)	33 (25–40)	1	
Metastatic sites				
Lung				
Yes	251 (70)	25 (18–31)	1.187	0.218
No	110 (30)	33 (19–45)	1	
Lung only	129 (36)	32 (22–42)	0.811	0.123
Others	232 (64)	22 (16–30)	1	
Lymph nodes				
Yes	73 (20)	14 (11–35)	1.403	0.023
No	288 (80)	27 (22–36)	1	
Lymph nodes only	14 (4)	38 (12–59)	0.956	0.885
Others	347 (96)	25 (20–32)	1	
Bone				
Yes	104 (29)	18 (12–22)	1.708	<0.001
No	257 (71)	33 (24–42)	1	
Bone only	35 (10)	21 (14–27)	1.540	0.024
Others	326 (90)	27 (20–36)	1	
Liver				
Yes	43 (12)	12 (9–13)	1.875	<0.001
No	318 (88)	31 (22–37)	1	
Liver only	11 (3)	12 (8–24)	1.653	0.136
Others	350 (97)	27 (21–35)	1	
Prognostic metastatic group				
Liver only or bone only or >2 sites	193 (53)	16 (12–22)	1.800	<0.001
Others	168 (47)	41 (32–53)	1	
Previous nephrectomy				
No	68 (19)	8 (6–9)	4.872	<0.001
Yes	293 (81)	37 (29–44)	1	
Time from initial diagnosis to treatment				
<12 months	251 (70)	15 (12–20)	3.095	<0.001
≥ 12 months	110 (30)	65 (49–162)	1	
ECOG-PS				
≥ 1	144 (40)	12 (10–16)	2.322	<0.001
0	207 (57)	41 (32–51)	1	
Unknown	10 (3)	99 (7–69)		
Hemoglobin (mg/dL)				
<13.0/11.5	184 (51)	15 (11–19)	2.036	<0.001
≥ 13.0/11.5	140 (39)	44 (32–53)	1	
Unknown	37 (10)	36 (18–44)		
Lactate dehydrogenase				
>1.5× ULN	23 (6)	9 (6–10)	2.226	<0.001
≤ 1.5× ULN	299 (83)	28 (22–36)	1	
Unknown	39 (11)	29 (12–44)		
Corrected Ca (mg/dL)				
>10	24 (7)	11 (5–13)	2.278	<0.001
≤ 10 mg/dL	301 (83)	27 (21–35)	1	
Unknown	36 (10)	36 (18–60)		
C-Reactive protein (mg/dL)				
>0.3	174 (48)	14 (11–18)	3.031	<0.001
≤ 0.3 mg/dL	78 (22)	53 (48–118)	1	
Unknown	109 (30)	29 (20–40)		

CCRCC, clear cell renal cell carcinoma; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival; RCC, renal cell carcinoma; ULN, upper limit of normal.

Table 3. Multivariate analysis based on pretreatment factors in 361 patients who received interferon- α -based therapy

Factor	Poor prognostic category	Hazard ratio	P-value
Time from initial diagnosis to treatment	<12 months	2.596	<0.001
Hb	<13.0/11.5 mg/dL	1.681	<0.001
LDH	>1.5 \times ULN	1.883	0.012
Prognostic metastatic group	Liver only, bone only multiple metastases	1.479	0.005

Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

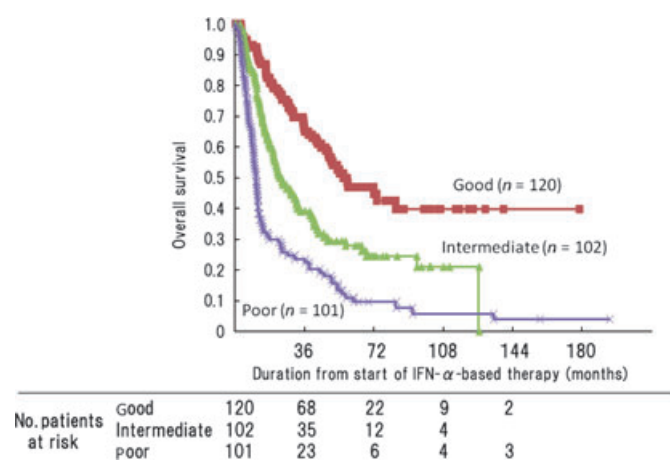


Fig. 2. Overall survival stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification ($n = 323$) into good, intermediate, and poor risk groups. Thirty-eight patients for whom one or more of the risk factors were missing were excluded from the analysis. IFN- α , interferon- α .

Table 4. Survival outcome in each risk group classified by the Japanese Metastatic Renal Cancer prognostic classification (original data)

Risk group	n (%)	Median OS (months)	2-year OS (95% CI)
Favorable	120 (33)	51	77 (72–81)
Intermediate	101 (28)	21	50 (44–55)
Poor	102 (28)	10	29 (25–34)
Unclassified	38 (11)	36	63 (58–68)

Favorable risk, poor prognostic factor = 0 or 1; intermediate risk, poor prognostic factor = 2; poor risk, poor prognostic factor = 3 or 4; CI, confidence interval; OS, overall survival.

Internal validation of the JMRC prognostic classification using the bootstrap method. Using original datasets in 361 patients, the validity of the JMRC prognostic classification was determined using the bootstrap method. Table 6 shows the results of multivariate analysis using the bootstrap method. The hazard ratio was 2.654 for the time from initial diagnosis to treatment, 1.680 for Hb, 2.042 for LDH, and 1.482 for poor metastatic site. These results were similar to the hazard ratios for the original dataset. The c-index based on bootstrap samples was 0.72, which was similar to that for the original dataset.

External validation of the JMRC prognostic classification using an independent dataset from four Japanese institutions. For external validation, the JMRC prognostic classification was applied to 136 patients with metastatic RCC treated with IFN-

α -based therapy during the same period in four institutions across Japan and OS evaluated (Table 7). All 136 patients received natural IFN- α . There were 34 (25%), 50 (37%), and 48 (35%) patients in the favorable, intermediate, and poor risk groups, respectively, and four patients (3%) could not be classified. The median OS was 56, 28, and 12 months in the favorable, intermediate, and poor risk groups, respectively. The OS rates at 2 years were 79% (95% CI 73–86%), 60% (95% CI 52–68%), and 40% (95% CI 31–48%) in the favorable, intermediate, and poor risk groups, respectively. The c-index was 0.73 when the JMRC prognostic classification was applied to independent dataset.

Discussion

The present study shows that time from initial diagnosis to treatment <1 year, anemia, elevated LDH, and poor prognostic metastatic group are important factors indicating a poor prognosis and associated with OS. By combining these four factors, we developed a JMRC prognostic classification for patients with metastatic RCC. The validity of this prognostic classification was confirmed by internal validation using the bootstrap method, as well as by external validation using data from four randomly selected institutions across Japan.

Some risk classifications have been proposed for the evaluation of the outcomes of metastatic RCC. Of these, the most widely used system is the MSKCC risk classification, which was established on the basis of data from 400 patients who underwent cytokine therapy between 1975 and 1996. The MSKCC system consists of five poor prognostic factors (time from initial diagnosis to treatment <1 year, Karnofsky performance status <80%, anemia, elevated LDH, and elevated cCa).⁽¹⁾ External validation of this risk classification was performed by the Cleveland Clinic Foundation (CCF) group, and its appropriateness has been confirmed.⁽⁹⁾ External validation of this risk classification system was also performed in Japan⁽⁷⁾ and the MSKCC risk classification system was shown to be applicable to Japanese RCC patients. However, when this classification was applied to Japanese patients, patients in the favorable risk group and those in the poor risk group accounted for 10% and 40% of all patients, respectively, a high percentage in the poor risk group compared with that in Western countries. In addition, even the poor risk group, which accounted for a high percentage of the total, had a survival period of 10 months, suggesting a marked difference between Japanese patients and patients in Western countries, even for those in the same poor risk group.⁽⁷⁾

Previous studies have demonstrated the effectiveness of cytokine therapy against pulmonary and lymph node metastases.^(15,16) Mekhail *et al.*⁽⁹⁾ reported that the number of distant metastatic lesions was one of the significant prognostic factors in patients who underwent cytokine therapy. Negrier *et al.*⁽¹⁰⁾ reported that the number of metastases and the number of organs showing metastasis were prognostic factors. In the present study, liver-only metastasis, bone-only metastasis, and multiple organ metastases were included as possible poor prognostic variables for analysis. Multivariate analysis showed that poor prognostic metastatic group is an important factor for poor prognosis in addition to time from initial diagnosis to treatment <1 year, anemia, and elevated LDH in the MSKCC risk classification system.

Using these four factors, the JMRC prognostic classification system was developed and the system was tested to determine whether it allows for appropriate classification of the outcomes of the different patient groups. Approximately one-third of patients were in each of the favorable, intermediate, and poor risk groups, with median survival periods of 51, 21, and 10 months, respectively. Comparing the JMRC

Table 5. Comparison of Japanese Metastatic Renal Cancer prognostic classification and Memorial Sloan-Kettering Cancer Center risk classification

MSKCC risk group	JMRC risk groups					
	Favorable		Intermediate		Poor	
	No. patients	Median OS (months)	No. patients	Median OS (months)	No. patients	Median OS (months)
Favorable	48	NR	0		0	
Intermediate	70	34	72	26	24	11
Poor	0		28	12	76	10

A total of 43 patients were unclassified by either the Japanese Metastatic Renal Cancer (JMRC) prognostic classification or the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification. NR, not reach; OS, overall survival.

Table 6. Multivariate analysis based on pretreatment factors in bootstrap dataset

Factor	Poor prognostic category	Hazard ratio	95% CI
Time from initial diagnosis to treatment	<12 months	2.654	1.444–3.515
Hb	<13.0/11.5 mg/dL	1.680	1.089–2.220
LDH	>1.5× ULN	2.042	0.310–2.934
Prognostic metastatic group	Liver only, bone only multiple metastases	1.482	0.981–1.925

CI, confidence interval; Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 7. Survival outcome in each risk group classified by the Japanese Metastatic Renal Cancer prognostic classification (independent data set)

Risk group	n (%)	Median OS (months)	2-year OS (95% CI)
Favorable	34 (25)	56	79 (73–86)
Intermediate	50 (37)	28	60 (52–68)
Poor	48 (35)	12	40 (31–48)
Unclassified	4 (3)	9	20 (13–27)

Favorable risk, poor prognostic factor = 0 or 1; intermediate risk, poor prognostic factor = 2; poor risk, poor prognostic factor = 3 or 4; CI, confidence interval; OS, overall survival.

classification system with the MSKCC system shows that our system can equally classify patients into three groups while overcoming the problem of the disproportion number of patients belonging to each risk group that is seen when the MSKCC risk classification system is applied to Japanese patients. This is because the JMRC classification system reclassifies the subset of patients identified by the MSKCC as having intermediate risk, but who actually have a better outcome, as having favorable risk, whereas those with a poorer prognosis are classified as having poor risk.

The JMRC prognostic classification may be applicable to many patients with metastatic RCC, but its consistency needs to be determined. Therefore, for internal validation, the bootstrap method was used with the original dataset and the hazard ratio for each poor prognostic factor used in the present study was determined and the c-index confirmed. The hazard ratio obtained using bootstrap samples was

similar to that using the original dataset, and the c-index was 0.72, which was no different. These results suggest that there is no problem with the internal consistency of the JMRC prognostic classification. Subsequently, external validation of the risk classification system was performed. Using results of 137 patients who were treated in four institutions across Japan revealed no marked differences from the results using the original dataset. The c-index for the 137 patients was 0.73, which was only 0.1 higher than that obtained using the original dataset. These results confirm the external consistency of the JMRC prognostic classification.

The results of the present study suggest that the JMRC prognostic classification is useful for Asian patients treated with cytokine therapy. However, because the present study was a retrospective analysis, there is the possibility of various biases (e.g. selection bias, treatment dose and duration of IFN- α -based therapy). Future prospective studies are needed to confirm the findings of the present study. In addition, it is not clear whether the JMRC prognostic classification system is applicable to patients undergoing molecular targeted therapy and this needs to be addressed in future studies.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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Appendix I

The members of the Hokkaido Immunotherapy Research Group are as follows: Yoshihiro Sasaki, Obihiro Kosei Hospital; Tango Mochizuki, Sapporo City Hospital; Akira Kashiwagi, Teine Keijinkai Hospital; Kouichi Kanagawa, Asahikawa City Hospital; Kinuya Matsumura, Jinyukai Urological Hospital; Tatsuya Mori, Asahikawa Kosei Hospital; Yuichiro Shinno, Otaru City Hospital; Haruo Seki, Hokkaido Urological Memorial Hospital; Kunihiro Tsuchiya, Hakodate Central Hospital; Masashi Murakumo, Kushiro Rosai Hospital; Hidenori Katano, Iwamizawa City Hospital; Junri Shindo, Kushiro City Hospital; Ichiro Takeuchi, Tomakomai City Hospital; Sosyu Sato, Ebetsu City Hospital; Takanori Yamashita, Nayoro City Hospital; Shinji Kamoda, Abashiri Kosei Hospital; Shin Suzuki, Konan Medical Center; Rintaro Machino, KKR Tonan Medical Center; Kazushi Hirakawa, Keiyukai Cancer Hospital; Osamu Nonaka, Chitose City Hospital.