Assessing Tumor Response and Detecting Recurrence in Metastatic Renal Cell Carcinoma on Targeted Therapy: Importance of Size and Attenuation on Contrast-Enhanced CT

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OBJECTIVE. The aim of this study was to improve response assessment in patients with metastatic renal cell carcinoma (RCC) on antiangiogenic targeted therapy by evaluating changes in both tumor size and attenuation and by detecting unique patterns of contrast enhancement on contrast-enhanced CT (CECT).

MATERIALS AND METHODS. Tumor long-axis measurements and volumetric mean tumor attenuation of target lesions on CECT images were correlated with time to progression in 53 patients with metastatic clear cell RCC treated with first-line sorafenib or sunitinib. The frequencies of specific patterns of tumor progression were assessed. The data were used to develop new imaging criteria, the size and attenuation CT (SACT) criteria. CECT findings were evaluated using the SACT criteria, Response Evaluation Criteria in Solid Tumors (RECIST), and modified Choi criteria, and the Kaplan-Meier method was used to estimate survival functions.

RESULTS. One or more target metastatic lesions had decreased attenuation of ≥ 40 HU in 59% of patients with progression-free survival of > 250 days ($n = 44$) after initiating targeted therapy; 0% of patients with earlier disease progression ($n = 9$) had this finding. A favorable response based on SACT criteria had a sensitivity of 75% and specificity of 100% for identifying patients with progression-free survival of > 250 days, versus 16% and 100%, respectively, for RECIST and 93% and 44% for the modified Choi criteria.

CONCLUSION. Objectively measuring changes in both tumor size and attenuation on the first CECT study after initiating targeted therapy for metastatic RCC markedly improves response assessment. Distinct patterns of disease recurrence are seen in patients with metastatic RCC on targeted therapy.

Keywords: contrast-enhanced CT, metastatic renal cell carcinoma, response assessment, tumor attenuation, tumor recurrence

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At the time of diagnosis, 20–30% of patients with renal cell carcinoma (RCC) have metastases, and metastatic RCC has an overall poor response to cytotoxic chemotherapy and cytokine therapies [1, 2]. Recent advances in the understanding of metastatic clear cell RCC angiogenesis have led to the development and approval of molecular targeted therapy, particularly tyrosine kinase (TK) inhibitors.

Metastatic RCC is a highly vascular tumor and is ideally suited for antiangiogenic therapy. Clear cell RCC, which accounts for 85% of all RCC, is a particularly hypervascular tumor with a high frequency of mutations in the von Hippel-Lindau (*VHL*) gene; mutations in the *VHL* gene and other genes lead to upregulation of receptor and cellular TKs involved in tumor proliferation and angiogenesis [3]. Multitargeted TK inhibitors, including sunitinib and sorafenib, block these receptor and intracellular TKs, resulting in significantly improved progression-free survival in patients with metastatic RCC [4–10]. Despite progress in the therapeutic arena, little research has been conducted to accurately assess therapeutic response and to identify specific contrast-enhanced CT (CECT) patterns that foretell therapeutic failure in these patients.

The traditional method of evaluating therapy response in patients with solid tumors is based on measurements of long-axis tumor size on axial CT according to the Response Evaluation Criteria in Solid Tumors (RECIST) [11]. TK inhibitors have relatively limited efficacy for metastatic RCC tumor shrinkage, especially in sorafenib-treated metastatic RCC, and response to therapy using current size-based imaging response criteria is thought to be inadequate early in the course of therapy [6]. In recent studies, investigators have documented that TK inhibitor–treated metastatic

clear cell RCC exhibits decreased attenuation on CECT after TK inhibitor therapy [8, 12–14]. For example, markedly decreased attenuation with minimal size change has been observed on CECT in a retroperitoneal metastatic clear cell RCC mass after neoadjuvant sunitinib therapy; the decreased attenuation correlated with pathologic evidence of necrosis on resection of the mass [12]. Such attenuation changes are not accounted for by RECIST [11].

Similarly, RECIST has been shown to underestimate tumor response to therapy in patients with metastatic gastrointestinal stromal tumor (GIST), another hypervascular solid tumor now conventionally treated with first-line TK inhibitor therapy [14–20]. In TK inhibitor–treated metastatic GIST, decreased tumor attenuation on CECT is a predictor of improved therapeutic response [14–20]. Likewise, detecting recurrence using RECIST is limited in TK inhibitor–treated metastatic GIST. Progressive disease in metastatic GIST includes not only the findings of increased tumor size and a new metastasis, but also the finding of a nodule in a mass, which is defined as the development of a new enhancing solid nodule in a low-attenuating mass [20, 21]. A "nodule-in-a-mass" is an independent sign of progressive disease in TK inhibitor–treated metastatic GIST [20, 21]. To our knowledge, this unique pattern of recurrence has not been reported in TK inhibitor–treated metastatic RCC. Similar development of irregular eccentric thickening of the margin of an ablation defect or of a new tumor nodule has been shown to represent local tumor recurrence in radiofrequency-ablated liver tumors [22].

To improve objective response evaluation in metastatic RCC after TK inhibitor therapy and obtain predictive information based on the first CECT examination after therapy, we evaluated changes in tumor size and attenuation on the initial posttreatment CECT and correlated these changes with time to progression and disease-specific survival to assess their clinical impact. We also studied enhancement patterns in target lesions at or just before disease progression to identify changes that may herald therapeutic failure. We hypothesized that in TK inhibitor–treated metastatic RCC, first, RECIST assessment underestimates tumor response; second, posttherapy decreased tumor attenuation on CECT correlates with improved clinical outcome; and, third, the development of new enhancement in a TK inhibitor–treated low-attenuating nonenhancing metastasis is associated with and may herald therapeutic failure.

Materials and Methods

Patient Population

In this institutional review board–approved HIPAA-compliant retrospective study, a search of our institution's outpatient electronic medical record database from 2000 through 2007 was performed for all patients who were treated with sorafenib or sunitinib TK inhibitor therapy. Patients who received sorafenib (Nexavar, Bayer Corporation) and those who received sunitinib (Sutent, Pfizer) for the treatment of metastatic RCC totaled 77 and 156, respectively. Patients with pathology-proven metastatic clear cell RCC who received first-line TK inhibitor therapy were included in this study. The patients treated with sorafenib had 400 mg of continuous daily therapy, and those treated with sunitinib had repeated 6-week cycles of 50 mg of daily therapy for 4 weeks followed by 2 weeks off. Patients were excluded if they were off therapy for any reason for > 1 week during an on-therapy portion of the protocol within the first 9 months of therapy. Patients with dose reductions but continuous therapy were included.

The patients included in this study periodically underwent CECT throughout the course of therapy; those who underwent unenhanced CT were excluded from the study. A total of 53 patients (13 women and 40 men; mean age, 60 years; age range, 34–77 years; 21 patients on sorafenib and 32 patients on sunitinib therapy) were included in the study. For each patient, multiple CECT examinations were assessed including the following: the CECT study performed before initiating therapy (pre–TK inhibitor CT), the first CECT study after initiating TK inhibitor therapy (post–TK inhibitor CT), the CECT study before the final CECT (prefinal CT), and the final CECT study (final CT). Most of the patients (n = 37) had progressive disease according to RECIST on the final CT study; the remaining (n = 16) were progression free and still on TK inhibitor therapy at the time of the final CT study.

The electronic medical records were searched for the date of initiation of therapy; the dates of pre–TK inhibitor, post–TK inhibitor, prefinal, and final CT scans; and the date and cause of disease progression and death. The imaging test, time of the study showing disease progression, and location of disease progression or new metastases were recorded if relevant. Time to progression was defined as the length of time on TK inhibitor therapy until therapy was discontinued because of metastatic disease progression determined by the clinical oncologist's notes in the electronic medical record. All patients had progressive disease according to RECIST based on size criteria or new metastases at the time of disease progression. No patients in this population had disease progression due to clinical deterioration without imaging findings of progressive disease. Disease-specific survival was the length of time from initiating TK inhibitor therapy until patient death from progressive metastatic disease.

Imaging

All images were acquired through a single academic institution. Standard CECT at our institution was conducted on MDCT scanners (Emotion Duo, Volume Zoom, and Sensation 16, Siemens Healthcare) and included oral contrast material and 150 mL of IV nonionic iodinated contrast material, usually injection of a nonionic water-soluble contrast agent (300 mg I/mL iopromide [Ultravist, Bayer HealthCare]). Chest images were obtained 20 seconds after injection and abdomen and pelvis images were obtained 70 seconds after IV contrast injection (i.e., during the portal venous phase). The specific CT parameters, contrast injection rate, and contrast dose were not consistently obtainable in this retrospective study.

Imaging Analysis

Target metastatic lesions > 1 cm in the long axis were analyzed using RECIST parameters and followed in each chest, abdomen, and pelvis CECT examination. Target lesions were chosen by the interpreting staff radiologist, an abdominal fellowship-trained academic radiologist with 8 years' experience. Up to 10 target lesions per patient were selected (219 total lesions; average, 4.2 lesions per patient; range, 1–10 lesions per patient) with up to five in any one body organ. Target lesions were chosen in proportion to their frequency in each organ when multiple lesions were present. The pre–TK inhibitor, post–TK inhibitor, prefinal, and final CT studies were assessed for the average change in tumor size and in mean volumetric tumor attenuation. The average change in tumor size was determined by the sum of the longest dimension axial size measurements of all target lesions. The mean volumetric attenuation (in Hounsfield units) of each nonlung target lesion (n = 174 lesions) was measured using volumetric software (Oncocare, Siemens Healthcare) at all four time points (i.e., pre–TK inhibitor, post–TK inhibitor, prefinal, and final CT studies) [23, 24]. The applied version of software allowed the user to select the tumor in any dimension, and the edge of the lesion was calculated using attenuation changes in the local body surroundings. The user could then adjust the edges in 3D until satisfactory selection of the lesions occurred. Lung parenchyma lesions (45 lung lesions in 16 patients with lung and nonlung lesions

and in four patients with only lung lesions) were not measured using the volumetric software because of inconsistent mean attenuation results from volume averaging between soft tissue and air. Lung lesions were assessed for the development of central cavitation on post–TK inhibitor CT. Volumetric measurements were calculated using semiautomated edge-detection software by a senior radiology resident; image scenes (i.e., containing multiplanar images in three orthogonal planes and a volumetric rendition of target lesions) were saved, reviewed, and confirmed by the interpreting staff radiologist in consensus.

The timing or phase of IV contrast was compared on each CECT study with target lesions. For CECT of the chest, the phase of IV contrast on the pre–TK inhibitor and post–TK inhibitor CT study was compared by assessing the attenuation of IV-injected contrast material in the cardiac chambers and great thoracic vessels. For CECT of the abdomen and pelvis, the phase of IV contrast was compared by assessing the nephrogenic phase of enhancement with supplementary information from the enhancement of the liver and spleen and the attenuation of contrast material in the aorta at the celiac level, in the portal vein, and in the distal external iliac vessels. Note was made if the contrast phase on post–TK inhibitor CT was earlier, similar, or delayed relative to pre–TK inhibitor CT.

The prefinal and final CT examinations in 53 patients (174 nonlung target lesions) were assessed for the presence of a "nodule-in-a-mass" sign, which was originally described with locally recurrent GIST [21]. The number of patients with one or more lesions with marked central fill-in—defined as a change from marked central necrosis in a mass to significant or near complete enhancement of solid tumor centrally—was recorded. This finding was visually distinguished from mildly increased nodularity or partial central fill-in. The number of patients who had developed new enhancement in a previously homogeneously hypoattenuating, nonenhancing mass was also recorded; this finding was distinguished from increased enhancement of previously mildly enhancing tumor. Imaging findings were correlated with time to progression.

Response Criteria Assessment

The results of our initial image analysis, including changes in size and attenuation of tumor and the presence of specific signs of progression of metastatic RCC on TK inhibitor therapy, were incorporated into the Size and Attenuation CT (SACT) criteria and tested on this population. The post–TK inhibitor CT study was compared with the pre–TK inhibitor CT study, and volumetric attenuation data were used for assessing attenuation in conjunction with changes in the longest axial dimension. Assessment for specific signs of disease progression was performed on axial CECT. On the basis of these findings, patients were categorized as having a favorable response to therapy, indeterminate response, or unfavorable response.

Axial CECT scans were also used for RECIST assessment, and patients were categorized as having complete response, partial response, stable disease, or progressive disease [11].

The Modified CT Response Evaluation Criteria described by Choi et al. [17] in 2007 were applied to our patient population except that mean volumetric attenuation data were used instead of the mean attenuation of the tumor on the most representative axial image; we refer to these criteria as the "modified Choi criteria." Volumetric tumor attenuation measurements were combined, and a mean attenuation for each patient was computed. The percentage change in tumor attenuation for each patient was calculated. A good response according to the modified Choi criteria was defined as a mean decrease in tumor size of ≥ 10% or a decrease in mean tumor attenuation of ≥ 15% in a patient. Patients not meeting a good response were classified as having a poor response. Axial CECT scans were used to assess for new disease when applying the modified Choi criteria.

Therapy response according to each of the three imaging criteria was determined in consensus by two reviewers; imaging responses were correlated with time to progression and disease-specific survival. Imaging responses based on SACT criteria were also correlated with the phase of IV contrast on post–TK inhibitor CT relative to pre–TK inhibitor CT.

Statistical Analysis

The Kaplan-Meier (product-limit) method was used to estimate survival functions for time to progression and disease-specific survival. All cases in which progression was not observed were treated as right-censored with respect to time to progression; it was assumed that disease in all patients would eventually progress. Similarly, all cases without a date of metastasis-related death were treated as right-censored in analyzing disease-specific survival. Survival functions were statistically compared between independent groups of patients using log-rank tests. The homogeneity hypothesis for proportions from independent groups was assessed using Fisher's exact test. Correlated proportions were compared through the use of the McNemar test. When the unit of measurement was a lesion, rather than a patient, continuous variables were compared through the use of F tests in a mixed-model analysis of variance to account for multiple (and possibly correlated) observations in a patient.

Results

Size and Attenuation Changes After Initiating TK Inhibitor Therapy

The time of CECT and duration of therapy relative to the start date of TK inhibitor therapy are presented in Table 1. Sixteen patients were still on TK inhibitor therapy at the time of the final CECT study. Most patients (51 of 53) underwent standard CECT of the chest concurrently with CECT of the abdomen and pelvis. Two patients underwent triphasic pre–TK inhibitor CT of the abdomen, and the contrast phase closest to the portal venous phase was used for analysis. Slice thickness for chest CECT ranged from 1 to 5 mm (1–3 mm in 52% of patients) and from 3 to 5 mm for abdomen and pelvis CECT (5 mm in 83% of patients). All but five of the 32 patients on sunitinib therapy were scanned during the on-therapy portion of their treatment cycle. The median time of scanning for the post–TK inhibitor CT was 8.7 weeks (range, 4.0–16.9 weeks) after initiating therapy.

The average tumor size (sum of longest axial dimensions of target lesions) in 53 patients (33 chest and 31 abdomen and pelvis CECT studies; total of 219 lesions) was 15 cm (range, 1.7–62.2 cm) before TK inhibitor therapy and 13 cm (range, 1.7–66.3 cm) after therapy, with an average decrease in size

TABLE 1: Time of Imaging and Duration of Therapy Relative to Start of Tyrosine Kinase Inhibitor Therapy

Imaging and Clinical End Points	Time (d)	
	Median	Range
Time of pre–TK inhibitor CT	–7	–38 to 0
Time of post–TK inhibitor CT	61	28 – 114
Time of pre final CT	349	28 – 932
Time of final CT[a]	433	112 – 1,026
Duration of therapy	502	114 – 1,309

[a] At the time of the final CT, 16 of 53 patients were still on therapy. TK = tyrosine kinase.

TABLE 2: Response Evaluation: Tumor Size

Disease Status	% Change in Longest Dimension of Tumor	% of Patients With Tumors Showing				No. of Patients
		> 30% Decrease in Size	> 20% Decrease in Size	> 10% Decrease in Size	> 20% Increase in Size	
Progression-free survival > 250 d	–16	16	39	70	2	44
Early progression < 250 d	4	0	0	22	22	9
p	< 0.0005[a]	0.33[b]	0.04[b]	0.019[b]	0.07[b]	

[a]Two-sample Student's *t* test.
[b]Fisher's exact test.

TABLE 3: Response Evaluation: Tumor Attenuation

Disease Status	Change in Attenuation (HU)	% of Patients With			No. of Patients
		One or More Lesions With ≥ 40 HU Decrease	At Least Half of Lesions With ≥ 20 HU Decrease	> 15% Decrease in Mean Attenuation	
Progression-free survival > 250 d	–34	59	68	80	44
Early progression < 250 d	–2	0	0	33	9
p	< 0.0001[a]	0.002[b]	0.0002[b]	0.011[b]	

[a]Two-sample Student's *t* test.
[b]Fisher's exact test.

of 2 cm (13%). In patients on sorafenib and sunitinib, CECT showed a decrease in tumor size after therapy of 0.6 cm (4%) and 2.9 cm (19%), respectively, with a statistically significant difference between the two treatments ($p = 0.008$, two-sample Student's *t* test). None of the lung lesions showed central cavitation on the post–TK inhibitor CT study.

Marked differences in tumor size were seen between the pre–TK inhibitor and post–TK inhibitor CT studies in the patients with progression-free survival of > 250 days compared with those with early progression (i.e., < 250 days [Table 2]). The 16% decrease in tumor size in patients with progression-free survival of > 250 days is statistically significantly different ($p < 0.0005$) from the 4% increase in those with early progression (< 250 days). A ≥ 30% decrease in tumor size (partial response according to RECIST) was present in 16% of patients with progression-free survival of > 250 days, which is not significantly different from 0% of patients with early progression (Table 2). Smaller size decreases were more frequent and were significantly different in these patient groups. More than 39% of patients with progression-free survival of > 250 days had a decrease in tumor size of ≥ 20%, which is statistically significantly different ($p = 0.04$) from 0% of the patients with early progression (Table 2). A ≥ 10% decrease in size (used in the modified Choi criteria) was present in 70% of patients with progression-free survival of > 250 days but was also seen in 22% of patients with early progression (Table 2). Of the patients with early progression (< 250 days), 22% had an increase in tumor size of ≥ 20% (progressive disease according to RECIST), not significantly different from 2% of patients with progression-free survival of > 250 days (Table 2).

Marked differences in tumor attenuation were seen between the pre–TK inhibitor and post–TK inhibitor CT studies in patients with progression-free survival of > 250 days compared with those with early progression (Table 3). The average tumor attenuation of nonlung lesions ($n = 174$ target lesions) was 93 HU before TK inhibitor therapy and 60 HU after therapy, with an average decrease in attenuation of 33 HU (35%) after initiating therapy. A mean decrease of 40 HU in tumor attenuation after therapy was statistically different ($p = 0.0005$, F test) and was more pronounced in patients on sunitinib therapy ($n = 99$) than the mean decrease of 22 HU in patients on sorafenib therapy ($n = 75$). The mean decrease in attenuation of 34 HU seen in patients with progression-free survival of > 250 days was significantly different from the 2-HU decrease seen in those with early progression (Table 3). Decreased attenuation of ≥ 40 HU was present in one or more lesions in 59% of patients with progression-free survival of > 250 days, which is statistically significantly different from 0% of patient with early progression (Table 3). Furthermore, 68% of patients with progression-free survival of > 250 days had at least half of their lesions show a decrease of ≥ 20 HU, also statistically significantly different from 0% of patients with early progression (Table 3). Although 80% of patients with progression-free survival of > 250 days had a decrease in mean attenuation of ≥ 15% (used in the modified Choi criteria), 33% of patients with early progression also had such a change.

Specific CT Signs Associated With Disease Progression During TK Inhibitor Therapy

The mean volumetric attenuation of target lesions was measured on the prefinal and final CT studies in patients with disease progression and those still on therapy with progression-free survival of > 250 days. The attenuations of target lesions on the prefinal CT were compared with the attenuations of target lesions on the post–TK inhibitor CT, and the attenuations of target lesions on the final CT were compared with those on the prefinal CT. No significant difference in the slight increase in attenuation was seen between patient groups at these time points (data not shown).

Of the patients with progressive disease on TK inhibitor therapy ($n = 41$ patients, 138 nonlung lesions), none had a nodule-in-a-mass sign in any of their target or nontarget lesions on the prefinal or final CT study. Of the patients with progressive disease on TK inhibitor therapy ($n = 41$ patients), findings of marked central fill-in (Fig. 1) were seen in three patients on the prefinal CT, and new enhancement in a homogeneously hypoattenuating, nonenhancing mass (Fig. 2) was seen in two patients on the prefinal CT. Either one of these findings was seen in 12% of patients on the prefinal CT study in patients who later developed progressive disease. In patients with progressive disease, marked central fill-in was seen on the final CT in an additional four patients, and new enhancement in a homogeneously hypoattenuating, nonenhancing mass was seen on the final CT in one additional patient. Marked central fill-in or new enhancement in a homogeneously hypoattenuating, nonenhancing mass was seen in 24% of patients with progressive disease on either the prefinal or final CT study. These findings were not seen in patients with early progression (< 250 days; $n = 9$ patients) and were seen only in patients who had one or more target lesions with a decreased attenuation of ≥ 40 HU after initiating TK inhibitor therapy ($n = 32$ patients).

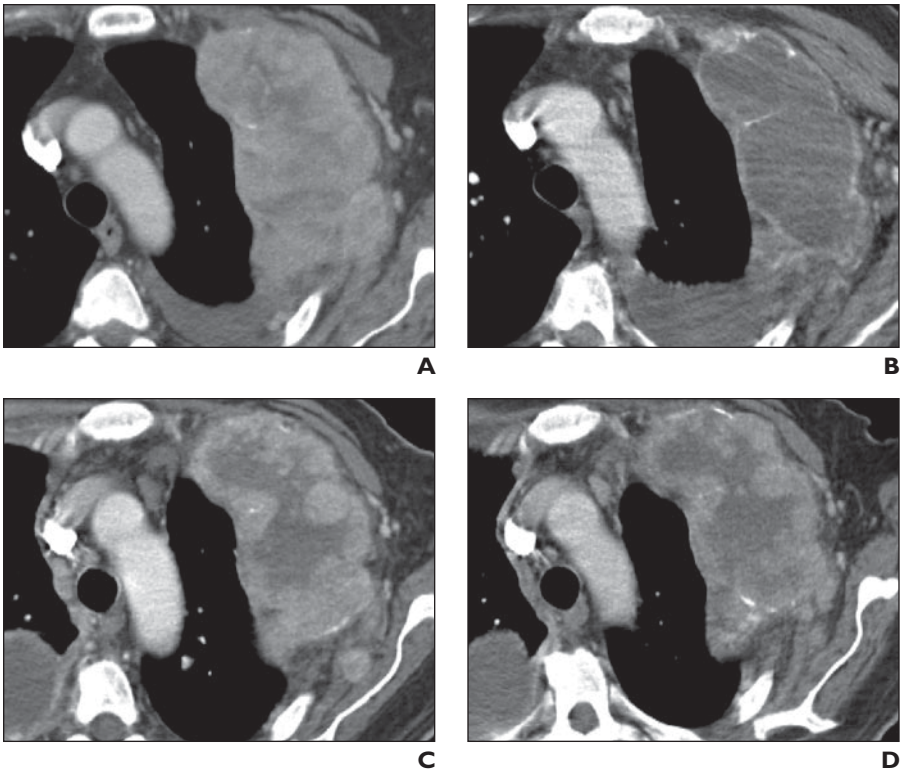

Fig. 1—58-year-old man with metastatic renal cell carcinoma (RCC). Contrast-enhanced CT (CECT) depicts RCC metastasis in left chest wall at various stages of sorafenib therapy.
A, CECT scan obtained 38 days before initiating therapy shows solid enhancing chest wall metastasis (mean attenuation, 72 HU).
B, CECT scan obtained 59 days after initiating therapy shows markedly decreased enhancement and decreased attenuation (> 40 HU) of tumor, especially centrally. Mean attenuation of tumor is 28 HU. Note thin peripheral rim of enhancement, marked central necrosis, and minimal overall change in longest axial dimension size.
C, CECT scan obtained 423 days after initiating therapy shows marked central fill-in of solid enhancing tumor with interval increase in size of mediastinal lymph nodes and development of loculated right pleural effusion, although tumor measurements do not yet meet size criterion for progressive disease according to Response Evaluation Criteria in Solid Tumors (RECIST). Mean attenuation of tumor is 55 HU.
D, CECT scan obtained 483 days after initiating therapy shows marked central fill-in with overall RECIST progressive disease by size progression of mediastinal and pleural metastases (not shown). Mean attenuation of tumor is 64 HU.

Response Criteria Assessment

When patients were evaluated by SACT criteria (Table 4) on their first CECT after initiating TK inhibitor therapy, significant differences in time to progression were observed between responses (p = 0.001, log-rank test) (Fig. 3A). Similarly, with RECIST, significant differences in time to progression were observed between responses (p = 0.002, log rank test) (Fig. 3B). None of the patients had complete response according to RECIST. All patients with a favorable response by SACT (n = 33) or partial response by RECIST (n = 7) had progression-free survival of > 250 days. The main difference between the two criteria was the substantially larger number of patients identified with progression-free survival of > 250 days by SACT criteria (Table 5).

When the modified Choi criteria were used to assess tumor response, no significant difference was observed in the long-term prognosis (time to progression) between good versus poor responders (p = 0.244, log rank test) (Fig. 3C). The modified Choi criteria tended to classify most patients as good responders regardless of long-term prognosis (time to progression).

Although SACT criteria were able to discriminate patients with early progression from those with more prolonged, progression-free survival, no significant difference was observed in disease-specific survival between responses (p = 0.628, log rank test; data not shown). Similarly, no significant difference in disease-specific survival was seen between responses by RECIST or modified Choi criteria (p = 0.760 and p = 0.722, log rank test; data not shown).

A favorable response by SACT criteria had a 75% sensitivity for identifying patients with progression-free survival of > 250 days, which is statistically significantly different from 16% sensitivity for RECIST partial response (p < 0.0001, McNemar test) (Table 4). The specificity of SACT favorable response and RECIST partial response for identifying patients with progression-free survival of > 250 days was 100% in this patient population. A good response by the modified Choi criteria had a 93% sensitivity for identifying patients with progression-free survival of > 250 days, which is statistically significantly different from the 75% sensitivity for SACT criteria favorable response (p = 0.0026, McNemar test) (Table 4). However, the 0% false-positive rate of SACT criteria is substantially lower than that for the modified Choi criteria at 56%, which corresponds to a specificity of 100% for the SACT criteria and 44% for the modified Choi criteria (Table 4).

An unfavorable response by SACT criteria and progressive disease by RECIST resulted in identical curves by Kaplan-Meier analysis. All patients with either of these responses had progression within 315 days. This is distinct from a poor response by modified Choi criteria whereby 40% of the patients with a poor response (n = 5) had progression-free survival for > 1 year. A poor response by the modified Choi criteria more closely resembles an indeterminate response by SACT criteria than an unfavorable response by SACT criteria.

Although SACT criteria had a high sensitivity and specificity, we noticed patterns of attenuation changes in the tumors that may have limited our ability to detect patients with prolonged progression-free survival. Occasionally patients with progression-free survival of > 250 days failed to meet SACT criteria for favorable response, even though they had tumors with markedly decreased attenuation centrally (Fig. 4). Several patients (n = 6) had metastases with markedly decreased attenuation centrally but with hyperenhancement and increased attenuation of the peripheral solid tissue. This hyperenhancing and hyperattenuating peripheral tissue effectively raised the mean volumetric attenuation of the tumor beyond the threshold for a favorable response according to the SACT criteria. All of these patients with marked central necrosis had an indeterminate response by SACT criteria but had progression-free survival of > 250 days.

Substantial differences were seen between responses in sorafenib-treated patients (n = 21) and sunitinib-treated patients (n = 32). In

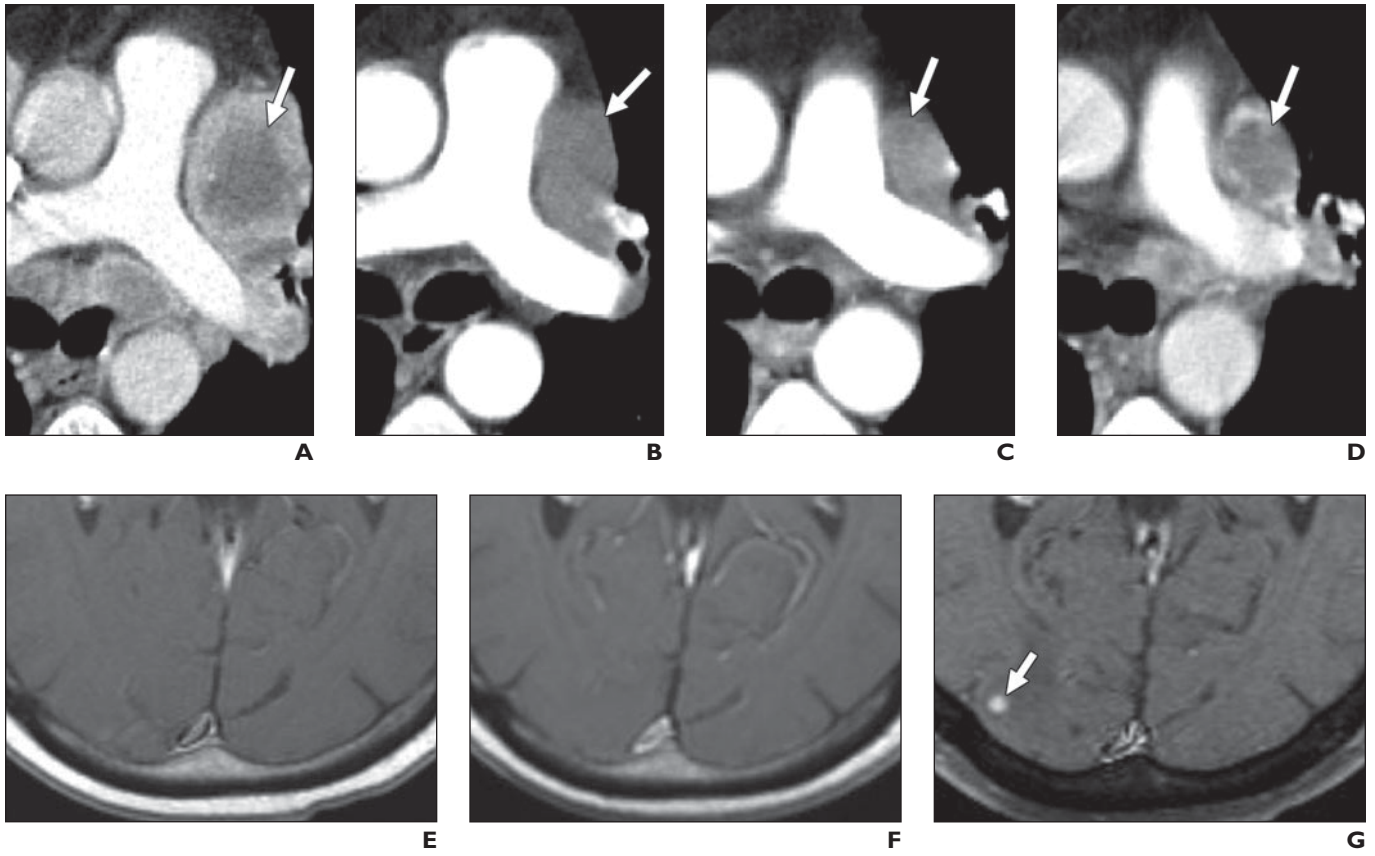

Fig. 2—49-year-old man with metastatic renal cell carcinoma (RCC). Contrast-enhanced CT (CECT) at various stages of sunitinib therapy depicts mediastinal/hilar RCC metastases and contrast-enhanced T1-weighted MR images of head depict normal brain initially and brain metastasis later.
A, CECT image obtained just prior to initiation of therapy shows enhancing mediastinal and hilar metastases. Large left mediastinal/hilar metastasis (*arrow*) has low attenuation centrally with substantial enhancing solid tissue peripherally.
B, CECT image obtained after initiating therapy shows interval markedly decreased enhancement and decreased attenuation (> 40 HU) in left mediastinal/hilar metastasis (*arrow*) and in other metastases. Entire left mediastinal/hilar mass is homogeneously low in attenuation and without enhancement.
C, CECT image obtained 71 days after initiation of therapy shows left mediastinal/hilar mass (*arrow*) is homogeneously hypoattenuating, nonenhancing, and smaller.
D, CECT image obtained 496 days after initiation of therapy shows new nodular enhancement (peripherally) in the previously homogeneously hypoattenuating nonenhancing left mediastinal/hilar mass (*arrow*) in this patient with Response Evaluation Criteria in Solid Tumors (RECIST) progressive disease.
E, MR image obtained before initiating therapy shows normal brain with no metastasis.
F, MR image obtained 496 days after initiating therapy shows no metastasis.
G, MR image obtained 595 days after initiating therapy shows progressive disease (*arrow*) with new right occipital enhancing metastasis with surrounding hypointense T1 signal, representing edema.

the sorafenib-treated patients, the sensitivity for identifying patients with progression-free survival of > 250 days (n = 15) was 0% for RECIST partial response, which is statistically significantly different from the 47% for SACT criteria favorable response (p = 0.0233, McNemar test). In sunitinib-treated patients, the sensitivity for identifying patients with progression-free survival of > 250 days (n = 29) was 24% for RECIST partial response, statistically significantly different from 90% for SACT criteria favorable response (p < 0.0001, McNemar test). The specificity was 100% for each criteria and therapy.

The patients on sorafenib therapy were less responsive to therapy by both RECIST and SACT criteria compared with the response rates of patients treated with sunitinib. Of the patients with progression-free survival of > 250 days, 0% of patients treated with sorafenib (n = 15) met RECIST partial response compared with 24% of patients treated with sunitinib (n = 29; p = 0.077, Fisher's exact test). Of the patients with progression-free survival of > 250 days, 47% treated with sorafenib (n = 15) had SACT criteria favorable response, which is statistically significantly different from 90% of patients treated with sunitinib (n = 29) with SACT criteria favorable response (p = 0.003, Fisher's exact test).

A comparison of the timing or phase of IV contrast was performed between the post–TK inhibitor and pre–TK inhibitor CT examinations. Approximately 94% of the CECT studies used to evaluate lesion attenuation (n = 69) had similar timing or phase of IV contrast on the pre–TK inhibitor and post–TK inhibitor CT scans. The post–TK inhibitor CT had a delayed phase of contrast in two studies (4%), with one patient having a favorable response by SACT criteria and the other having an indeterminate response. Similarly, the post–TK inhibitor CT had an earlier phase of contrast in two studies (4%), with one patient having an unfavorable response by SACT criteria and the other having an indeterminate response. Although early and delayed phases of IV contrast were not commonly seen, differences in

TABLE 4: Size and Attenuation CT (SACT) Criteria

Response	SACT Criteria
Favorable	No new lesion and any of the following:
	1. Decrease in tumor size[a] of ≥ 20%
	2. Decrease in tumor size[a] of ≥ 10% and ≥ half of the nonlung target lesions with ≥ 20 HU decreased mean attenuation
	3. One or more nonlung target lesions with ≥ 40 HU decreased mean attenuation
Indeterminate	Does not fit criteria for favorable or unfavorable
Unfavorable	Any of the following:
	1. Increase in tumor size[a] of ≥ 20%
	2. New metastases, marked central fill-in[b] of a target lesion, or new enhancement in a homogeneously hypoattenuating nonenhancing mass

[a]Tumor size is the sum of the longest axial diameters of target lesions (including lung and nonlung lesions) as defined by Response Evaluation Criteria in Solid Tumors.
[b]Marked central fill-in is defined as change from marked central necrosis to near complete enhancement of solid tumor centrally.

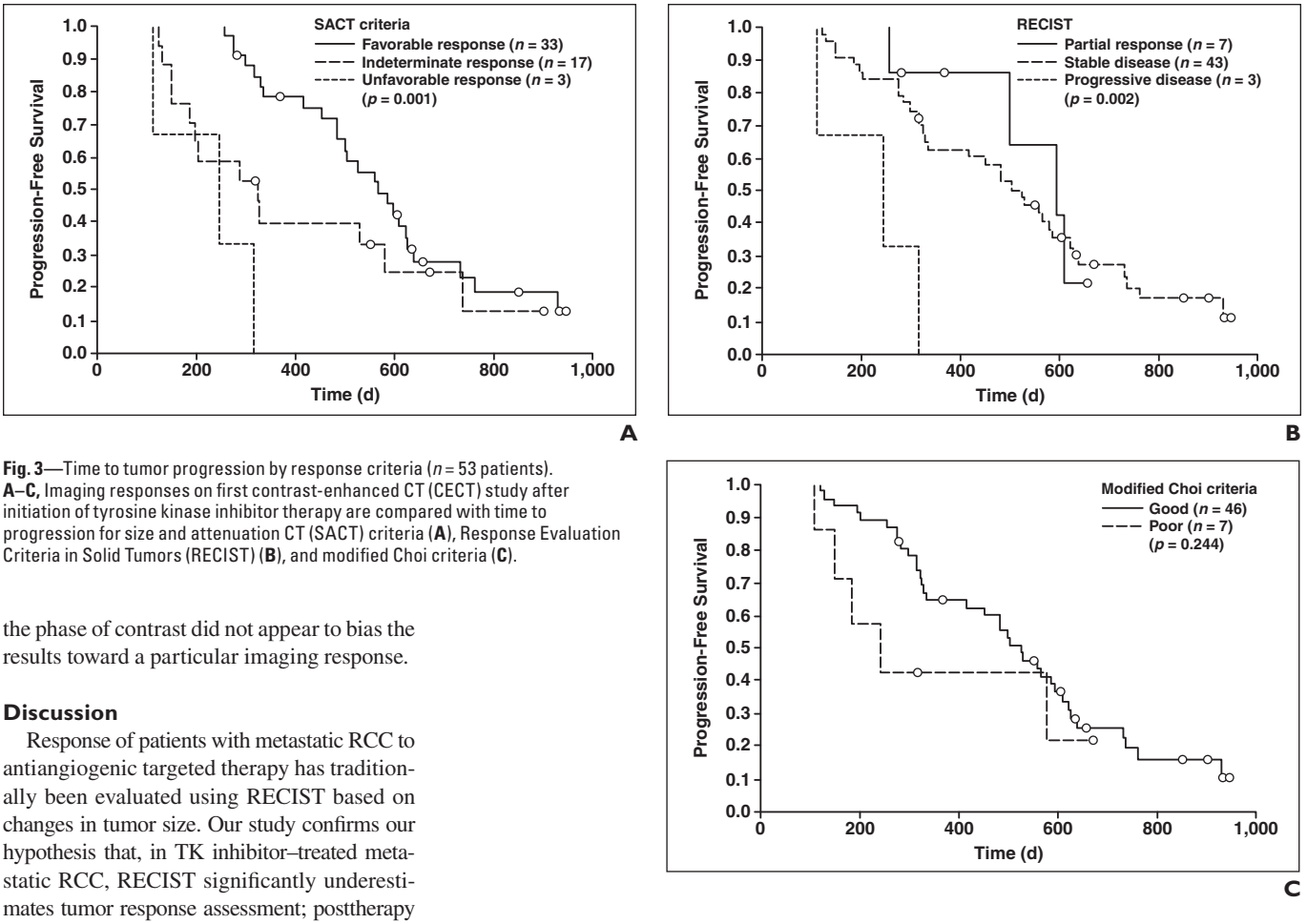

Fig. 3—Time to tumor progression by response criteria ($n = 53$ patients). **A–C,** Imaging responses on first contrast-enhanced CT (CECT) study after initiation of tyrosine kinase inhibitor therapy are compared with time to progression for size and attenuation CT (SACT) criteria (**A**), Response Evaluation Criteria in Solid Tumors (RECIST) (**B**), and modified Choi criteria (**C**).

the phase of contrast did not appear to bias the results toward a particular imaging response.

Discussion

Response of patients with metastatic RCC to antiangiogenic targeted therapy has traditionally been evaluated using RECIST based on changes in tumor size. Our study confirms our hypothesis that, in TK inhibitor–treated metastatic RCC, RECIST significantly underestimates tumor response assessment; posttherapy decreased tumor attenuation on CECT correlates with improved clinical outcome; and the development of new enhancement in a TK inhibitor–treated, low-attenuating, nonenhancing metastasis is associated with and may herald therapeutic failure. RECIST does not account for tumor attenuation changes or morphologic enhancement patterns associated with therapeutic failure that are commonly encountered in TK inhibitor–treated metastatic RCC.

Tumor angiogenesis is directly related to contrast enhancement on CT [25, 26]. Several investigators have studied tumor attenuation in TK inhibitor–treated metastatic GIST using CECT images and have correlated decreased attenuation with increased time to progression [14–20]. Others studying perfusion contrast-enhanced MDCT have shown that blood flow and enhancement decrease in sorafenib-treated adenocarcinoma in an animal model [27]. The prevailing theory is that the antiproliferative and antiangiogenic effects of TK inhibitor therapy lead to decreased tumor perfusion and thereby decreased attenuation on CECT studies. These changes in tumor blood flow and attenuation are thought to precede changes in size.

Our proposed SACT criteria had the best combination of a high sensitivity and very high specificity for response evaluation of

TABLE 5: Imaging Response Evaluation

Disease Status	% of Patients			No. of Patients
	Favorable Response by SACT Criteria	Partial Response by RECIST	Good Response by Modified Choi Criteria	
Progression-free survival > 250 d	75	16	93	44
Early progression < 250 d	0	0	56	9
p	< 0.0001[a]	0.33[a]	0.012[a]	

Note—SACT criteria = size and attenuation CT criteria, RECIST = Response Evaluation Criteria in Solid Tumors.
[a]Fisher's exact test.

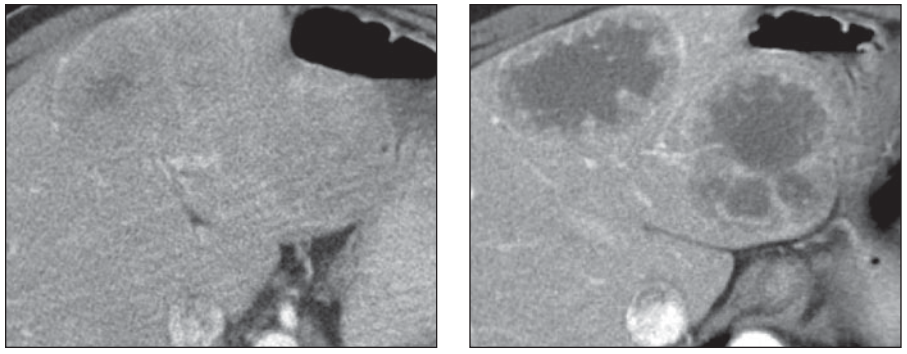

Fig. 4—64-year-old man with metastatic renal cell carcinoma (RCC). Contrast-enhanced CT (CECT) depicts two RCC metastases to liver before and after initiation of sorafenib therapy.
A, CECT scan obtained just before initiating therapy later that day shows solid enhancing liver metastases. Mean attenuation of lesions measured 97 and 86 HU. Note that peripheral attenuation of lesions is similar in attenuation to enhancing liver parenchyma).
B, CECT scan obtained 76 days after initiating tyrosine kinase inhibitor therapy shows interval marked central necrosis in both liver metastases (84 and 81 HU) with markedly decreased central attenuation. There is now relative hyperenhancement and increased attenuation of peripheral solid portions of both lesions relative to pretherapy CECT and adjacent normal enhancing liver. Overall, there is minimal decrease in mean volumetric attenuation (< 20 HU) in both lesions, even though bulk of these lesions are now centrally necrotic. Patient underwent successful therapy until progressive disease by Response Evaluation Criteria in Solid Tumors size criterion in these and other metastases (not shown) at 538 days.

TK inhibitor–treated metastatic RCC. Comparatively, the modified Choi criteria (similar to the modified CT response evaluation criteria for TK inhibitor–treated GIST described by Choi et al. [17] in 2007) had a low specificity, and RECIST had low sensitivity. A favorable response by SACT criteria was present on the first CECT after initiating therapy in 75% of patients with progression-free survival of > 250 days and was absent in those with early progression (< 250 days). SACT criteria discriminated patients with earlier progression from those with more prolonged progression-free survival; this distinction may provide important predictive information.

Although this study was not designed to compare the efficacy of sunitinib or sorafenib therapy, sunitinib therapy resulted in a more significant decrease in tumor size and attenuation in our patient population. These findings are consistent with the literature, which supports that sunitinib has higher efficacy than sorafenib [4, 5].

Several patients with progression-free survival of > 250 days had marked central necrosis (decreased attenuation centrally) but failed to meet SACT criteria for favorable response because of an insufficient decrease in size or volumetric attenuation. This was due to relative hyperenhancement at the periphery of the mass that effectively raised the mean volumetric attenuation of the tumor beyond the threshold for SACT criteria for a favorable response. Although assessment of attenuation along with size changes markedly improved response evaluation, such objective assessment of size and attenuation alone likely underestimates detection of patients who will have prolonged progression-free survival on TK inhibitor therapy. Future investigations should incorporate tumor morphologic and structural changes such as marked central necrosis that appear to correlate with prolonged progression-free survival.

Specific CECT patterns, such as marked central fill-in and new enhancement in a homogeneously hypoattenuating, nonenhancing mass, were commonly seen at or just before the time of progression and may, at times, herald disease progression. These findings were typically seen late in the course of therapy in patients with progression-free survival of > 250 days and were not seen in patients with early progression or in any patient on the first CECT study after initiating first-line TK inhibitor therapy. Such imaging findings may be seen in patients with early second-line TK inhibitor therapy failure after first-line TK inhibitor treatment drug intolerance, though this has not yet been confirmed. Based on our results, findings of marked central fill-in and new enhancement in a homogeneously hypoattenuating, nonenhancing mass should prompt the reader to search for other signs of progression, such as new metastases elsewhere. Interestingly, the nodule-in-a-mass sign denoting disease recurrence in TK inhibitor–treated metastatic GIST was not evident in our TK inhibitor–treated metastatic clear cell RCC patient population. Further understanding of tumor-specific molecular biology may shed a light on understanding the unique morphologic patterns of local tumor recurrence in various TK inhibitor–treated malignancies.

There are several potential limitations of our retrospective study. These include a small sample size (n = 53), the use of a consensus interpretation of images, and differences in imaging techniques. Of note, the high sensitivity and low specificity achieved with SACT criteria suggest that the differences in imaging technique did not adversely affect the results. In particular, the contrast phase on CECT did not appear to bias the results toward a particular SACT criteria imaging response.

In conclusion, the objective measurement of both target lesion size and attenuation using SACT criteria on the first CECT after initiating targeted therapy for metastatic clear cell RCC markedly improved therapeutic response assessment. TK inhibitor–treated metastatic RCC behaves differently than TK inhibitor–treated metastatic GIST, both in its initial response to TK inhibitor therapy and in its unique patterns of local tumor recurrence. The proposed SACT criteria were able to stratify patients with progression-free survival of > 250 days from those with earlier progression. This may provide predictive information. Future refinement of SACT criteria incorporating findings of tumor morphology,

attenuation, size, and structure may improve predictive performance.

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