CME/SAM

Relationship of Pathologic Factors to Efficacy of Sorafenib Treatment in Patients With Metastatic Clear Cell Renal Cell Carcinoma

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Key Words: Clear cell renal cell carcinoma; Metastasis; Sorafenib; Effectiveness; Growth pattern

Am J Clin Pathol April 2015;143:492-499

DOI: 10.1309/AJCPM8RJ2ECAWOGQ

ABSTRACT

Objectives: *To evaluate the predictive value of growth patterns in patients undergoing sorafenib treatment for metastatic clear cell renal cell carcinomas (CCRCCs).*

Methods: *Forty-eight patients were analyzed, each of whom underwent nephrectomy and received sorafenib treatment for metastatic CCRCC. Progression-free survival (PFS) was predicted using pathologic parameters, including pathologic stage, Fuhrman nuclear grade (FNG), the presence of a sarcomatoid component, lymphovascular invasion, tumor necrosis, and growth pattern.*

Results: *Three (6%) patients showed partial response, 20 (42%) patients showed stable disease, and 25 (52%) patients showed progressive disease. Univariate analyses demonstrated that FNG, the presence of a sarcomatoid component, tumor necrosis, and growth pattern were significantly associated with PFS. In the multivariate analysis, growth pattern was the only parameter that was significantly and independently predictive of PFS.*

Conclusions: *As a novel histologic prognostic parameter, growth pattern may be useful for predicting response to sorafenib treatment.*

Upon completion of this activity you will be able to:
- define the pathologic features of growth patterns in clear cell renal cell carcinomas (CCRCCs).
- compare various pathologic parameters to predict progression-free survival in patients with CCRCCs treated by sorafenib.
- describe the clinical significance of growth patterns in patients with CCRCCs treated by sorafenib.

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The authors of this article and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.

Questions appear on p 605. Exam is located at www.ascp.org/ajcpcme.

Major clinical trials have demonstrated that tyrosine kinase inhibitors (TKIs) provide efficacious therapies for clear cell renal cell carcinoma (CCRCC).[1-4] Consequently, TKI therapies have become standard treatments.[5,6] Sorafenib is an orally administered multitargeted TKI that acts through vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors and prevents neovascularization.[7] It has been demonstrated that sorafenib confers significant improvements to progression-free survival (PFS) in patients with metastatic CCRCC.[1] However, responses and PFS times vary considerably among patients who receive sorafenib treatment, suggesting that treatment selection could be improved substantially. Prognostic parameters can help to optimize strategies for treatment. Several previous studies of metastatic CCRCC have identified prognostic parameters for sorafenib-based therapies.[2,3,8] These prognostic parameters have generally been clinical features.

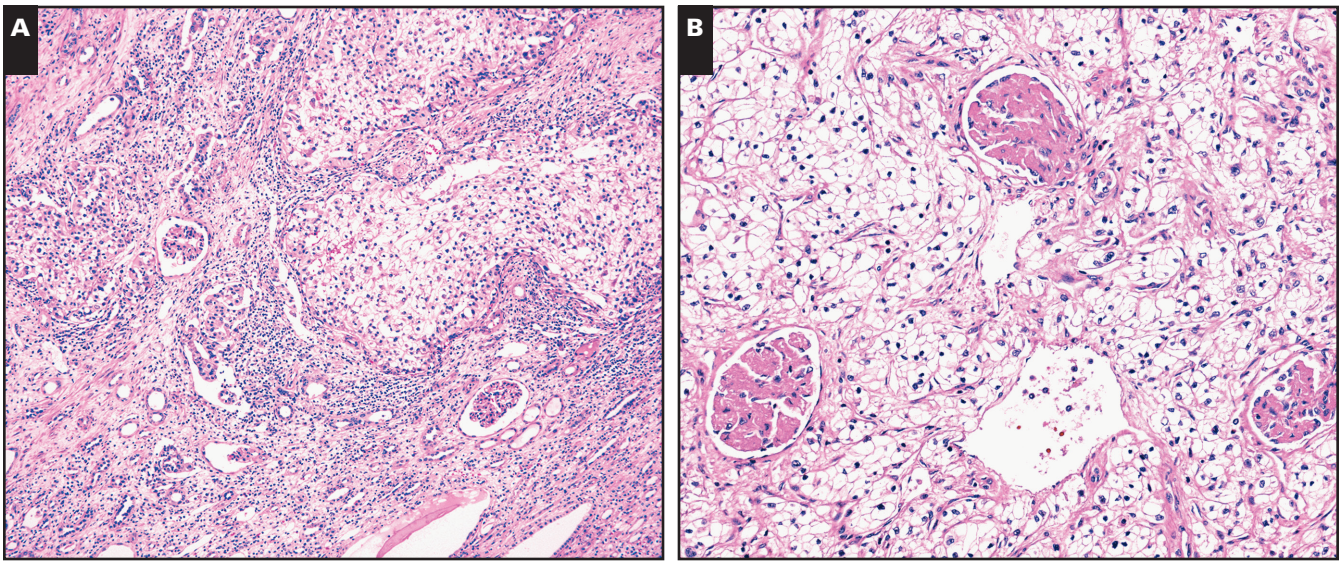

Image 1 Representative examples of the growth patterns.[14] **A**, Tumor cells extensively infiltrate normal renal tissue (H&E, ×100). **B**, Normal renal tissue (glomeruli) is present in the tumor (H&E, ×400).

Several pathologic features also provide useful predictions of patient outcomes. Some of these pathologic features have influenced the designs of clinical trials. Indeed, it has been reported that pathologic stage (pT), Fuhrman nuclear grade (FNG), sarcomatoid component, and tumor necrosis are predictive of prognostic outcomes in cases of CCRCC.[9-11] Recently, the presence of a sarcomatoid component in CCRCC was shown to be a negative predictive parameter in TKI treatment.[3] In a study of sorafenib treatment for CCRCC, carbonic anhydrase 9 expression was not found to be predictive of treatment efficiency.[12] With the exception of these studies, however, limited data are available concerning pathologic parameters that are predictive of patient outcomes in TKI-treated cases of metastatic CCRCC.

Recently, we have demonstrated that growth pattern, a pathologic parameter, is independently predictive of the outcomes of patients with CCRCC.[13,14] However, no studies have investigated whether growth pattern could be used to predict the outcomes of patients with CCRCC who are receiving TKIs. Accordingly, we have retrospectively investigated the set of pathologic parameters that may be predictive of response rates and PFS in cases of metastatic CCRCC that are treated with sorafenib.

Materials and Methods

Patient Selection

Sixty-five patients were enrolled in this study, each of whom had metastatic CCRCC after radical nephrectomy and received sorafenib between May 2008 and January 2011 at either Nagoya University Hospital or one of the affiliated hospitals. Medical records from all patients were available for review. Seventeen patients were excluded because sufficient follow-up data were lacking, pathologic information was incomplete, or low-dose treatments had been provided. Specifically, cases were excluded because of the poor quality of clinical data regarding sorafenib administration (n = 7), because no glass slides were available (n = 6), and because severe adverse events had resulted in the cessation of treatment (n = 4). The cases with low-dose treatments included treatment interruptions or dose reductions below 400 mg every other day, for example, as a result of drug-related toxicities. After excluding patients for the noted reasons, a total of 48 patients were available for analysis.

This retrospective study was approved by the institutional review boards of Nagoya University.

Pathologic Examination

For each CCRCC, all initial H&E-stained slides were reviewed by a single expert uropathologist (T.T.), who was blinded to the patients' clinical outcomes and disease response. A median of seven (range, 2-15) slides were reviewed per patient. The analyzed pathologic parameters were as follows: FNG, sarcomatoid component, lymphovascular invasion (LVI), tumor necrosis, and growth pattern. Recently, growth pattern has been proposed as a novel pathologic prognostic factor for CCRCC.[13,14] In brief, the presence of an "expansive pattern" was defined as a well-circumscribed tumor margin without the presence of normal renal tissue in the tumor, and the presence of an "infiltrating pattern" was defined as an ill-circumscribed tumor margin with cancer cells that were extensively infiltrating normal renal tissues **Image 1**.[14] All cases were defined as having either an expansive pattern or an infiltrating pattern.

DOI: 10.1309/AJCPM8RJ2ECAWOGQ

Table 1
Demographic, Clinical, and Pathologic Features of the Patient Cohort (n = 48)[a]

Characteristic	Value
Sex, male/female	37/11
Age, mean (range), y	64 (31-80)
Performance status, 0/1/2/3	23/24/1/0
Initial state at the time of sorafenib treatment, distant metastasis/local recurrence	22/26
MSKCC risk factor, favorable/intermediate/poor	9/27/12
Metastatic sites, lung/bone/lymph nodes/others	43/13/8/20
No. of metastatic sites, 1/2/≥3	25/9/14
Prior treatment, INFα only/INFα + IL-2/INFα + others	41/10/1
Pathologic parameter	
Sarcomatoid component	10
Tumor necrosis	37
LVI	24
Growth patterns, expansive/infiltrating	37/11
FNG, I/II/III/IV	0/16/19/13

FNG, Fuhrman nuclear grade; IL-2, interleukin 2; INFα, interferon α; LVI, lymphovascular invasion; MSKCC, Memorial Sloan-Kettering Cancer Center.
[a] Values are presented as numbers unless otherwise indicated.

Treatment Response and Outcome Parameters

The patients were classified according to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk criteria.[15] The primary study end point was PFS, and the secondary end points were overall survival (OS) and the rate of best response. All end points were evaluated in accordance with the revised Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).[16]

Statistical Analyses

PFS and OS survival rates were estimated using the Kaplan-Meier method. Log-rank tests were used to compare the objective response rates between patient subgroups. We used univariate and multivariate Cox regression to assess the prognostic significance of the examined pathologic characteristics and to estimate associations between these characteristics and patient survival. Statistical significance was defined as $P < .05$. The tumor maximum variations, according to five pathologic parameters, were compared using unpaired two-sample Mann-Whitney U tests. SPSS version 18 (SPSS, Chicago, IL) was used for all statistical analyses.

Results

Patient Characteristics

The descriptive clinicopathologic characteristics of the study cohort are summarized in **Table 1**. A total of 48 patients (37 men and 11 women; median age, 64 years; range, 31-80 years) were included in our analysis. Twenty-two patients had distant metastases at the time of nephrectomy, and 26 patients experienced recurrence after nephrectomy. Forty-one patients underwent pretreatment by interferon α.

Variability in Treatment Responses, PFS, and OS

The median duration of sorafenib treatment was 3.3 months (range, 0.5-16.5 months). The median duration of follow-up was 13.3 months (range, 0.6-17.2 months). Nineteen (40%) patients died of the disease. Sixteen (33%) patients showed tumor shrinkage from baseline values. One patient achieved complete response (CR), and two patients achieved partial response (PR). Interestingly, in the three patients who showed CR or PR, all metastatic lesions were limited to the lung. Nineteen (40%) patients showed stable disease (SD), and 26 patients (54%) showed progressive disease. Overall, 22 of the cases demonstrated CR, PR, or SD, none of which contained a sarcomatoid component and 20 of which showed an expansive growth pattern. The prevalences of growth pattern, tumor necrosis, the presence of a sarcomatoid component, and LVI each differed significantly according to treatment response ($P < .001$) **Figure 1**.

Prognostic Values of Pathologic Characteristics

The median PFS time was 5.9 months, and the median OS time was estimated to be 15.7 months. Univariate analyses demonstrated that FNG ($P = .001$), the presence of a sarcomatoid component ($P = .011$), growth pattern ($P = .005$), and tumor necrosis ($P = .005$) were significantly associated with PFS **Table 2** and **Figure 2**. Multivariate analysis demonstrated that growth pattern was the only parameter that was significantly and independently predictive of PFS ($P = .019$). Although univariate analyses demonstrated FNG ($P = .001$), sarcomatoid component ($P = .001$), and tumor necrosis ($P = .029$) were significantly associated with OS, no parameters were significantly and independently associated with OS in our multivariate analysis **Table 3**.

Discussion

Sorafenib, an oral agent, is a Raf kinase inhibitor that acts on both VEGF and PDGF receptors, simultaneously targeting both cancer cell proliferation and angiogenesis.[17] In a phase III randomized, placebo-controlled study (the Treatment Approaches in Renal Cancer Global Evaluation Trial [TARGET] study), sorafenib was observed to significantly increase PFS in patients with advanced renal cell carcinoma.[1] In a phase II study of patients with advanced renal cell carcinoma in Japan, Akaza et al[18] reported that 80.5% of the patients who received sorafenib therapy experienced tumor shrinkage. However, the median duration of PFS was 5.9 months in our study, which resembled the median PFS observed in the TARGET study. Although

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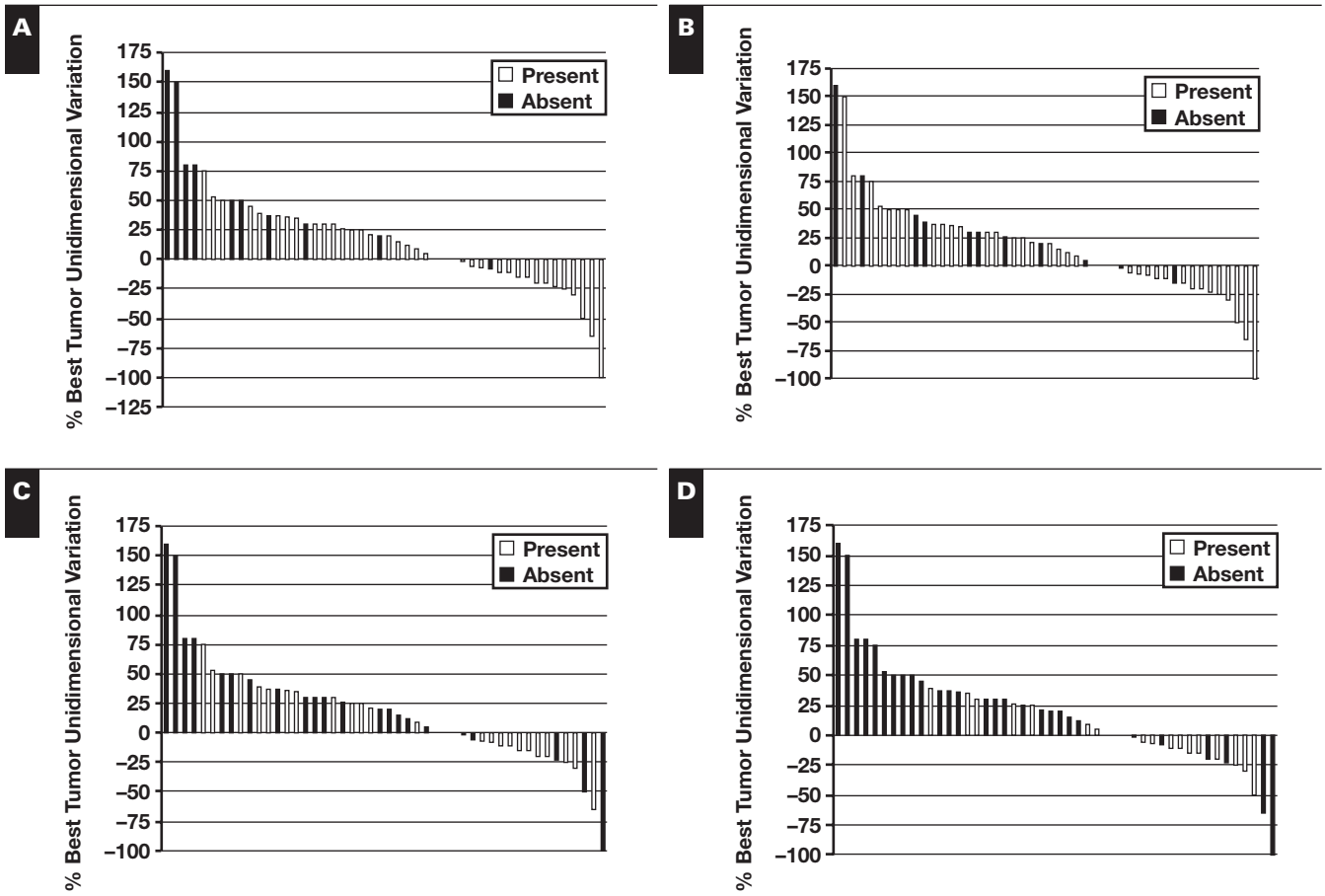

Figure 1 The best percentage variation in the sum of the longest diameters of the target lesions in patients receiving sorafenib. Each bar represents one patient. Results are presented for patients grouped by the following pathologic parameters: (**A**) sarcomatoid component ($P < .001$), (**B**) growth pattern ($P < .001$), (**C**) lymphovascular invasion ($P < .001$), and (**D**) tumor necrosis ($P < .001$).

Table 2
Univariate and Multivariate Analyses of Progression-Free Survival

	Univariate		Multivariate	
Pathologic Parameter	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Sarcomatoid component, absence vs presence	2.794 (1.261-6.193)	.011	1.299 (0.417-4.048)	.651
Tumor necrosis, absence vs presence	4.233 (1.551-11.554)	.005	2.503 (0.656-9.548)	.179
LVI, absence vs presence	2.079 (0.948-4.555)	.068		
Growth pattern, expansive vs infiltrating	3.208 (1.412-7.289)	.005	3.070 (1.194-7.894)	.019
FNG	7.983 (2.322-27.441)	.001	1.404 (0.595-3.315)	.439
2	[Reference]			
3	4.570 (1.415-14.757)	.011		
4	2.140 (1.242- 3.690)	.006		

CI, confidence interval; FNG, Fuhrman nuclear grade; HR, hazard ratio; LVI, lymphovascular invasion.

sorafenib is a second-line drug for metastatic and/or unresectable CCRCC, recent studies have demonstrated that the OS efficacy of sorafenib is equivalent to the OS efficacies of the TKIs axitinib, tivozanib, and dovitinib.[19-21] Therefore, current clinical practice could benefit from investigations of parameters that may be predictive of sorafenib's efficacy.

In this study, we analyzed the PFS and OS of patients receiving sorafenib for metastatic or unresectable CCRCC. We found that growth pattern was the only parameter that was significantly and independently predictive of PFS in patients receiving sorafenib. Recently, we reported that the infiltrating pattern was related to poor clinical outcomes in patients with CCRCC.[13,14] In the present study, we further

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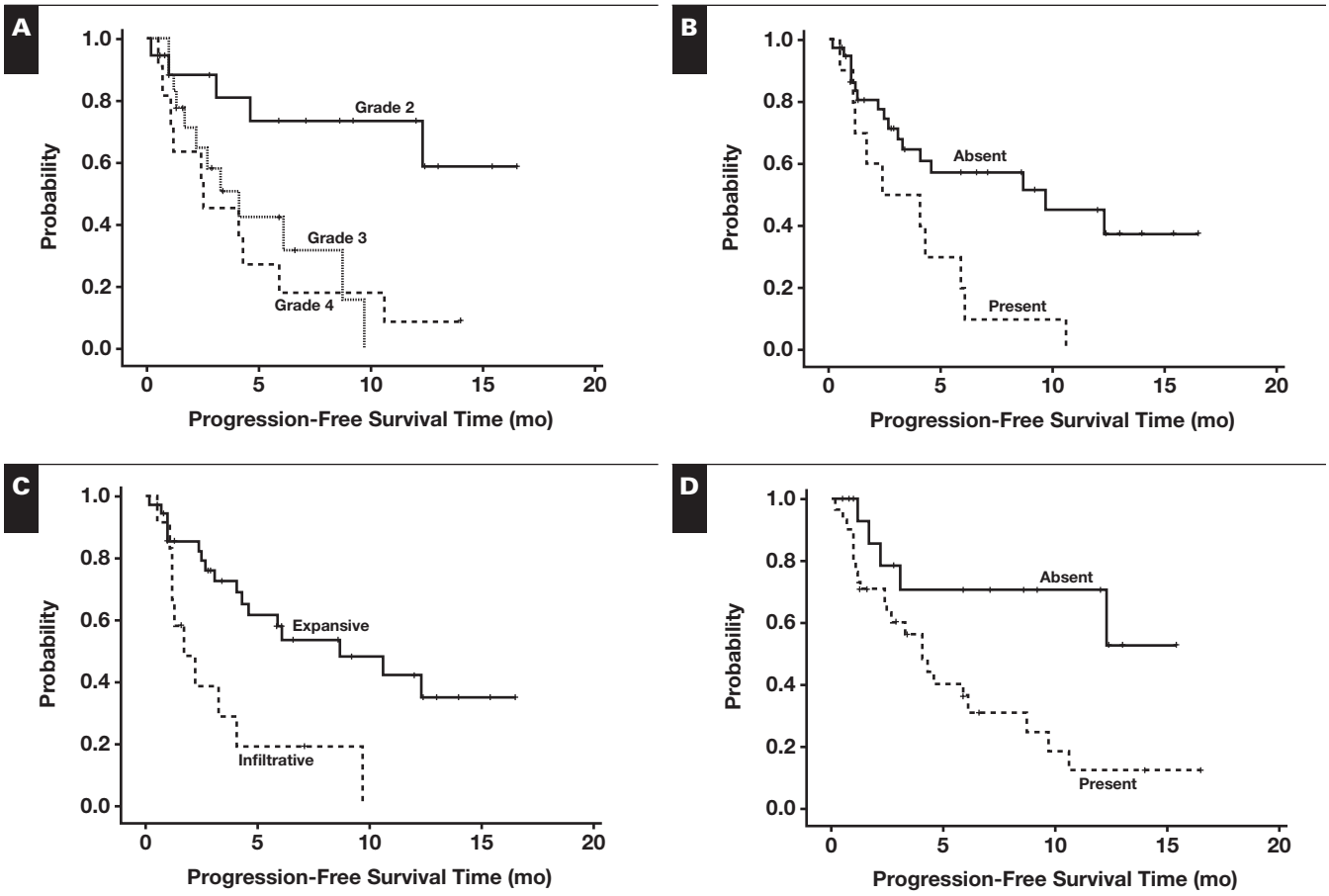

Figure 2 Kaplan-Meier progression-free survival curves for patients who had clear cell renal cell carcinoma and received sorafenib, according to (**A**) Fuhrman nuclear grade ($P = .001$), (**B**) sarcomatoid component ($P = .011$), (**C**) growth pattern ($P = .005$), and (**D**) tumor necrosis ($P = .005$).

Table 3
Univariate and Multivariate Analyses of Overall Survival

	Univariate		Multivariate	
Pathologic Parameter	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Sarcomatoid component, absence vs presence	3.615 (1.353-9.656)	.001	1.464 (0.435-4.932)	.538
Tumor necrosis, absence vs presence	3.974 (1.15-13.728)	.029	1.915 (0.438-8.366)	.388
LVI, absence vs presence	2.384 (0.929-6.119)	.071	ND	ND
Growth pattern, expansive vs infiltrating	2.425 (0.949-6.196)	.064	ND	ND
FNG	2.729 (1.518-4.905)	.001	2.010 (0.872-4.631)	.101
2	[Reference]			
3	4.860 (1.241-19.041)	.023		
4	3.182 (1.598-6.335)	.001		

CI, confidence interval; FNG, Fuhrman nuclear grade; HR, hazard ratio; LVI, lymphovascular invasion; ND, not done.

demonstrated that this new pathologic parameter is prognostic for patients treated with sorafenib. We observed an 8.7-month median duration of PFS in patients with an expansive pattern, which was considerably longer than the 1.7-month median PFS in patients with an infiltrating pattern. Therefore, the infiltrating pattern could be a critical pathologic parameter that is predictive of poor PFS in patients receiving sorafenib. We demonstrated that most CR, PR, and SD cases showed an expansive growth pattern. Since sorafenib has severe side effects,[1] the ability to predict sorafenib's efficacy in advance could be beneficial. We believe that the recognition of growth pattern will provide information that is useful for patient care. However, we were not able to demonstrate that growth pattern is also a negative prognostic parameter for OS. The limited duration of follow-up may or may not have obscured associations between growth pattern and OS;

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further investigation would be necessary to resolve this matter. Furthermore, it is not clear exactly how the therapeutic abilities of TKIs differ between the expansive and infiltrative patterns. Further studies are necessary to elucidate the underlying mechanism.

Many studies have evaluated various clinical parameters[8,15] and pathologic parameters[9-11] that might predict clinical outcomes or prognosis. Several prognostic models have been developed to predict outcomes after nephrectomy in patients with CCRCC. These include the stage, size, grade, and necrosis (SSIGN) score; the University of California, Los Angeles Integrated Staging (UISS) system; and the Kattan nomogram.[9,22,23] Frank et al[9] developed the SSIGN score to predict cancer-specific survival in patients treated for CCRCC with radical nephrectomy. The UISS grading system predicts patient outcomes, based on TNM staging, FNG, and Eastern Cooperative Oncology Group performance status.[22] Kattan's group proposed a new nomogram that includes six parameters (clinical symptoms, tumor size, pT, FNG, tumor necrosis, and LVI).[23] However, these nomograms did not take into account responses to the newer molecular targeted therapies. It has recently been reported that some molecular tumor markers provide additional prognostic information in the TKI era. For example, Heng et al[24] reported that neutrophil count and platelets were prognostic factors, in addition to four of the five prognostic factors that were identified by MSKCC. They also revaluated the associations between these six clinical factors and survival in patients treated with the newer molecular targeted agents, such as sunitinib, sorafenib, and bevacizumab. However, there are few studies regarding pathologic parameters that could be predictive of outcomes for patients receiving TKIs, with the exception of a prior study of a sarcomatoid component.[3] Therefore, we evaluated the predictive values of pathologic parameters with regard to the clinical outcomes of patients with advanced CCRCC who were treated with sorafenib.

Many studies have shown that high FNG is one of the most ominous prognostic parameters for CCRCC.[9-11,22,23,25] This phenomenon was also confirmed in our study, suggesting that patients with high FNG could be poor responders to sorafenib treatment. In addition, we also observed poor response to sorafenib therapy in patients whose cases involved a sarcomatoid component (median PFS, 2.4 months). In a study of cases treated with TKIs, Golshayan et al[3] reported that PFS and OS were associated with sarcomatoid component content volumes exceeding 20%. However, as Golshayan et al[3] noted, the volume of the sarcomatoid component may have depended on the extent of tissue sampling from the CCRCC during initial management, which could have differed systematically across patients, leading to selection bias. The area of the sarcomatoid component in H&E slides may not be representative of the overall fraction of the sarcomatoid component in the whole tumor. For these reasons, we evaluated only the presence or absence of a sarcomatoid component in the present study. We recently showed that sorafenib and other TKIs induce vasculopathies in tumor vessels, which themselves lead to tumor necrosis.[26] We also demonstrated that TKIs are ineffective for sarcomatoid components because these components contain few tumor vessels, which are the main targets of TKIs. The findings of the present study support our hypothesis that the main targets of TKIs are tumor vessels.

Some studies have proposed that LVI is a prognostic parameter for the recurrence of CCRCC.[25,27] However, this parameter was not able to predict response to sorafenib in the present study. Parameters that are predictive of recurrence may not always be predictive of response to TKI therapy. Similarly, the prognostic value of tumor necrosis remains controversial.[9,28] Some groups have suggested that tumor necrosis provides an indication of aggressive renal cell carcinoma biology.[9,29] In the present study, the group of patients with tumor necrosis had poor response to sorafenib, with a mean PFS of 4.1 months. Although tumor necrosis was a significant negative prognostic parameter in our univariate analysis, it did not remain significant in our multivariate analysis. Further studies are necessary to elucidate the usefulness of tumor necrosis as a predictor of TKI response.

FNG, sarcomatoid component, growth pattern, LVI, tumor necrosis, and other pathologic parameters have the potential to be prognostically useful because they can be assessed easily at the time of nephrectomy. Our results may help clinicians select those patients who are most likely to respond to TKI agents, such as sorafenib. Sorafenib treatment is recommended for patients who have metastatic renal cell carcinoma, whose disease is refractory to cytokines, and who meet the MSKCC criteria for favorable or intermediate risk.[5,6] The results of our study also suggest that histologic information could have a positive impact on drug selection for individual patients. In the first stage of targeted therapy, other targeted agents (such as the mammalian target of rapamycin inhibitors) should be considered when ominous predictive parameters are identified, including infiltrating growth patterns and high FNG. Our study demonstrated that pathologic parameters can help to predict response and PFS in patients receiving sorafenib therapy. Further studies are necessary to validate the significance of these pathologic parameters in patients who are administered other molecular targeted agents.

There are several limitations to this study. First, this study is vulnerable to typical biases found in retrospective analyses as a consequence of data incompleteness, the absence of a study design, and the inevitable variation in clinical management among the 11 participating hospitals. Second, nephrectomy specimens were not handled in a uniform manner, and

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a mean of only seven slides were available per patient. The features identified on these slides may not have been fully representative of the whole CCRCC tumor. Third, this study included a limited number of enrolled patients. Despite these limitations, our study is the first to identify growth pattern as adversely predictive of response to sorafenib treatment in patients with metastatic CCRCC.

In conclusion, the present study is the first to assess the relationships between pathologic parameters of CCRCC and clinical outcomes in patients receiving sorafenib therapy. Our results indicate that growth pattern is an independent predictor of PFS. This information could be beneficial to clinicians who are deciding whether to select sorafenib treatment in cases of metastatic and/or unresectable CCRCC.

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Acknowledgments: The following contributors and institutions were involved in this study: Koichi Suzuki, MD, of Japanese Red Cross Nagoya Daiichi Hospital, Toshikazu Otani, MD, of Chubu Rosai Hospital, Yoshio Tsumura, MD, of Ichinomiya Municipal Hospital, Toshinori Nishikimi, MD, of Japanese Red Cross Nagoya Daini Hospital, Norhisa Takeuchi, MD, of Narita Memorial Hospital, Hideo Kakei, MD, of Yokkaichi Municipal Hospital, Norhisa Fukuhara, MD, of Kasugai Municipal Hospital, and Akitoshi Fukatsu, MD, of Komaki City Hospital.

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