



Morphology, Attenuation, Size, and Structure (MASS) Criteria: Assessing Response and Predicting Clinical Outcome in Metastatic Renal Cell Carcinoma on Antiangiogenic Targeted Therapy

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OBJECTIVE. The objective of our study was to evaluate response assessment and predict clinical outcome in patients with metastatic renal cell carcinoma (RCC) receiving antiangiogenic targeted therapy. Target lesions were assessed on routine contrast-enhanced CT (CECT) images obtained during the portal venous phase using new response criteria.

MATERIALS AND METHODS. Standard CECT examinations of patients with metastatic clear cell RCC on first-line sunitinib or sorafenib therapy ($n = 84$) were retrospectively evaluated using Mass, Attenuation, Size, and Structure (MASS) Criteria; Response Evaluation Criteria in Solid Tumors (RECIST); Size and Attenuation CT (SACT) Criteria; and modified Choi Criteria. The objective response to therapy was compared with clinical outcomes including time to progression (TTP) and disease-specific survival. The Kaplan-Meier method was used to estimate survival functions.

RESULTS. A favorable response according to MASS Criteria had a sensitivity of 86% and specificity of 100% in identifying patients with a good clinical outcome (i.e., progression-free survival of > 250 days) versus 17% and 100%, respectively, for RECIST partial response. The objective categories of response used by MASS Criteria—favorable response, indeterminate response, and unfavorable response—differed significantly from one another with respect to TTP ($p < 0.0001$, log-rank test) and disease-specific survival ($p < 0.0001$, log-rank test).

CONCLUSION. Assessment of metastatic RCC target lesions on CECT for changes in morphology, attenuation, size, and structure by MASS Criteria is more accurate than response assessment by SACT Criteria, RECIST, or modified Choi Criteria. Furthermore, the use of MASS Criteria for imaging response assessment showed high interobserver agreement and may predict disease outcome in patients with metastatic RCC on targeted therapy.

Keywords: contrast-enhanced CT, MASS Criteria, renal cell carcinoma, response criteria, tumor attenuation, tumor morphology

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Response assessment of metastatic renal cell carcinoma (RCC) to antiangiogenic targeted therapy has traditionally been based on changes in target lesion size and the presence of new metastases on a cross-sectional imaging technique such as contrast-enhanced CT (CECT). However, recent data have shown the inadequacy of Response Evaluation Criteria in Solid Tumors (RECIST) in assessing therapeutic response in patients with metastatic clear cell RCC who have received antiangiogenic targeted therapy with tyrosine kinase inhibitors (TK-inhibitors) [1].

More recently, changes in tumor attenuation and morphology, not accounted for in RECIST, have been detected on CECT in patients with metastatic RCC on TK-inhibitor therapy [1–6]. Our previous study showed that objective analysis of both tumor size and attenuation on CECT improves response

evaluation in patients with metastatic clear cell RCC; specifically, decreased tumor size and decreased attenuation on CECT more frequently correlate with increased progression-free survival than lesion size changes alone by RECIST [1]. In addition, our study revealed specific patterns of target lesion enhancement: marked central fill-in of a previously centrally necrotic metastasis or new enhancement in a homogeneously hypoattenuating nonenhancing mass is associated with or is indicative of disease progression [1]. These findings were incorporated into Size and Attenuation CT (SACT) Criteria.

Composed of objective response criteria based on the evaluation of tumor size and attenuation on portal venous phase CECT examinations, SACT Criteria effectively stratified patients with earlier progression from those with more prolonged progression-free survival [1]; however, there were limitations.

Criteria to Assess TKI-Treated Metastatic RCC

SACT Criteria did not account for specific morphologic or structural changes (e.g., tumor necrosis) in treated metastases [1]. Attenuation measurements by SACT Criteria involved 3D volumetric assessment of metastases using advanced proprietary image analysis software that was time consuming to use and labor intensive [1]. Some patients on targeted therapy with prolonged progression-free survival had metastases with marked decreased central attenuation but with hyperenhancing peripheral solid tissue with little change in volumetric attenuation, a pattern that was often categorized as an indeterminate response but that was thought to represent a good response to antiangiogenic therapy.

To improve response assessment in TK-inhibitor-treated metastatic RCC, we attempted to correct the deficiencies in SACT Criteria and to simplify the assessment criteria. We eliminated the need for advanced 3D lesion analysis and accounted for changes in lesion morphology, attenuation, size, and structure on routine axial portal venous phase CECT images. The objective of this study was to assess whether decreased target lesion size and marked decreased attenuation or marked central necrosis of target lesions on portal venous phase CECT correlate with prolonged progression-free survival and whether modified response criteria will yield greater accuracy in assessing tumor response than SACT Criteria, RECIST, or modified Choi Criteria.

Materials and Methods

Patient Population

Informed consent was waived in this institutional review board–approved HIPAA-compliant retrospective study. A search of the outpatient electronic medical record database from January 2000 through December 2007 was performed for all patients who were treated with first-line sorafenib or sunitinib. All included patients had pathology-proven metastatic clear cell RCC and either were continuously taking daily oral therapy with 400 mg of sorafenib (Nexavar, Bayer HealthCare) or were taking 50 mg of sunitinib (Sutent, Pfizer) daily oral therapy for 4 weeks followed by 2 weeks off therapy, with the 6-week cycles being repeated. Patients were excluded if they were off therapy for any reason for more than 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.

All included patients were on first-line sunitinib or sorafenib therapy and underwent CECT before TK-inhibitor therapy (pre-TK-inhibitor CT) and initially after starting TK-inhibitor ther-

TABLE 1: Morphology, Attenuation, Size, and Structure (MASS) Criteria

Objective Response	MASS Criteria Description
Favorable response	No new lesion and any of the following: 1. Decrease in tumor size ^a of $\geq 20\%$ 2. One or more predominantly solid enhancing lesions with marked central necrosis or marked decreased attenuation (≥ 40 HU) ^b
Indeterminate response	Does not fit criteria for favorable response or unfavorable response
Unfavorable response	Any of the following: 1. Increase in tumor size ^a of $\geq 20\%$ in the absence of marked central necrosis or marked decreased attenuation 2. New metastases, marked central fill-in ^c , or new enhancement of a previously homogeneously hypoattenuating nonenhancing mass

^aTumor size is the sum of the longest diameters of target lesions as defined by Response Evaluation Criteria in Solid Tumors parameters. Brain lesions were excluded from MASS Criteria analysis.

^bMarked central necrosis is defined as $> 50\%$ of the enhancing central portion of a predominantly solid enhancing mass subjectively changing to near fluid attenuation (necrosis) after treatment. Marked decreased attenuation is defined as decreased attenuation of all or almost all of a mass by ≥ 40 HU using region-of-interest measurements of lesions on axial contrast-enhanced CT images. Parenchymal lung lesions and predominantly cystic or necrotic lesions seen on the CT study performed before initiating tyrosine kinase inhibitor therapy were not assessed for marked central necrosis or marked decreased attenuation.

^cMarked central fill-in is defined as a subjective change from marked central necrosis to complete or near complete central intratumoral enhancement on contrast-enhanced CT.

apy (post-TK-inhibitor CT). Two patient groups were studied. For patients in the training group, long-axis size measurements and mean volumetric attenuation of target lesions and RECIST evaluation had already been performed on the pre- and post-TK-inhibitor CT studies on these patients from our prior study [1]. None of the patients in the test group had been previously evaluated.

The electronic medical records were searched for the date of initiation of therapy, dates of pre-TK-inhibitor and post-TK-inhibitor CECT scans, and date and cause of disease progression as well as death. Time to progression (TTP) was defined as the length of time on TK-inhibitor therapy until discontinuation because of metastatic disease progression as determined by the clinical oncologist's notes in the electronic medical record. Disease-specific survival was the length of time from initiating TK-inhibitor therapy until death from progressive metastatic disease. The imaging test, date of the study showing disease progression, and location of disease progression or new metastases were recorded.

Imaging

All images were acquired in a single academic medical center. CECT images were obtained at our institution with MDCT scanners (Emotion Duo, Volume Zoom, and Sensation 16; Siemens Healthcare) and included oral contrast material and 150 mL of IV nonionic iodinated water-soluble contrast material (usually 300 mg I/mL iopro-

midate [Ultravist, Bayer HealthCare]). Chest images were obtained 20 seconds after IV contrast 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.

Response Criteria Assessment

For each patient, the post-TK-inhibitor CT study was compared with the pre-TK-inhibitor CT study using Morphology, Attenuation, Size, and Structure (MASS) Criteria, RECIST, SACT Criteria, and modified Choi Criteria. Parameters included in MASS Criteria were derived from our previous study with assessment of lesions limited to axial CT images without postprocessing software [1]. Our previous work confirmed the importance of marked decreased attenuation (≥ 40 HU) and marked central necrosis in addition to size changes in early tumor response assessment. These findings and findings associated with tumor progression—new metastases, marked central fill-in, and new enhancement in a previously homogeneously enhancing metastasis—were incorporated into MASS Criteria.

The imaging response categories used by MASS Criteria were favorable response, indeterminate response, or unfavorable response (Table 1). The imaging response categories used by RE-

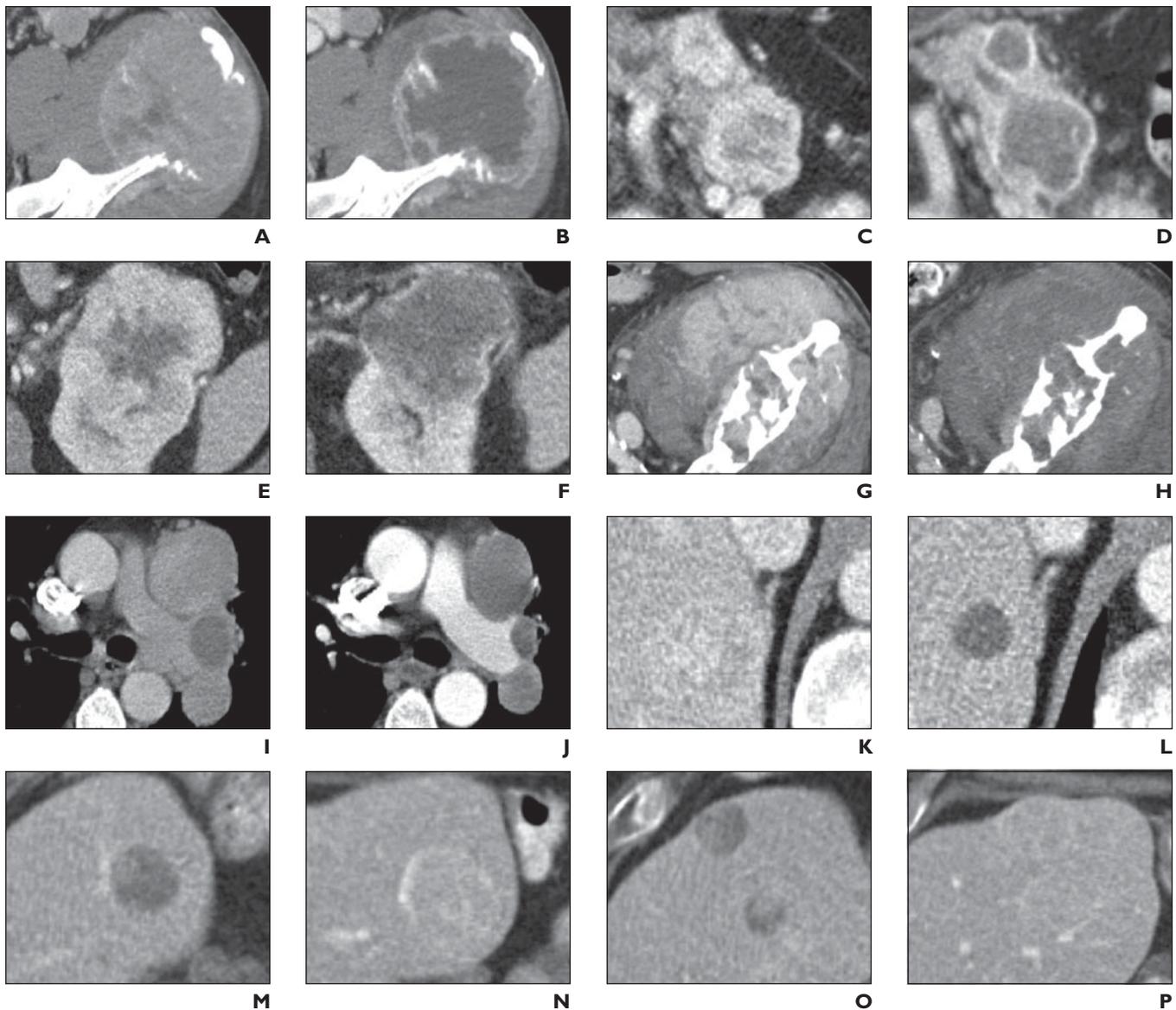


Fig. 1—Multiple contrast-enhanced CT (CECT) examinations of renal cell carcinoma (RCC) metastases in different patients before and shortly after initiating antiangiogenic tyrosine kinase inhibitor (TK-inhibitor) therapy. Images depict examples of morphologic, attenuation, and structural changes used in Morphology, Attenuation, Size, and Structure (MASS) Criteria.

A and B, 34-year-old man. CT images obtained before (**A**) and after (**B**) TK-inhibitor therapy show marked central necrosis. Predominantly solid enhancing left iliac wing metastasis develops marked decreased attenuation centrally (> 50% of mass now with fluid attenuation), shows persistent peripheral enhancement, and shows minimal change in size after initiating TK-inhibitor therapy (**B**).

C and D, 71-year-old woman. CT images obtained before (**C**) and after (**D**) TK-inhibitor therapy show marked central necrosis. Adjacent, predominantly solid, avidly enhancing pancreatic metastasis (**C**) develops marked decreased attenuation centrally (> 50% of masses), shows persistent peripheral enhancement, and shows minimal change in size after initiating TK-inhibitor therapy (**D**).

E and F, 63-year-old man. CT images obtained before (**E**) and after (**F**) TK-inhibitor therapy show marked central necrosis. Large predominantly solid enhancing renal metastasis (**E**) develops marked decreased attenuation centrally (> 50% of mass), shows persistent nodular peripheral enhancement, and is decreased in size after initiating TK-inhibitor therapy (**F**).

G and H, 69-year-old man. CT images obtained before (**G**) and after (**H**) TK-inhibitor therapy show marked decreased attenuation. Intensely and heterogeneously enhancing left iliac wing metastasis (**G**) shows interval near-complete diffuse decrease in enhancement (≥ 40 HU decrease) and minimal change in size after initiating TK-inhibitor therapy (**H**).

I and J, 64-year-old man. CT images obtained before (**I**) and after (**J**) TK-inhibitor therapy show marked decreased attenuation. Three enhancing left hilar and mediastinal metastases (**I**) show interval diffuse decrease in enhancement (≥ 40 HU decrease) and small decrease in long-axis size (**J**).

K and L, 63-year-old man. CT images obtained before (**K**) and after (**L**) TK-inhibitor therapy show marked decreased attenuation. Liver metastasis with slightly increased enhancement relative to adjacent normal liver parenchyma (**K**) shows marked interval decreased enhancement (≥ 40 HU decrease) and is hypoattenuating relative to adjacent normal liver parenchyma (**L**).

M–P, 75-year-old man who had progressive disease on first-line sunitinib therapy. CT images obtained before (**M** and **O**) and after (**N** and **P**) TK-inhibitor therapy show marked central fill-in. Three hypoattenuating liver metastases show mild heterogeneous enhancement (**M** and **O**). After initiation of sorafenib therapy (second-line TK-inhibitor therapy, **N** and **P**), metastases have increased in size and now have complete homogeneous central intratumoral enhancement and more solid appearance (**N** and **P**). Overall progression of disease with regard to tumor size is evident on this CECT, and sorafenib therapy was discontinued.

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CIST were complete response, partial response, stable disease, or progressive disease. The imaging response categories used by SACT Criteria were favorable response, indeterminate response, or unfavorable response [1]. The imaging response categories used by modified Choi Criteria were good or poor.

For each criterion, the long-axis size measurements of the target lesions, which were 1 cm in length or greater, were followed in each chest, abdomen, and pelvis CECT study using RECIST parameters [7]. Up to 10 target lesions per patient were chosen with up to five in any one body organ. All target lesion measurements were made by an abdominal imaging fellow, observer 1, and were confirmed by an experienced fellowship-trained academic abdominal radiologist, observer 2. Lesions were chosen in proportion to their preponderance in each organ when multiple were present, and the largest lesions in each body region were chosen. Osseous lesions with a soft-tissue component of more than 1 cm were included, whereas sclerotic osseous lesions were excluded. Brain metastases were excluded from any measurements because they were imaged predominantly with MRI and often had adjuvant treatment with gamma knife therapy.

For assessment using MASS Criteria, predominantly solid enhancing target lesions were evaluated for marked central necrosis or marked decreased attenuation on axial CECT images. Although long-axis size measurements of lung parenchymal target lesions and of predominantly cystic or necrotic target lesions on the pre-TK-inhibitor CT studies were made, these target lesions were not evaluated for marked central necrosis or marked decreased attenuation (features of MASS Criteria, favorable response) because of limitations resulting from partial volume effects and limited enhancing components, respectively.

Marked central necrosis was defined as more than 50% of the enhancing central portion of a predominantly solid enhancing mass subjectively changing to near fluid attenuation (necrosis) after treatment (Fig. 1). Marked decreased attenuation was defined as decreased attenuation of all or almost all of a predominantly solid enhancing mass by 40 HU or greater (Fig. 1). As part of MASS Criteria unfavorable response category, all nonlung lesions were assessed for the presence of marked central fill-in or new intratumoral enhancement in a previously homogeneously hypoattenuating nonenhancing mass on the post-TK-inhibitor CT study. Marked central fill-in was defined as a subjective change from marked central necrosis to complete or near-complete central intratumoral enhancement (Fig. 1).

Contrast-enhanced CT studies from the training group were assessed by observers 1 and 2 in

consensus, and imaging responses based on the different assessment criteria were recorded. The training group had previously been evaluated using SACT Criteria, RECIST, and modified Choi Criteria [1]. Assessments of the training group using SACT Criteria and modified Choi Criteria were conducted using measurements of mean volumetric attenuation (HU) of each nonlung target lesion by observer 1 using volumetric software (Oncocare, Siemens Healthcare) [1]. Volumetric measurements were calculated using semiautomated edge-detection software by observer 1; image scenes containing multiplanar images in three orthogonal planes and a volumetric rendition of target lesions were saved, reviewed, and confirmed by observer 2 in consensus [1].

According to SACT Criteria, a favorable response was assigned if any of the following criteria were met: a decrease in tumor size of $\geq 20\%$, a decrease in tumor size of $\geq 10\%$ and ≥ 20 HU decrease in mean attenuation of one half or more of the nonlung target lesions or a ≥ 40 HU decreased mean attenuation of one or more nonlung target lesions. An unfavorable response consisted of either an increase in tumor size of $\geq 20\%$ or one of the following: a new metastasis, marked central fill-in of a target lesion, or new enhancement in a homogeneously hypoattenuating nonenhancing mass. An indeterminate response was the default category if response was determined to be neither favorable nor unfavorable.

For modified Choi Criteria, volumetric tumor attenuation measurements were combined, and a mean attenuation (HU) for each patient was computed. The percentage change in mean volumetric tumor attenuation for each patient was calculated. A good response according to modified Choi Criteria was defined as $\geq 10\%$ mean decrease in tumor size or a $\geq 15\%$ decrease in mean tumor attenuation in a patient. Patients not meeting the

criteria for a good response were classified as having a poor response.

Long-axis size measurements of target lesions from patients in the test group were made on pre- and post-TK-inhibitor CT studies by observer 1 and subsequently were independently evaluated using MASS Criteria and RECIST by experienced fellowship-trained abdominal radiologists, observer 2 and observer 3, each of who was blinded to clinical outcomes. For all patient groups, the interpreting reader was permitted to use a region-of-interest (ROI) measurement tool on axial images to measure mean tumor attenuation. A consensus assessment was made when the readers disagreed on the final response assessment. The final consensus imaging responses were subsequently correlated with TTP and disease-specific survival.

MASS Criteria imaging responses were correlated with the phase of IV contrast on the post-TK-inhibitor CT study relative to the pre-TK-inhibitor CT study to assess the importance of the CECT phase of IV contrast administration on response evaluation. Comparison of the timing or phase of IV contrast was made on each CECT study with target lesions. A single reader (observer 2) blinded to patient outcome subjectively determined if the contrast phase on the post-TK-inhibitor CT study was earlier, similar, or delayed relative to the pre-TK-inhibitor CT study.

Statistical Analysis

The Kaplan-Meier (product-limit) method was used to estimate survival functions for TTP and disease-specific survival. All cases for which progression was not observed were treated as right-censored with respect to the TTP; 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

TABLE 2: Patient Demographics and Therapy

Characteristic	Training Group	Test Group
No. of patients	53	31
No. of target lesions	219	159
Sex (no. of patients)		
Male	40	25
Female	13	6
Age (y)		
Mean	60	58
Range	34–77	41–78
TK-inhibitor therapy (no. of patients)		
Sunitinib	32	22
Sorafenib	21	9

Note—TK-inhibitor = tyrosine kinase inhibitor.

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.

Results

Patient demographics, the number of target lesions, and the specific TK-inhibitor therapy are shown in Table 2. Three patients on sunitinib therapy were excluded from the study because they were temporarily off therapy for more than 1 week during an on-therapy portion of the protocol.

Most patients with pre- and post-TK-inhibitor CECT examinations (80 of 84) underwent standard CECT of the chest concurrently with portal venous phase CECT of the abdomen and pelvis. In the remaining four patients who had a triphasic pre-TK-inhibitor CECT of the abdomen, the sequence closest to the portal venous phase was used for analysis.

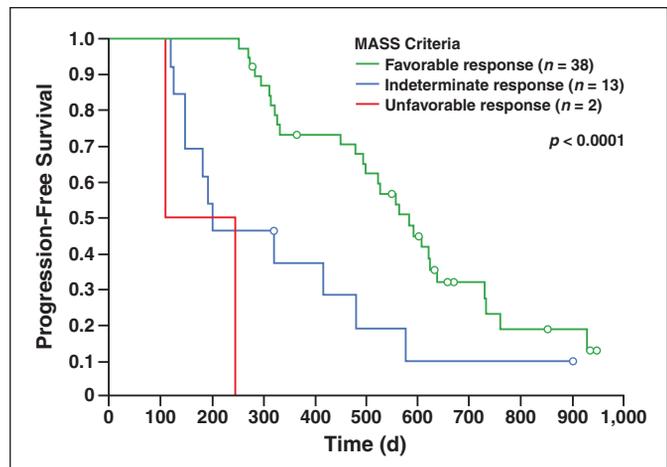
Several patients had only lung target lesions (four patients in the training group and three patients in the test group), and analysis of these lesions was limited to long-axis size measurements only. Several patients had brain metastases (five patients in the training group and one patient in the test group); all of these patients had additional extracranial metastases that were evaluated using MASS Criteria and RECIST.

The slice thickness for the chest CECT examinations ranged from 1 to 5 mm; 70% of the examinations had 5-mm slice thickness. The slice thickness for the abdomen and pelvis CECT examinations ranged from 3 to 5 mm; 82% had 5-mm slice thickness. The median time of scanning for pre-TK-inhibitor CT was 10 days before initiating therapy (range, 0–39 days). The median time of scanning for the post-TK-inhibitor CT was 61 days after initiating therapy (range, 28–129 days).

No patients had RECIST complete response on the first CECT study after initiating TK-inhibitor therapy. Three patients on sunitinib therapy in the test group had disease progression due to clinical deterioration not attributable to therapy alone. All other patients in the study had RECIST progressive disease based on size criteria or the presence of new metastases at the time of disease progression.

When patients in the training group ($n = 53$) were evaluated using MASS Criteria on the first CECT after initiating therapy, significant differences in TTP were observed be-

Fig. 2—Tumor response assessment by Morphology, Attenuation, Size, and Structure (MASS) Criteria. Imaging responses on first contrast-enhanced study after initiating antiangiogenic tyrosine kinase inhibitor therapy were compared with time to progression for training group ($n = 53$ patients).



tween favorable, indeterminate, and unfavorable responses ($p < 0.0001$, log-rank test; Fig. 2). Compared with the previously reported responses by SACT Criteria in these patients [1], MASS Criteria yielded better separation between the curves and a smaller p value by log-rank test (MASS Criteria vs SACT Criteria, $p < 0.0001$ vs $p = 0.001$).

Table 3 compares the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of MASS Criteria, SACT Criteria, modified Choi Criteria, and RECIST in the training group for identifying patients with progression-free survival of more than 250 days; data from the latter three criteria had been previously obtained using the same patient population [1]. The response assessment tool with the highest accuracy for identifying patients with a good clinical outcome (progression-free survival of > 250 days) was MASS Criteria. MASS Criteria, SACT Criteria, and RECIST had similar detection rates for patients with poor clinical outcome (disease progression in < 250 days). Modified Choi

Criteria had higher sensitivity but substantially lower specificity than MASS Criteria. Although not specifically measured, the time to interpret images using MASS Criteria on axial CECT images (≈ 10 minutes per patient) was substantially less than the time to interpret images using SACT Criteria (≈ 1 – 2 hours per patient), which includes volumetric attenuation measurements on an advanced 3D workstation.

Similar to the training group, significant differences in TTP were observed between MASS Criteria objective responses in patients in the test group ($n = 31$; $p < 0.0001$, log-rank test). Significant differences in TTP were also observed between RECIST objective responses in the test group ($p < 0.0001$, log-rank test).

All patients with MASS Criteria favorable response ($n = 56$) or RECIST partial response ($n = 11$) had a good clinical outcome (progression-free survival of > 250 days). The sensitivity of MASS Criteria favorable response for predicting a good clinical outcome using the first CECT after initiating

TABLE 3: Evaluation of Response to Therapy in the Training Group ($n = 53$)

Performance Measure for Identifying Patients With a Good Clinical Outcome	Progression-Free Survival > 250 d ($n = 44$)			
	MASS Criteria Favorable Response	SACT Criteria Favorable Response	Modified Choi Criteria Good Response	RECIST Partial Response
Sensitivity (%)	86	75	93	16
Specificity (%)	100	100	44	100
PPV (%)	100	100	89	100
NPV (%)	60	45	57	20
Accuracy (%)	89	79	85	30

Note—MASS Criteria = Morphology, Attenuation, Size, and Structure Criteria; SACT Criteria = Size and Attenuation CT (SACT) Criteria; RECIST = Response Evaluation Criteria in Solid Tumors; PPV = positive predictive value; NPV = negative predictive value.

Criteria to Assess TKI-Treated Metastatic RCC

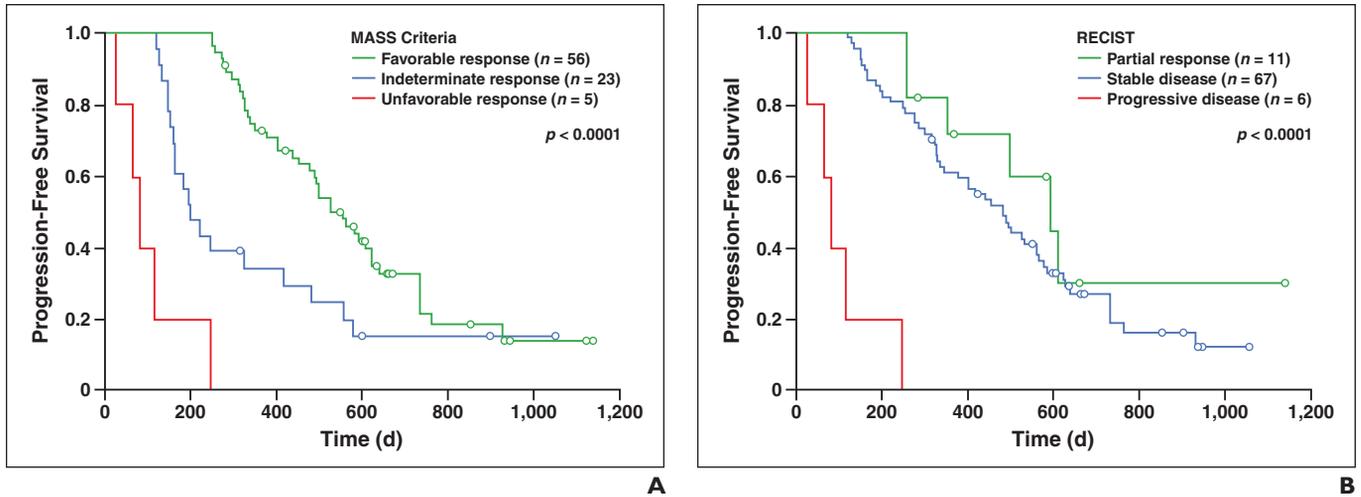


Fig. 3—Time to progression (TTP) by response criteria. Imaging responses on first contrast-enhanced study after initiating therapy were compared with TTP in all patients ($n = 84$ patients, combined training and test groups).

A and B, TTP according to Morphology, Attenuation, Size, and Structure (MASS) Criteria (**A**) and to Response Evaluation Criteria in Solid Tumors (RECIST) (**B**).

TK-inhibitor therapy was 86% in the training group ($n = 44$) and 86% in the test group ($n = 21$), which are statistically significantly different from the sensitivities of RECIST partial response, 16% and 13% ($p < 0.03$ and $p = 0.0005$, respectively, McNemar test).

For all patients ($n = 84$; combined training and test groups), significant differences in TTP were observed between MASS Criteria objective responses ($p < 0.0001$, log-rank test; Fig. 3A). Similar differences in TTP were also observed between RECIST objective responses in these patients ($p < 0.0001$, log-rank test; Fig. 3B), although the detection rate for patients with a good clinical outcome (progression-free survival of > 250 days) was substantially higher using MASS Criteria.

Table 4 compares the sensitivity, specificity, PPV, NPV, and accuracy of MASS Criteria and RECIST for identifying patients with progression-free survival of more than 250 days or progression-free survival of more than 1 year in all patients ($n = 84$; combined training and test groups). The sensitivity of a favorable response according to MASS Criteria on the first CT after initiating antiangiogenic therapy for identifying patients with a good clinical outcome was 86% for patients with progression-free survival of more than 250 days ($n = 65$) and 85% for patients with progression-free survival of more than 1 year ($n = 47$), which are statistically significantly different from the 17% and 15% sensitivities, respectively, of RECIST partial response ($p < 0.0001$ and $p < 0.0001$, respectively, McNemar test).

The specificity and accuracy of MASS Criteria favorable response were 100% and 89%

TABLE 4: Evaluation of Response to Therapy in All Patients ($n = 84$)

Performance Measure for Identifying Patients With a Good Clinical Outcome	Progression-Free Survival > 250 d ($n = 65$ patients)		Progression-Free Survival > 1 y ($n = 47$ patients)	
	MASS Criteria Favorable Response	RECIST Partial Response	MASS Criteria Favorable Response	RECIST Partial Response
Sensitivity (%)	86	17	85	15
Specificity (%)	100	100	59	89
PPV (%)	100	100	73	64
NPV (%)	68	26	76	45
Accuracy (%)	89	36	74	48

Note—MASS Criteria = Morphology, Attenuation, Size, and Structure Criteria; SACT Criteria = Size and Attenuation CT (SACT) Criteria; RECIST = Response Evaluation Criteria in Solid Tumors; PPV = positive predictive value; NPV = negative predictive value.

for identifying patients with progression-free survival of more than 250 days, substantially higher than 59% and 74%, respectively, for identifying patients with progression-free survival of more than 1 year. No patients with a good clinical outcome (progression-free survival of > 250 days) had MASS Criteria unfavorable response on their first CT after initiating TK-inhibitor therapy.

Early progression (< 250 days) was present in 19 of 84 patients in this study. All patients with an unfavorable response according to MASS Criteria ($n = 5$) on the first CECT after initiating TK-inhibitor therapy had early progression (conferring 100% specificity); the remaining patients with early progression were classified as having an indeterminate response by MASS Criteria. Of patients with an indeterminate response according to MASS Criteria ($n = 23$), nearly three fourths of patients (74%) had early progression.

For all patients ($n = 84$, combined training and test groups), significant differences in disease-specific survival were seen between MASS Criteria objective responses and between RECIST objective responses ($p < 0.0001$ and $p = 0.004$, respectively, log-rank test) (Fig. 4). For MASS Criteria, patients with unfavorable response on their first CT after initiating therapy had earlier disease-specific death than patients with either favorable response or indeterminate response. Similarly, with RECIST, patients with progressive disease had earlier disease-specific death than patients with either partial response or stable disease.

Marked central necrosis and marked decreased attenuation were seen on CECT examinations in metastases in nearly all body regions including the chest wall, thyroid, pleura, mediastinum, hila, muscle, bone, liver, gallbladder, pancreas, adrenals, kidneys, retroperitoneum,

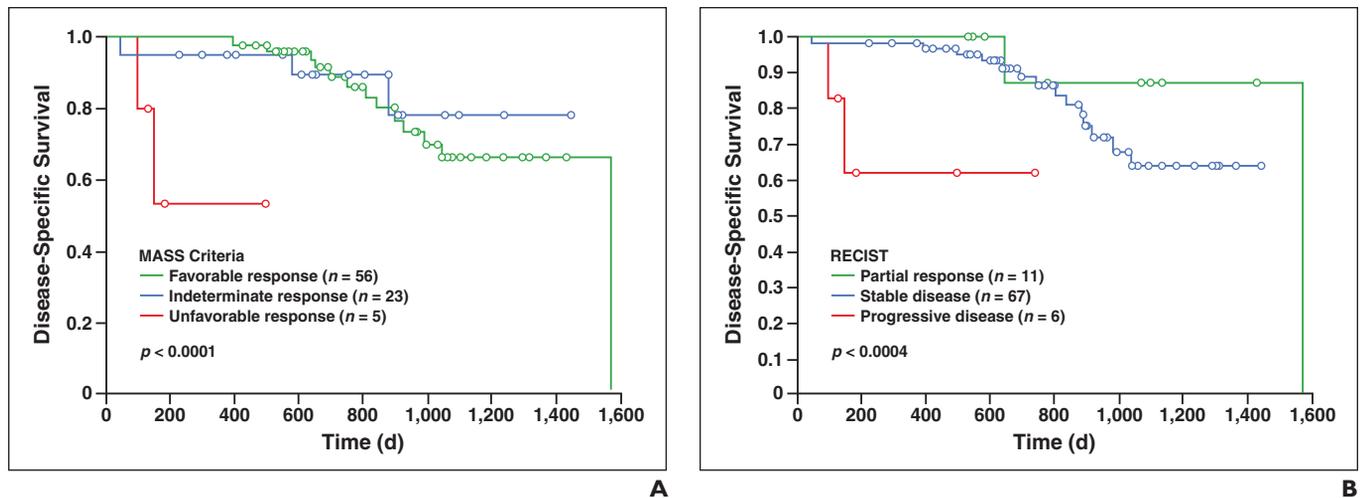


Fig. 4—Disease-specific survival by response criteria. Imaging responses on first contrast-enhanced study after initiating therapy were compared with disease-specific survival for all patients ($n = 84$ patients, combined training and test groups).

A and B, Disease-specific survival according to Morphology, Attenuation, Size, and Structure (MASS) Criteria (**A**) and to Response Evaluation Criteria in Solid Tumors (RECIST) (**B**).

inferior vena cava, and mesentery and in the lymph nodes of the mediastinum, hila, retrocaval space, retroperitoneum, mesentery, and pelvis. Of the 65 patients with a good clinical outcome (progression-free survival of > 250 days), 74% had one or more target lesions that showed marked central necrosis or marked decreased attenuation (meeting MASS Criteria favorable response), 45% of patients had a decrease in size of more than 20% (also meeting MASS Criteria favorable response), and 17% of patients had a decrease in size of more than 30% (meeting RECIST partial response). Although no lung metastases were assessed for morphologic, attenuation, or structural changes, some of the larger lung nodules showed decreased attenuation in patients with a good clinical response. None of the patients on first-line TK-inhibitor therapy ($n = 84$) had marked central fill-in or new enhancement in a homogeneously hypoattenuating nonenhancing mass on the first CECT study after initiating TK-inhibitor therapy.

Blinded reader agreement on classifying objective response using MASS Criteria (favorable response, indeterminate response, or unfavorable response) was 97% for patients in the test group ($n = 31$; 95% CI, 91–100%). Readers 1 and 2 classified objective response as favorable in 15 and 14 of the 31 cases, respectively; this difference was not significant ($p = 0.32$, McNemar test). In the one patient in whom there was reader discordance (favorable response vs indeterminate response) on the initial post-TK-inhibitor CT, a final consensus of indeterminate response was made; that patient had progression-free survival of more than 250 days.

Because attenuation values of the metastatic lesions were critical to our assessment on the contrast-enhanced pre- and post-TK-inhibitor CT studies, particularly for the finding of marked decreased attenuation (≥ 40 HU), a comparison of the timing or phase of contrast enhancement was performed. Approximately 94% of all CECT studies used to evaluate lesion morphology, attenuation, and structure ($n = 101$) had similar timing or phase of contrast enhancement on the pre- and post-TK-inhibitor CT images. Post-TK-inhibitor CT had a delayed phase of enhancement in two studies (2%); in one patient, MASS Criteria objective response was favorable response and in the other patient, indeterminate response. Similarly, the post-TK-inhibitor study had an earlier phase of contrast enhancement in four studies (4%), with MASS Criteria favorable response in one patient, indeterminate response in two patients, and unfavorable response in one patient. The occasional differences in the phase of contrast enhancement did not appear to bias the results toward selecting a particular MASS Criteria imaging response category.

Discussion

Recent investigations have suggested that size measurements alone using RECIST substantially underestimate metastatic RCC response to antiangiogenic targeted therapy [1–3, 8, 9]. Objective measurements of changes in both tumor size and attenuation on the first CECT study after initiating antiangiogenic targeted therapy for metastatic RCC have been shown to markedly improve

the accuracy of therapeutic response assessment [1]. The use of MASS Criteria, which incorporate assessment of tumor morphology and structure in addition to tumor size and attenuation, further improves accuracy.

MASS Criteria account for the presence of new metastases and incorporate changes in axial long-axis tumor size as well as morphologic, attenuation, structural, and enhancement changes in target lesions on CECT in patients on targeted antiangiogenic therapy for metastatic RCC. Lesion assessment using MASS Criteria on routine portal venous phase CECT images allows a robust and rapid method of response assessment compared with assessment using SACT Criteria or modified Choi Criteria, which require advanced proprietary image analysis software that is time consuming to use or that is not universally available on all imaging workstations. Although less objective than the strict volumetric attenuation tolerances of SACT Criteria or modified Choi Criteria, the assessment of attenuation on axial images and additional assessment of tumor morphology and structure showed high interobserver agreement in our test group.

In patients with metastatic clear cell RCC on antiangiogenic targeted therapy, both MASS Criteria favorable response and RECIST partial response strongly correlated with a good clinical outcome (i.e., increased TTP and increased disease-specific survival). Conversely, both MASS Criteria unfavorable response and RECIST progressive disease strongly correlated with a poor clinical outcome (i.e., decreased TTP and de-

creased disease-specific survival). The differences in response assessments between these criteria are the markedly improved sensitivity (and thereby accuracy) of MASS Criteria for identifying patients with a good clinical outcome as measured by progression-free survival.

MASS Criteria favorable response in patients with TK-inhibitor-treated metastatic RCC on first-line therapy had a sensitivity of 86%, specificity of 100%, PPV of 100%, and NPV of 68% for detecting patients with a good clinical outcome—namely, progression-free survival of more than 250 days. MASS Criteria favorable response had an overall accuracy of 89% for predicting a good clinical outcome, which is higher than that obtained by a favorable response by SACT Criteria, a good response by modified Choi Criteria, or a partial response by RECIST. An unfavorable response by MASS Criteria was relatively more infrequent but was 100% specific for identifying patients with early disease progression (< 250 days). One should note that although sensitivity and specificity are independent of disease prevalence, variables such as accuracy, PPV, and NPV are dependent on disease prevalence and may vary among different patient populations.

Identifying marked central necrosis and marked decreased attenuation on CECT examinations improved detection of a good clinical outcome (vs size measurements alone) when assessing the first CECT study after initiating TK-inhibitor therapy. Presumably, the benefit of MASS Criteria in assessing unenhanced CT studies would be limited because marked decreased attenuation (≥ 40 HU) is unlikely to be present and because marked central necrosis would be more difficult to identify in the absence of IV contrast material.

In our experience, MASS Criteria seem to best stratify patients into those with early disease progression (< 250 days) and those with progression-free survival of more than 250 days. Although 1 year is the standard time point used in oncologic follow-up, the 250-day time point may relate to the biologic activity of TK-inhibitor-treated metastatic RCC. In our cohort, the ability of MASS Criteria to discriminate between those patients whose disease will progress in less than 1 year after therapy from those with progression-free survival of more than 1 year was less specific.

The predictive information available based on MASS Criteria can be obtained from a routine CECT without the cost of addition-

al radiation or imaging and with minimal added work by the interpreting radiologist. In addition, information from tumor assessment using MASS Criteria can be gained from the first CT after initiating antiangiogenic targeted therapy, often before significant tumor size changes that are captured by RECIST. This predictive information could influence imaging surveillance in patients with MASS Criteria unfavorable response or indeterminate response to identify early disease progression.

Because MASS Criteria are limited to response assessment by CT only, the added value of other clinical prognostic factors is yet to be correlated or tested. Prognostic clinical nomograms have identified clinical factors that have been used to stratify patients with TK-inhibitor-treated metastatic RCC into different risk categories before initiating therapy [10–12]. Future improvement in predicting clinical outcome of metastatic RCC on targeted therapy may include a combination of clinical and laboratory information and early imaging patterns after initiating therapy.

There are potential limitations of our retrospective study. MASS Criteria parameters were derived from our prior study using images from the training group ($n = 53$), and consensus interpretation was used in this study when assessing these patients [1]. MASS Criteria were, however, subsequently upheld when tested independently by two readers blinded to clinical outcome in the test group ($n = 31$) with high interobserver agreement. Similar sensitivity, specificity, PPV, NPV, and accuracy were obtained in the test group ($n = 31$), a population of patients similar in composition to the training group.

Although it is plausible that differences in the phase of IV contrast between the pre- and posttherapy CECT examinations could limit interpretation by MASS Criteria, which incorporates evaluation of tumor attenuation changes between studies, the infrequent differences in the phase of IV contrast did not appear to bias the results toward selecting a particular MASS Criteria imaging response category in our patient population.

MASS Criteria parameters have not been validated in patients using unenhanced CT studies, although it seems plausible that MASS Criteria could be applied in a limited fashion to evaluate response in patients with unenhanced CT. Last, the ability of MASS Criteria to predict patient outcome may be limited in patients when TK-inhibitor thera-

py is interrupted (e.g., cytoreductive therapy) because these patients were excluded from the study when therapy was interrupted for more than 1 week.

In conclusion, MASS Criteria can be applied to standard CECT examinations of the chest, abdomen, and pelvis with high accuracy and interobserver agreement. Patients with RCC metastases that showed marked central necrosis ($> 50\%$), marked decreased attenuation (≥ 40 HU), and decreased size of more than 20% on the first CECT after initiating antiangiogenic targeted therapy had improved progression-free survival compared with those who did not. Assessment of metastatic RCC response to antiangiogenic targeted therapy with TK-inhibitors is more accurate with MASS Criteria than with RECIST, modified Choi Criteria, or SACT Criteria and may predict disease outcome as measured by progression-free survival.

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