Original Article

Pretreatment Assessment of Tumor Enhancement on Contrast-Enhanced Computed Tomography as a Potential Predictor of Treatment Outcome in Metastatic Renal Cell Carcinoma Patients Receiving Antiangiogenic Therapy

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BACKGROUND: Tumor vascularity is a potential predictor of treatment outcomes in metastatic renal cell carcinoma (mRCC), and contrast enhancement of tumors in computed tomography (CT) is correlated significantly with microvessel density. In this study, the authors investigated whether tumor enhancement in contrast-enhanced CT (CECT) is useful for predicting outcomes in patients with mRCC who are receiving antiangiogenic therapy. **METHODS:** Attenuation values were reviewed retrospectively on CECT images of all metastatic lesions in 66 patients from February 2007 to November 2008. All patients received a tyrosine kinase inhibitor (either sunitinib or sorafenib). Tumor response was evaluated on CECT studies every 12 weeks. The authors analyzed the association between contrast enhancement and treatment outcomes, including objective response, tumor size reduction rate, time to response, and time to progression. **RESULTS:** In 46 patients, 198 metastatic lesions were assessed. Tumor size was reduced in 140 lesions (70.7%) and was increased in 58 lesions (29.3%). The mean reduction in size was 23.8%. The overall mean time to response and the time to progression were 8.6 months and 16.4 months, respectively. In multivariate analyses, tumor enhancement and enhancement pattern were associated with objective responses ($P = .003$ and $P = .028$, respectively). In addition, tumor enhancement was associated with tumor size reduction ($P = .004$). In Cox proportional hazards models, only tumor enhancement was associated significantly with the time to size reduction and progression-free survival ($P = .03$ and $P = .015$, respectively). **CONCLUSIONS:** Tumor enhancement on CECT images was associated with treatment outcomes and was identified as a potential predictor of treatment outcomes after antiangiogenic therapy in patients with mRCC. ***Cancer* 2010;116:2332–42.** © *2010 American Cancer Society.*

KEYWORDS: renal cell carcinoma, metastasis, targeted therapy, computed tomography, attenuation, contrast enhancement, response, prognosis.

The incidence and mortality rates of renal cell carcinoma (RCC) have been rising steadily worldwide at a rate of ~2% to 3% per decade.[1,2] The annual incidence of metastatic RCC (mRCC) in major European countries, the United States, and Japan ranges from 1500 to 8600 cases.[2] However, treatment options are few because of the high resistance of these tumors to conventional chemotherapy and radiotherapy. Although cytokine-based therapies have produced response rates of 10% to 20% in patients with mRCC, their overall clinical value is limited.[3]

Targeted therapy recently has evolved as a treatment for malignancy and has changed the treatment paradigms for advanced or metastatic disease in several malignancies, including mRCC. This innovation is based on a better understanding of cell signal transduction and the molecular pathways of growth factors and receptors associated with tumor

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angiogenesis. Targeted agents inhibit angiogenesis, reducing tumor growth and progression through the inhibition of tyrosine kinase activity of growth factor receptors. Treatment of mRCC with sunitinib and sorafenib has improved response and prolonged progression-free survival significantly.[4-7]

Several clinical factors are associated with outcome in patients with mRCC, including performance status, disease-free interval, number of metastatic sites, and laboratory variables like hemoglobin, calcium, and lactate dehydrogenase levels.[8-10] Although recent studies suggest that these factors remain pertinent,[11-13] because cytokine-based therapy and targeted therapy have different mechanisms of action, optimal clinical factors associated with outcomes of targeted therapy in mRCC should be reinvestigated. Theoretically, tumor vascularity may be a predictive factor for outcomes of targeted therapy. Preliminary results with serum measures, including plasma vascular endothelial growth factor (VEGF) and circulating endothelial cells, have produced only modest success and are in relatively early stages of refinement.[14,15] Microvessel density may be an optimal predictive factor for outcomes of antiangiogenic therapy, but the difficulty of applying it to all lesions means that it has limited widespread use in clinical practice.[16] Other methods for the assessment of tumor vascularity, such as molecular imaging or measures of blood volume or flow change using magnetic resonance imaging (MRI), have been proposed but remain in the experimental stage.[15,17-19]

The imaging method that is used most commonly to evaluate metastatic lesions during treatment is contrast-enhanced computed tomography (CECT). Several studies have demonstrated that tumor enhancement on CECT is correlated significantly with microvessel density, a pathologic marker that represents tumor vascularity in RCC.[16,20] Therefore, contrast enhancement of metastatic lesions may be a predictive factor for outcome after targeted therapy in patients with mRCC. However, to our knowledge, the association between tumor enhancement on CECT and outcomes of targeted therapy has not been investigated. In the current study, we examined whether tumor enhancement on CECT could predict treatment outcomes after targeted therapies in patients with mRCC.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the institutional review board of the Center (NCCNCS-09-217). By using a kidney cancer database that was collected prospectively by the Center, we identified patients who received tyrosine kinase inhibitor (TKI) therapy for mRCC from February 2007 to November 2008. The inclusion of patients in this study was subject to the following criteria: histologic confirmation of a clear cell type tumor component using tissue biopsies or resection of primary renal lesions, the presence of measurable metastatic tumors that measured >10 mm in greatest dimension, the use of TKIs for initial targeted therapy, at least 2 cycles of TKI therapy, the existence of follow-up CECT images after the initial 2 cycles of TKI therapy, and the use of chest or abdominal CECT scans as the follow-up imaging method. We identified 66 patients who received TKI therapy. Of these, 20 were excluded for the following reasons: follow-up of <2 cycles in 8 patients, discontinuation of TKIs because of toxicity before 2 cycles in 6 patients, loss of follow-up before the first response evaluation in 4 patients, and the use of nonenhanced CT or MRI instead of CECT because of impaired renal function in 2 patients. Forty-six patients met the criteria for inclusion in this study.

Tyrosine Kinase Inhibitor Therapy

We followed the protocols of phase 3 trials of sunitinib and sorafenib for administration schedules.[4,5] The patients received 1 of 2 treatment regimens: 1) sunitinib maleate (Sutent; Pfizer Pharmaceuticals Inc., Seoul, Korea) administered orally at a dose of 50 mg once daily, taken without regard to meals, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment; or 2) sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Inc., Seoul, Korea) administered orally at a dose of 400 mg twice daily in continuous 6-week cycles.[4,5] TKIs were discontinued temporarily when grade 3 or 4 toxicity occurred according to National Cancer Institute Common Toxicity Criteria version 3.0, and continuation depended on whether the patient recovered from toxicity. Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[21]

Computed Tomography Imaging Protocol

Patients underwent baseline CECT scans before the initiation of antiangiogenic treatment and received CECT scans for response evaluation of metastatic lesions every 12 weeks after treatment began, regardless of the TKI administered. CT imaging was performed using 4-channel and 16-channel MDCT scanners (Mx 8000: Marconi Medical Systems, Tel Aviv, Israel; and LightSpeed Pro 16:

GE Healthcare, Milwaukee, Wis, respectively). Images were obtained in a craniocaudal direction.[22] A CT scan was performed before contrast injection. Patients were administered intravenous contrast material (Iopromide, Ultravist 300; Schering, Berlin, Germany) through an antecubital vein using a mechanical injector (120 mL at 3 mL per second). Scanning for early phase images began 35 seconds after the start of intravenous contrast injection either from the lower thorax to the lower pelvis or from the neck to the upper abdomen. The following scanning parameters were used for the Light Speed Ultra CT scanner: peak tube voltage, 120 kVp; tube current, 120 to 400 mA; rotation time, 0.5 seconds; reconstruction thickness, 2.5 mm; and detector configuration, 16-detector rows with a pitch of 0.938. The following parameters were used for the MX 8000 scanner: peak tube voltage, 120 kVp; tube current, 140 mA; rotation time, 0.75 seconds; reconstruction thickness, 3.2 mm; and detector configuration, 4-detector rows with a pitch of 1.75.

Evaluation of Tumor Enhancement

All images were examined using a picture archiving and communication system, which displayed image data on monitors, by 2 radiologists (D.C.J. and H.J.C.) with 6 years and 8 years of experience in uroradiology, respectively. To obtain attenuation values, quantitative evaluation of regional enhancement was performed by manual measurements using a round or ovoid, manually controllable region of interest (ROI) placed in the center of metastatic nodules by consensus between the 2 radiologists. Circular ROIs $>mm^2$ were drawn to encompass as much of the nodule as possible, covering >50% of the nodule but excluding peripheral areas to avoid partial volume effects from adjacent normal parenchyma. In addition, calcification, blood vessels, and necrotic and cystic areas were excluded from ROI measurements as much as possible. The attenuation values of the ROIs were measured an average of 3 times.

Data Collection

Baseline patient data, including age, sex, Karnofsky performance status, history of primary tumor removal, histologic type of the primary tumor, histologic type of metastases, history of cytokine-based therapy, type of TKI, number of metastases, and levels of serum hemoglobin, serum calcium, corrected calcium,[9] and lactate dehydrogenase, were collected from patient interviews and reviews of medical records. Tumor characteristics, including metastatic site, tumor size, growth pattern, existence of necrosis, enhancement pattern, and quantitative contrast enhancement measurements, were evaluated from reviews of the serial CECT images. Brain lesions were excluded in this study. Blastic bone lesions were excluded in principle; however, lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that could be evaluated by CT were considered measurable lesions when the soft tissue component fulfilled the definition of measurability.[23] Tumor size was defined as the greatest dimension of the tumor lesion. Round or lobulated tumors with clear margins were classified as conglomerated, and tumors with irregular shapes or margins were classified as infiltrative. The existence of necrosis was defined as the presence of a nonenhanced portion within the tumor lesion. Enhancement patterns were classified as either homogeneous or heterogeneous. Homogenous enhancement was defined as an even distribution of contrast uptake within an enhanced portion of a lesion, and heterogeneous enhancement was defined as an unequal distribution of contrast uptake within an enhanced portion of a lesion. A consensus between the 2 radiologists was required to classify each enhancement pattern. Tumor enhancement was defined as the difference in Hounsfield units (HUs) between nonenhanced and enhanced phases on CECT scans.

Statistical Analyses

The first endpoint of the study, the objective response of individual metastatic lesions, was evaluated using 2 different methods. Objective responses initially were classified as either responsive or nonresponsive according to RECIST guidelines. A chi-square test or Fisher exact test was performed for binomial variables, and biserial correlation analysis was used for continuous variables. Logistic regression was used in multivariate analyses. Objective response was considered a continuous variable, with the tumor size reduction rate calculated as follows: (final reduced size − initial size)/initial size. Independent Student *t* tests and analyses of variance were used in univariate analysis for binomial variables, and correlation coefficient analyses were used for continuous variables. Multivariate linear regression analysis was used in multivariate analysis. A receiver operating characteristic (ROC) curve was used to summarize the accuracy of tumor enhancement on CECT and to evaluate the true-positive rate against the false-positive rate for the different possible cutoff points of the CECT attenuation value. The area under the curve (AUC) was calculated. According to the different cutoff

points, sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

To evaluate the time to response of individual metastatic lesions, we used the Kaplan-Meier method and a Cox regression model in univariate survival analysis and a Cox hazard regression model in multivariate survival analysis. The time to size reduction was defined as the time from the initiation of TKIs to a reduction >30% in the initial tumor size. The second endpoint of the study was the time to progression of individual metastatic lesions, which was defined as the time from the initiation of TKIs to an increase >20% in the initial tumor size. The Kaplan-Meier method and a Cox regression model used in univariate survival analysis, and a multivariate Cox hazard regression model was used in multivariate survival analysis.

To control for individual confounding factors in the analysis of metastatic tumors, tumor variables were adjusted with respect to the patient variables using multivariate analysis. Patient variables were used only for statistical adjustment and, thus, were not interpreted as predictors. All multivariate analyses used variables that were significant ($P < .05$) in the univariate analyses. Statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 for Windows (SPSS Inc., Chicago, Ill). All tests were 2-sided and performed at the 5% significance level.

RESULTS

Patient Characteristics

Table 1 lists the clinical and pathologic characteristics of the 46 patients. The median follow-up was 15 months (range, 3-40 months), and the median number of cycles of TKI therapy was 4 (range, 2-13 cycles). Overall, 14 patients (30.4%) responded to TKI therapy. There were no complete responses; however, a partial response was observed in 14 patients (30.4%). Stable disease was observed in 17 patients (40.0%), and progression was observed in 15 patients (37.5%). In 22 patients (47.8%), the responses were identical for all individual metastases; however, in 24 patients (52.2%), the responses of individual metastatic lesions varied, with mixed responses observed among patients who had lesions within the same organ. In addition, responding and nonresponding lesions within the same organ occurred in 10 patients (21.7%), and lesions of increasing and decreasing size were observed in 12 patients (26.1%).

Table 1. Patient Characteristics

Characteristic	No. of Patients (%)
Total	46 (100)
Sex	
Men	33 (71.7)
Women	13 (28.3)
Median age [range], y	59 [32-74]
Karnofsky performance status, %	
90	18 (39.1)
80	16 (34.8)
70	8 (17.4)
60	4 (8.7)
Histologic type	
Primary renal tumor	
Clear cell	37 (80.4)
Clear cell with SD	2 (4.3)
Mixed	7 (15.2)
Metastases	
Clear cell	24 (52.2)
Clear cell with SD	3 (6.5)
Mixed	1 (2.2)
Unclassified	9 (19.6)
Insufficient or missing data	9 (19.6)
Median no. of metastases [range]	4 [1-30]
Removal of primary tumor	
Cytoreductive nephrectomy	30 (65.2)
No removal	16 (34.8)
History of cytokine-based therapy	
IL-2 and IFN-α	11 (23.9)
IFN-α	11 (23.9)
No history	24 (52.2)
Type of tyrosine-kinase inhibitor	
Sunitinib	29 (63)
Sorafenib	17 (37)
Baseline serum laboratory findings: Median [range]	
Hemoglobin, g/dL	11.4 [7.6-18.3]
Total calcium, mg/dL	9.3 [7.9-11.3]
Corrected calcium, mg/dL	8.7 [7.7-11.1]
Lactate dehydrogenase, U/L	174 [88-792]

SD indicates sarcomatoid differentiation; IL-2, interleukin-2; IFN- α, interferon alpha.

Characteristics of Metastatic Tumors

Table 2 lists the radiologic characteristics of 198 metastatic lesions. Tumor size was reduced in 140 lesions (70.7%) and increased in 58 lesions (29.3%). The mean (±standard deviation) reduction in size was 23.8% ± 56.6%. Tumor size was reduced by >30% in 91 metastatic lesions (46%) and by >50% in 63 metastatic lesions (31.8%). Ninety-three lesions (47%) remained stable, and 27 lesions (13.6%) progressed. The mean (±standard

Table 2. Characteristics of Individual Metastatic Lesions

Characteristic	No. of Patients (%)
Total	198 (100)
Sites	
Lung	85 (42.9)
Mediastinum	41 (20.7)
Lymph node	22 (11.1)
Pleura	18 (9.1)
Bone	10 (5.1)
Muscles	6 (3)
Adrenal gland	6 (3)
Liver	4 (2)
Others	6 (3)
Size, mm	
Mean ± SD	22.2 ± 15.1
Median [range]	17.8 [10.0-110.9]
Growth pattern	
Conglomerated	173 (87.4)
Infiltrative	25 (12.6)
Necrosis	
Absent	162 (81.8)
Present	36 (18.2)
Enhancement pattern	
Homogenous	152 (76.8)
Heterogeneous	46 (23.2)
Contrast enhancement on CT, HU	
Attenuation value at pre-enhanced phase	
Mean ± SD	36.3 ± 18.7
Median [range]	33.0 [−5.0 to 130.0]
Attenuation value at enhanced phase	
Mean ± SD	90.5 ± 39.7
Median [range]	89.5 [5-222]
Difference in attenuation values	
Mean ± SD	54.2 ± 35.9
Median [range]	48.5 [5-186]

SD indicates standard deviation; CT, computed tomography; HU, Hounsfield units.

deviation) values of tumor enhancement in responded and nonresponded lesions were statistically different (70.7 ± 33.46 HU and 39.85 ± 25.99 HU; respectively; $P <$ .001). Two cases that represent the changes in high-attenuated and low-attenuated lesions during the therapy are presented in Figure 1. The overall mean values for the time to response and the time to progression were 8.6 months (95% confidence interval [CI], 7.4-9.9 months) and 16.4 months (95% CI, 15.2-17.7 months), respectively (Fig. 2).

Objective Responses

In univariate analyses, tumor growth pattern ($P = .005$), tumor size ($P = .007$), and tumor enhancement ($P <$ .001) were associated with objective response, but necrosis ($P = .788$) and enhancement pattern ($P = .376$) were not. Multivariate logistic regression analyses adjusted for the patient parameters revealed that contrast enhancement (odds ratio [OR], 1.037; 95% CI, 1.013-1.062; $P =$ .003) and enhancement pattern (OR, 4.602; 95% CI, 1.176-18.008; $P = .028$) were associated with objective response (data not shown). ROC curves of contrast enhancement were constructed and are depicted in Figure 3. Sensitivity and specificity were calculated according to several cutoff points using the ROC curve, and the AUC was 0.754 (95% CI, 0.688-0.821; $P <$ .001).

Tumor Size Reduction

In univariate analyses, only contrast enhancement was associated with maximal size reduction of metastatic lesions ($P <$ .001). The linear association between contrast enhancement and tumor size reduction is depicted in Figure 4. Tumor growth pattern ($P = .059$), necrosis ($P = .490$) and enhancement pattern ($P = .608$) were not associated with tumor size reduction. In the multivariate linear regression analysis, only contrast enhancement was associated independently with tumor size reduction rate (Table 3).

Time to Response

In univariate analyses of the time to response, tumor size (hazard ratio [HR], 0.971; 95% CI, 0.951-0.991; $P =$ .05) and contrast enhancement (HR, 1.011; 95% CI, 1.006-1.016; $P <$ .001) were associated with the time to a 30% size reduction, but growth pattern ($P = .157$), necrosis ($P = .96$), and enhancement pattern ($P = .982$) were not. Multivariate Cox proportional hazard models adjusted for patient variables indicated that only contrast enhancement was associated significantly with the time to response (Table 4).

Time to Disease Progression

In univariate analyses of progression-free survival for individual metastatic lesions, tumor growth pattern ($P =$ .017) and contrast enhancement ($P = .007$) were associated significantly with the time to progression, but necrosis ($P = .962$), enhancement pattern ($P = .386$), and tumor size ($P = .373$) were not. Multivariate Cox proportional hazard models revealed that only contrast enhancement was associated with the time to progression of individual metastatic lesions (Table 5).

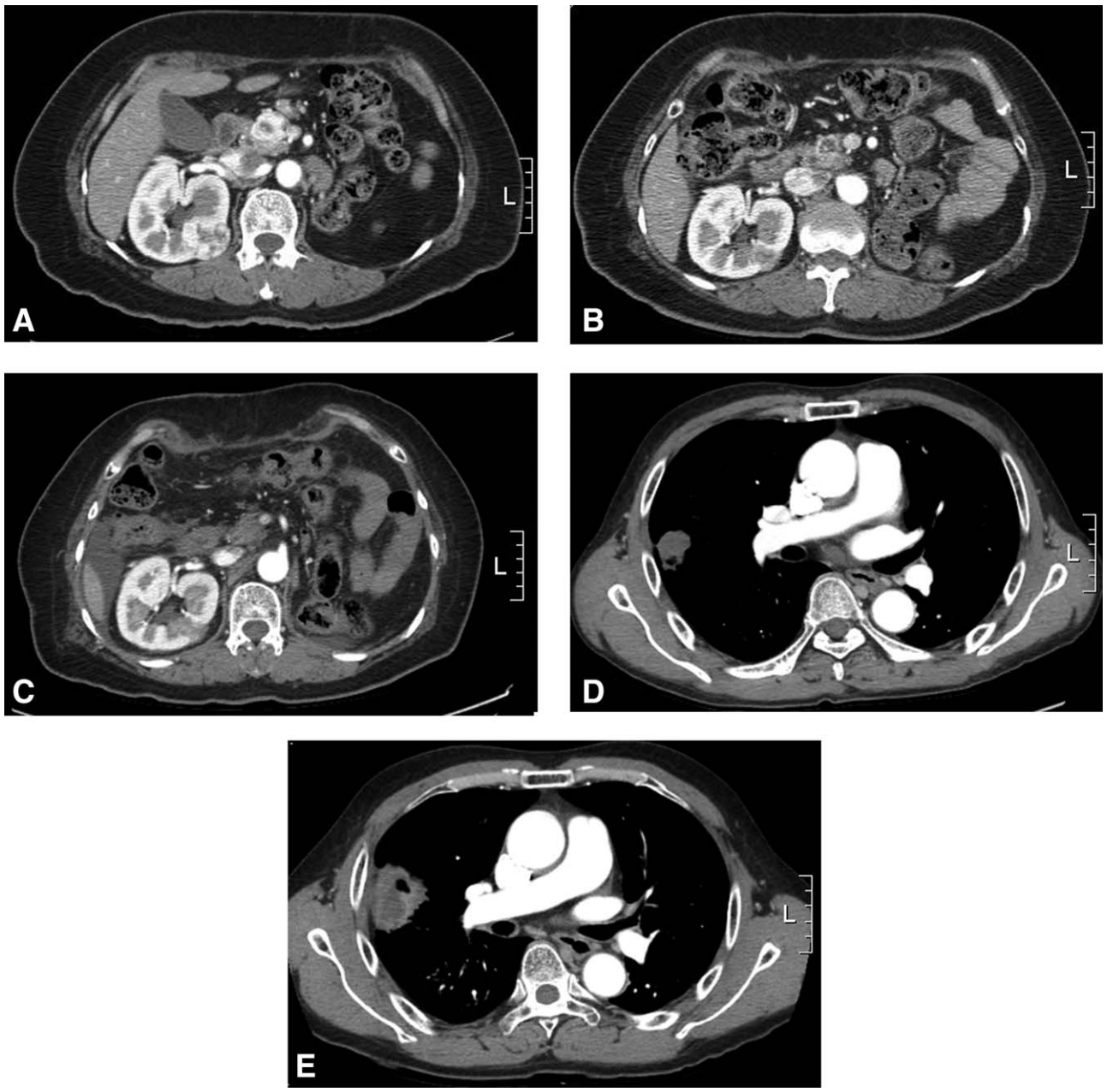

Figure 1. These photomicrographs illustrate the difference in response between lesions with high and low attenuation lesions. (A) A baseline computed tomography (CT) scan (tumor size, 17.5 mm; tumor enhancement in Hounsfield units [ΔHU], 173 Hounsfield units [HU]) reveals a pancreatic metastasis with a high attenuation value on an early phase contrast-enhanced CT (CECT) in 1 patient that disappeared on both (B) the initial follow-up CECT (tumor size, 13.2 mm; ΔHU, 44 HU) and (C) a sequential follow-up CECT (complete response), whereas (D) a lung metastasis with a low attenuation value on an early phase CECT from another patient (baseline CT: tumor size, 23.4 mm; ΔHU, 25 HU) progressed on (E) the initial follow-up CT (tumor size, 41.8 mm; ΔHU, 39.5 HU).

Treatment Outcomes According to Tumor Enhancement

All metastatic lesions were classified into 4 groups according to the degree of tumor enhancement. Table 6 shows the overall relation between tumor enhancement and treatment outcome. All lesions with a tumor enhancement $\geq$125 HU had a nearly complete response, whereas partial responses were obtained in most lesions (70%) that had tumor enhancement between 70 HU and 125 HU. These 2 groups had a similar time to progression (Fig. 5). By

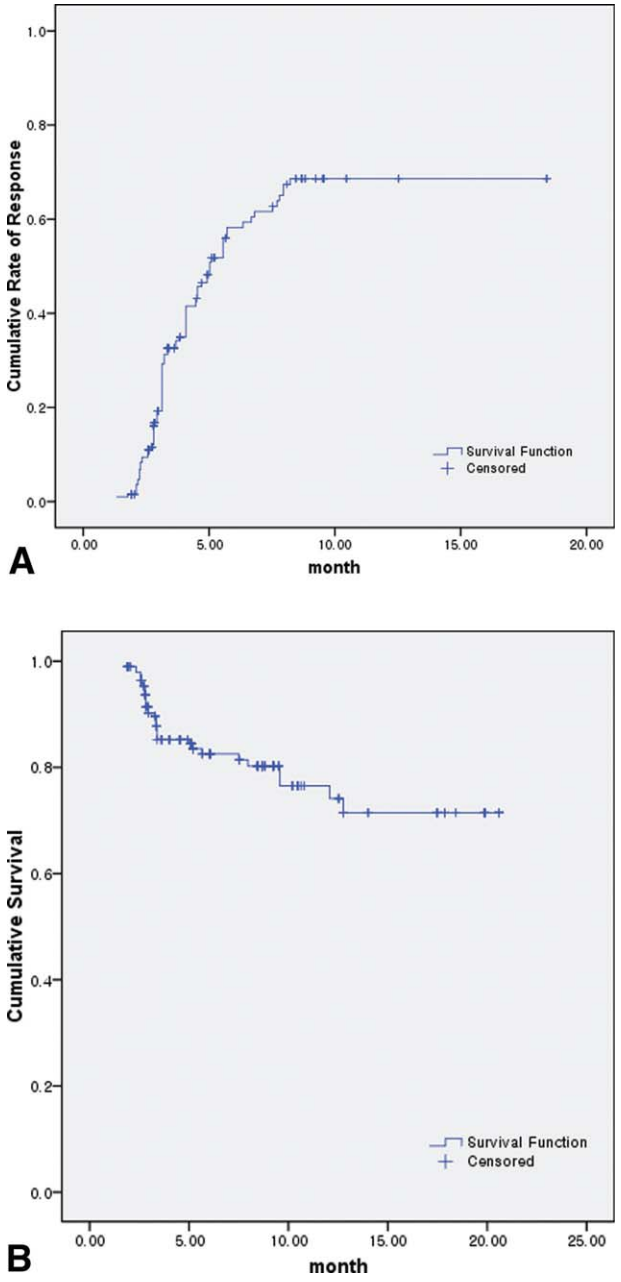

Figure 2. These Kaplan-Meier curves illustrate (A) the time to response and (B) the time to disease progression in metastatic lesions.

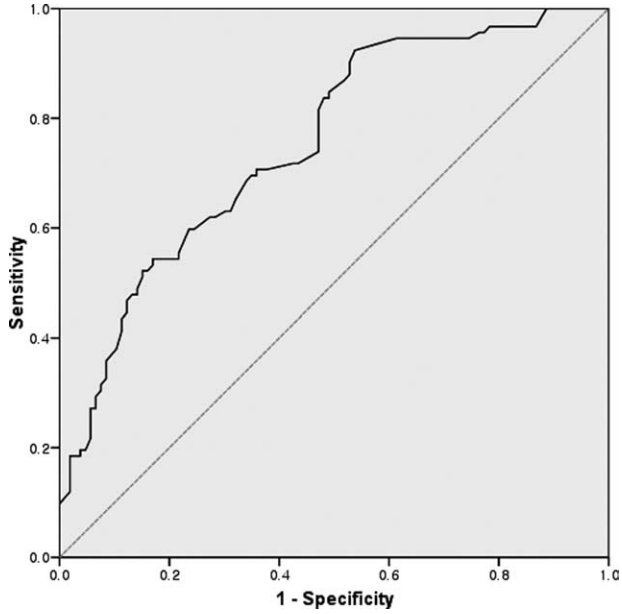

Figure 3. This graph illustrates the receiver operating characteristic curve of contrast enhancement for objective response.

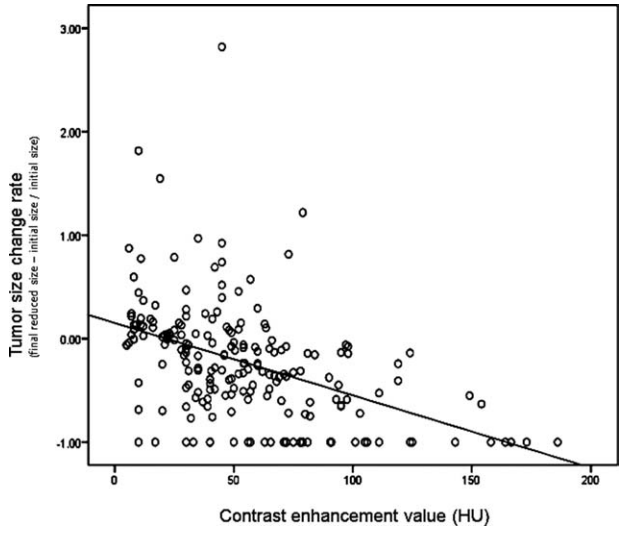

Figure 4. Correlations between tumor enhancement and changes in tumor size for individual metastatic lesions are shown. HU indicates Hounsfield units.

contrast, lesions with a tumor enhancement between 30 HU and 70 HU had a significantly lower response rate and a relatively short time to progression. Finally, most lesions that had tumor enhancement <30 HU did not respond to antiangiogenic treatment and rapidly progressed (Table 6) (Fig. 5).

DISCUSSION

Currently, targeted therapy is being incorporated into treatment strategies for several advanced malignancies. In the management of mRCC, the first choice of treatment is shifting from cytokine-based therapy to targeted therapies that are based mainly on the inhibition of tumor

Table 3. Multivariate Linear Regression Analysis for the Final Size Reduction Rate in Individual Metastatic Lesions

Covariate	β	95% CI	*P*
Karnofsky performance status, %			
60	—	—	—
70	0.087	−0.145 to 032	.459
80	0.908	0.175-1.64	.016
90	0.667	0.052-1.283	.034
Histology of primary tumor			
Clear cell	—	—	—
Clear cell with SD	0.427	−0.336 to 1.19	.27
Mixed	0.525	0.181-0.868	.003
Histologic type of metastasis			
Clear cell	—	—	—
Clear cell with SD	0.082	−0.502 to 0.666	.78
Mixed	0.213	−0.295 to 0.0821	.488
Unclassified	0.097	−0.344 to 0.149	.435
Removal of primary tumor			
No removal	—	—	—
Cytoreductive nephrectomy	0.079	−0.229 to 0.387	.611
Previous cytokine-based therapy			
No treatment	—	—	—
IFN-α	0.349	0.021-0.676	.037
IL-2 and IFN-α	−0.292	−0.586 to 0.02	.052
Site			
Lung	—	—	—
Mediastinum	0.054	−0.189 to −0.297	.661
Pleura	0.215	−0.209 to 0.639	.317
Lymph node	0.174	−0.146 to 0.495	.284
Adrenal	−0.035	−0.479 to 0.409	.876
Bone	0.288	−0.243 to 0.819	.284
Liver	0.402	−0.279 to 1.084	.244
Hemoglobin	0.034	-0.031 to 0.099	.297
Corrected calcium	0.058	−0.332 to 0.448	.769
Tumor enhancement	−0.004	−0.007 to −0.001	.004

CI indicates confidence interval; SD, sarcomatoid differentiation; IFN-α, interferon alpha; IL-2, interleukin-2.

Table 4. Multivariate Cox Proportional Hazards Models for the Time to Response in Individual Metastatic Lesions

Covariate	HR	95% CI	*P*
Karnofsky performance status, %			
60	—	—	—
70	0.450	0.125-1.626	.223
80	1.741	0.629-4.815	.285
90	0.457	0.234-0.890	.022
Histology of primary tumor			
Clear cell	—	—	—
Clear cell with SD	0.076	0.013-0.453	.005
Mixed	0.398	0.086-1.845	.239
Site			
Lung	—	—	—
Mediastinum	0.216	0.102-0.458	<.001
Pleura	0.923	0.304-2.807	.888
Lymph node	0.647	0.300-1.392	.265
Adrenal	0.095	0.019-0.478	.004
Bone	0.152	0.019-1.233	.078
Muscle	.0659	0.763-5.668	.157
Others	0.659	0.198-2.194	.497
Hemoglobin	1.220	1.061-1.402	.005
Corrected calcium	6.055	2.021-18.136	.001
No. of metastasis	1.072	1.018-1.128	.008
Tumor size	0.990	0.966-1.014	.401
Tumor enhancement	1.009	1.001-1.016	.03

HR indicates hazard ratio; CI, confidence interval; SD, sarcomatoid differentiation.

angiogenic activity. Therefore, we postulated that pretreatment contrast enhancement of tumors, with the ability to reveal the tumor vascularity, might predict treatment outcomes. To our knowledge, this is the first study to demonstrate that tumor enhancement on CECT independently predicts tumor response and prognosis after targeted therapy in individual mRCC lesions.

On the basis of multivariate analyses, contrast enhancement of the tumor was correlated independently with tumor size reduction and the time to response during antiangiogenic therapy (Tables 3 and 4). In addition, contrast enhancement was associated with the time to progression in individual metastatic lesions (Table 5). Although all multivariate analyses were adjusted for patient factors, contrast enhancement was a statistically significant predictor of treatment outcomes in metastatic lesions. Finally, we demonstrated that objective responses and the prognoses of individual metastatic lesions could be predicted by measuring pretreatment tumor enhancement in individual metastatic lesions (Table 6, Fig. 5). These findings suggest that tumor enhancement, as measured by CECT, may be used to predict outcomes for metastatic lesions during targeted therapy in patients with mRCC.

Several factors, such as vascularity, vascular density, vascular permeability, and blood flow, affect contrast uptake in tumors.[15-20] These influences are not understood completely and should be investigated further, although several studies have demonstrated that contrast enhancement in MRI mirrors the biologic and histologic properties of tumor angiogenesis.[15,17,18,24-26] These studies suggest the possibility of contrast enhancement as a potent predictor for the response or prognosis of metastases in mRCC; however, to our knowledge, no study to date has demonstrated this possibility using CECT in patients with mRCC. The measurement of contrast enhancement on CECT does not provide a quantitative

evaluation of kinetic variables, such as flow contribution, permeability, and extracellular volume fraction. Dynamic CECT or MRI may be more appropriate for evaluating these variables with respect to angiogenic activity. However, in clinical practice, CECT is used as a fairly standard protocol for measuring tumor vascularity. Furthermore, although several studies have demonstrated that measures using MRI are promising for the evaluation of tumor vascularity, the resolution of MRI is lower than that of CT for lung and abdominal organs, indicating that MRI is of limited use in evaluating metastases. However, CECT is the most commonly used follow-up method for serial changes in tumor lesions during treatment, and measures of tumor enhancement on CECT are included in the routine evaluation of tumor lesions in clinical practice and require no invasive tests or further processes.

Table 5. Multivariate Cox Proportional Hazards Models for the Time to Disease Progression in Individual Metastatic Lesions

Covariate	HR	95% CI	*P*
Age	0.980	0.952-0.995	.015
Karnofsky performance status, %			
60	—	—	—
70	4.574	0.563-37.138	.155
80	10.771	0.656-176.738	.096
90	4.128	0.634-26.863	.138
Histology of primary tumor			
Clear cell	—	—	—
Clear cell with SD	67.294	2.194-206.691	.016
Mixed	7.920	2.124-29.531	.315
Removal of primary tumor			
Not performed	—	—	—
Performed	0.349	0.045-2.712	.315
Previous cytokine-based therapy			
No treatment	—	—	—
IFN-α	2.241	0.765-6.525	.142
IL-2 and IFN-α	0.273	0.018-4.032	.344
Hemoglobin	0.947	0.636-1.410	.790
Lactate dehydrogenase	0.997	0.991-1.003	.290
No. of metastasis	1.065	0.940-1.208	.324
Tumor growth pattern			
Conglomerated type	—	—	—
Infiltrative type	2.234	0.765-6.525	.142
Tumor enhancement	0.973	0.952-0.995	.015

HR indicates hazard ratio; CI, confidence interval; SD, sarcomatoid differentiation; IFN-α, interferon alpha; IL-2, interleukin-2.

Our findings may have significant clinical implications. Variable responses of multiple metastases frequently are observed in patients undergoing systemic therapies. Genetically, metastases are heterogeneous in several malignancies, including RCC.[27] Even primary RCCs that grow with extensive angiogenesis can have metastases that express distinct angiogenic and nonangiogenic growth patterns.[28] The heterogeneity of metastases also was apparent in our study population, and many patients had variable contrast enhancement of their metastatic tumors. Because blood vessels are subject to the influence of the local microenvironment and cytokines produced by tumor cells,[14] clinical factors like serum VEGF levels are promising for predicting outcomes of antiangiogenic therapies for metastases from clear cell RCC. However, levels cannot predict the heterogeneous responses of metastatic tumors. Our results demonstrate that measures of contrast enhancement allow pretreatment prediction of outcomes for individual metastatic lesions during targeted therapy and may be useful for improving the selection of lesions that will benefit from targeted therapy in the treatment of mRCC.

The variability of contrast enhancement demonstrated in the current study means that, given the heterogeneity in the angiogenic dependency of individual metastatic tumors, which may be responsible for the failure of some antiangiogenic trials, and the nonangiogenic growth patterns of some metastases, such tumors probably would not respond to antiangiogenic agents.[28] In our study, 10 patients (21.7%) had both responding and

Table 6. Differences in Treatment Outcomes According to the Degree of Tumor Enhancement in Metastatic Renal Cell Carcinoma Lesions

Tumor Enhancement, ΔHU	No. of Lesions	No. of Objective Responses (%)[a]	Mean ± SD Size Reduction, %[b]	PFS Rate at 1 Year, %[c]
≥125	9	9 (100)	90.9 ± 18.2 [–]	100
From ≤70 to <125	45	32 (71.1)	53.2 ± 48.2 [–]	92.8
From ≤30 to <70	98	46 (46.9)	20.4 ± 53 [–]	66.7
<30	46	5 (10.9)	11.5 ± 50.4 [+]	57.2

SD indicates standard deviation; ΔHU indicates tumor enhancement in Hounsfield units; [–], decrease; [+], increase.
[a] $P < .001$ (chi-square test).
[b] $P < .001$ (analysis of variance).
[c] Kaplan-Meier curves, as depicted in Figure 5, were compared.

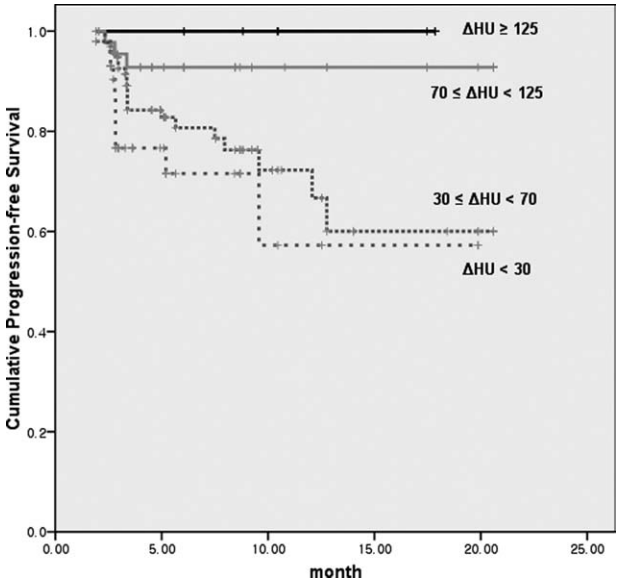

Figure 5. These Kaplan-Meier curves illustrate differences in progression-free survival according to the degree of tumor enhancement of metastatic renal cell carcinoma lesions (log-rank test; $P = .008$). HU indicates Hounsfield units; ΔHU indicates tumor enhancement in Hounsfield units.

nonresponding lesions. In 12 patients (26.1%), lesions of increasing size were present simultaneously with other lesions of decreasing size. The majority of clear cell RCCs have biallelic von Hippel-Lindau gene inactivation, which results in the overexpression of growth factors, including VEGF, allowing the hypervascular characteristics of RCC and a favorable response to antiantiogenic therapy[29]; whereas metastatic lesions may have tumor characteristics that differ from those of a primary renal tumor even within the same patient, because genetically diverse cancer cells can be seeded by the primary tumor, and genetic changes also can occur in the process of disease progression and metastases. Genetic heterogeneity of metastatic clones and diverse microenvironments supporting metastatic growths seem to allow different response patterns to antiangiogenic therapy. However, the exact mechanism should be investigated further.

Current strategies for cancer treatment tend to focus excessively on a patient's overall outcome. The RECIST, currently the most commonly used criteria for response, overcome this weakness by using the sum of the greatest tumor dimensions, but these criteria are insufficient for the individual evaluation of heterogeneous responses within a patient. In our study, some patients stopped using TKIs because a small number of metastases progressed, although most metastases responded well or were stable during TKI therapy. Metastasectomy after targeted therapy or after combination therapy with other agents might play a vital role in this patient population and is worthy of investigation.[30] These findings reflect the need to treat individual metastases in mRCC with multidisciplinary approaches that are chosen according to the characteristics of individual metastatic lesions before treatment is initiated. Our analysis using classification according to tumor enhancement suggests that lesional approaches, through the measurement of pretreatment contrast enhancement values, may be useful in outcome prediction and treatment selection.

Our study has limitations. Because of the retrospective nature of the study and our small cohort, we cannot rule out a possible bias in patient selection. In a significant number of patients, there was a high correlation between responses in different lesions within a patient rather than a heterogeneous response. We addressed this possible patient-based difference in tumor response by adjusting the tumor (lesion) variables based on patient variables by using multivariate analyses. Nevertheless, patient-based rather than lesion-based differences cannot be ruled out, and this is a limitation in this study design. A statistical model explaining the correlation among lesions remains to be established. In addition, survival analyses could not be performed, because the follow-up period was not long enough. Therefore, the significance of tumor enhancement in predicting overall survival and the cutoff point that can differentiate metastatic lesions with a good prognosis from those with a poor prognosis in patients with mRCC should be investigated further. Future prospective studies with long-term follow-up will be required to confirm our findings.

In summary, tumor enhancement on CECT was associated with tumor size reduction, time to response, and time to progression of individual metastases in patients with mRCC who received targeted therapy. Initial tumor enhancement on CECT may be useful as a clinical predictor during targeted therapy and to improve the selection of patients who may benefit from targeted therapy in the treatment of mRCC.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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