Revised Choi Imaging Criteria Correlate with Clinical Outcomes in Patients with Metastatic Renal Cell Carcinoma Treated with Sunitinib[1]

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Purpose: To compare revised Choi criteria that incorporate concurrent size and attenuation changes at early follow-up imaging with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and original Choi criteria in stratification of clinical outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib.

Materials and Methods: Institutional review board approved this retrospective study and waived informed consent. Baseline and first follow-up computed tomographic scans in 69 patients (50 men, 19 women; mean age, 60.3 years; range, 19–83 years) with mRCC treated with sunitinib from October 1, 2008, to March 1, 2013, were evaluated for tumor response by using RECIST 1.1, original Choi criteria, and revised Choi criteria. Correlations with overall survival (OS) and progression-free survival (PFS) were compared and stratified according to each radiologic criteria with Kaplan-Meier and multivariate Cox regression analysis.

Results: Median follow-up time was 29.7 months (95% confidence interval [CI]: 18.9, 45.9). Response according to revised Choi criteria was independently correlated with OS (hazard ratio, 0.47 [95% CI: 0.23, 0.99]; $P = .046$) and PFS (hazard ratio, 0.53 [95% CI: 0.29, 0.99]; $P = .047$). Response according to RECIST was not significantly correlated with OS (hazard ratio, 0.65 [95% CI: 0.27, 1.58]; $P = .344$) or PFS (hazard ratio, 0.89 [95% CI: 0.42, 1.91]; $P = .768$). Response according to original Choi criteria was not significantly correlated with OS (hazard ratio, 0.60 [95% CI: 0.32, 1.11]; $P = .106$) or PFS (hazard ratio, 0.59 [95% CI: 0.34, 1.02]; $P = .060$). Median OS and PFS in responders according to revised Choi criteria was 39.4 months (95% CI: 9.1, upper limit not estimated) and 13.7 months (95% CI: 6.4, 24.6), respectively, compared with 12.8 months (95% CI: 8.7, 18.0) and 5.3 months (95% CI: 3.9, 8.4), respectively, in nonresponders.

Conclusion: Contemporaneous reduction in tumor size and attenuation were correlated with favorable clinical outcomes. Response according to revised Choi criteria showed better correlation with clinical outcomes compared with that according to RECIST or original Choi criteria in patients with mRCC treated with sunitinib.

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The treatment of metastatic renal cell carcinoma (mRCC) recently shifted toward targeted agents that derive their efficacy in part by altering tumor angiogenesis (1). Antiangiogenic agents, such as sunitinib (Sutent; Pfizer, New York, NY), were shown to prolong survival and delay disease progression (2), but are costly and have substantial systemic toxicities. Therefore, it is important that clinicians are able to predict outcomes at an early stage of therapy to guide risk-stratified management decisions (3,4).

Imaging response assessment with Response Evaluation Criteria in Solid Tumors (RECIST) based on tumor diameter is important in oncologic science because there are strong correlations between RECIST-defined response and clinical outcomes in most solid tumors (5). However, many authors (2,6–9) noted that the use of RECIST underestimates response in assessment of antiangiogenic therapies. Antiangiogenic agents are frequently cytostatic rather than cytotoxic (10), and biologic response can therefore occur with minimal size regression, especially when imaging assessment is performed early. The marginal decrease in tumor size is often insufficient to meet RECIST-defined response. In mRCC patients who are administered antiangiogenic therapy, RECIST-based response assessment at early time points correlated poorly with clinical outcomes (11–14), and patients who would derive clinical benefit from these agents were therefore unable to be stratified at an early stage.

Alternative computed tomographic (CT) imaging response criteria, the Choi criteria, which incorporated measurements of tumor size and density, was proposed to address the relative insensitivity of RECIST for response in patients with gastrointestinal stromal tumors treated with the targeted agent imatinib (Gleevec; Novartis, Basel, Switzerland) (6). The inclusion of attenuation measurements was based on the premise that antiangiogenic agents targeting the vascular supply of tumors would cause decreased tumoral enhancement if the intended pharmacological effect was achieved. Choi criteria therefore deemed a patient to be responding if CT images showed either a 10% reduction in tumor size or a 15% reduction in CT attenuation. Choi et al (6) demonstrated that responders by these criteria showed significantly longer progression-free interval compared with nonresponders.

Several groups (11,12,15–18) applied the original Choi criteria to mRCC, but with a mixture of favorable and unfavorable results regarding its utility for prediction of clinical outcomes of disease survival and progression. Recently, Nathan et al (16) found in a small series of 20 patients treated with varied antiangiogenic agents that concurrent reductions in both tumor size and arterial-phase CT attenuation could better identify patients who have clinical benefit. To our knowledge, this has not been verified in a larger series or applied to portal venous phase CT datasets that are more commonly performed. We propose revised Choi criteria (Table 1) that incorporate the modifications of Nathan et al to the original Choi criteria.

The aim of our study was to compare revised Choi criteria that incorporate concurrent size and attenuation changes at early follow-up imaging with RECIST 1.1 and original Choi criteria in stratification of clinical outcomes in mRCC patients treated with sunitinib.

Advances in Knowledge

- Revised Choi CT imaging criteria applied to metastatic renal cell carcinoma (mRCC) patients on sunitinib showed significant correlation with patient outcomes (overall survival [OS] and progression-free survival [PFS], $P = .012$ and $P < .001$, respectively) after two cycles of therapy.
- Responders identified by using revised Choi criteria had longer median OS and PFS compared with nonresponders (responders: 39.4 and 13.7 months, nonresponders: 12.8 and 5.3 months respectively).
- There was good interobserver agreement for response categorization with the revised Choi criteria ($\kappa = 0.731$).

Implications for Patient Care

- Measurement of changes in tumor CT attenuation at portal venous phase imaging is useful for assessing mRCC response to antiangiogenic therapy because concurrent reduction in tumor size and CT attenuation is correlated with favorable clinical outcome.
- Revised Choi imaging criteria have potential for assessment of antiangiogenic therapies in mRCC patients.

Materials and Methods

Subjects

Institutional review board approval and waiver for informed consent was

Published online before print
10.1148/radiol.14132702 **Content codes:** GU CT

Radiology 2014; 273:452–461

Abbreviations:
CI = confidence interval
mRCC = metastatic renal cell carcinoma
OS = overall survival
PD = progressive disease
PFS = progression-free survival
PR = partial response
RECIST = Response Evaluation Criteria in Solid Tumors
SD = stable disease

Author contributions:
Guarantors of integrity of entire study, Y.T., A.G., H.L., A.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, Y.T., A.G., R.F., H.L., J.L., A.S.; clinical studies, Y.T., A.G., R.F., H.L., J.L.; experimental studies, A.G., H.L.; statistical analysis, Y.T., D.M.K.; and manuscript editing, Y.T., A.G., D.M.K., R.F., A.S.

Conflicts of interest are listed at the end of this article.

Table 1

RECIST 1.1, Choi, and Revised Choi Criteria

Response Criteria	Complete Response	Partial Response	Stable Disease	Progressive Disease
RECIST 1.1	Disappearance of all target lesions	≥30% decrease in the sum of the diameters of target lesions	Neither partial response nor progressive disease	≥20% size increase or new disease
Choi	Disappearance of all target lesions	≥10% decrease in the sum of the diameters of target lesions or ≥15% decrease in the tumor density	Neither partial response nor progressive disease	≥10% increase in tumor size and does not meet the criteria of PR in tumor density, or new disease
Revised Choi	Disappearance of all target lesions	≥10% decrease in the sum of diameters of target lesions and ≥15% decrease in the tumor density or in patients with no lesions suitable for density analysis, ≥30% decrease in the sum of diameters of target lesions	Neither partial response nor progressive disease	≥10% increase in tumor size or new disease

obtained for this retrospective study. Patients with mRCC treated with sunitinib at our institution during the period of October 1, 2008, to March 1, 2013, were selected for analysis. Inclusion criteria were patients with mRCC treated with sunitinib; and baseline contrast agent–enhanced CT imaging of the thorax, abdomen, and pelvis in the portal venous phase performed within 4 weeks before treatment commenced and again after two cycles of therapy to assess response. Exclusion criteria were as follows: *(a)* baseline or follow-up images were not available for review, *(b)* either baseline or follow-up scans were obtained without intravenous contrast enhancement, *(c)* a nonstandardized or suboptimal CT examination was performed (eg, inadequate scan coverage or grossly suboptimal enhancement), *(d)* no measurable disease at baseline, *(e)* less than two cycles of sunitinib therapy completed, and *(f)* patients who received short courses of sunitinib as neoadjuvant therapy prior to surgery rather than as maintenance regimen.

CT Image Acquisition

All patients underwent contrast-enhanced CT imaging of the chest, abdomen, and pelvis at baseline and follow-up by using a 16– or 128–detector row scanner (GE Lightspeed 16, GE Healthcare, Milwaukee, Wis; Somatom Definition Flash, Siemens, Erlangen, Germany). Intravenous administration of iohexol (300 mg iodine per milliliter, Omnipaque 300; GE Healthcare, Cork, Ireland) at a dose of 2 ml per kilogram of body weight was injected by using power injector at a flow rate appropriate to the cannula size (3 mL/sec for 20 gauge and 2 mL/sec for 22 gauge). Portal venous phase imaging was performed in a craniocaudal direction with aid of bolus tracking, with a 65–70-second delay (120 kVp; 170–350 mAs; collimation, 0.6 mm). Routine dataset reconstructions at 5-mm section thickness and 5-mm reconstruction increments were used for lesion measurements.

Image Analysis

Target lesions were defined per RECIST 1.1 criteria (five target lesions, maximum of two lesions per organ) (19). Unidimensional size and bidimensional attenuation measurements were performed only on a single section that represented the largest diameter of each target lesion. The sum of longest dimensions of all lesions was computed per RECIST 1.1 criteria. The CT attenuation (ie, attenuation value in Hounsfield units) of target lesions was determined by drawing a region of interest around the lesion margin on the section selected for size measurement at portal venous phase CT imaging, which gave a mean pixel attenuation (Fig 1). This was then averaged for all target lesions to give a mean CT attenuation. Because previous groups have reported pitfalls associated with attenuation measurements in sunitinib-induced air-filled cavitations in responding lung metastases that would markedly skew mean attenuation measurements (11,12,20), lung lesions were excluded from attenuation analysis a priori. The absolute and relative changes of the sum of diameters and mean CT attenuation from the pretreatment baseline to the first follow-up were calculated.

Target lesions were first assigned in consensus by two body radiologists (Y.T., 8 years of experience, and A.G., 13 years of CT imaging experience). After consensus agreement regarding the target lesions, the radiologists independently performed all diameter and CT attenuation measurements to determine interobserver variation for assignment of response categories to each set of response criteria. Measurements on the baseline and follow-up CT scans were made during the same session for each patient (a pairwise assessment). Both radiologists were blinded to the clinical data, patient outcomes, and the other's readings.

Response Assessment Criteria

Response evaluation at the first follow-up scan was performed by applying RECIST 1.1, Choi criteria, and revised Choi criteria (Table 1). Responders were defined as patients with complete response or partial response (PR), while nonresponders included patients with stable disease (SD) and progressive disease (PD). When attenuation measurements were not feasible, the

Figure 1

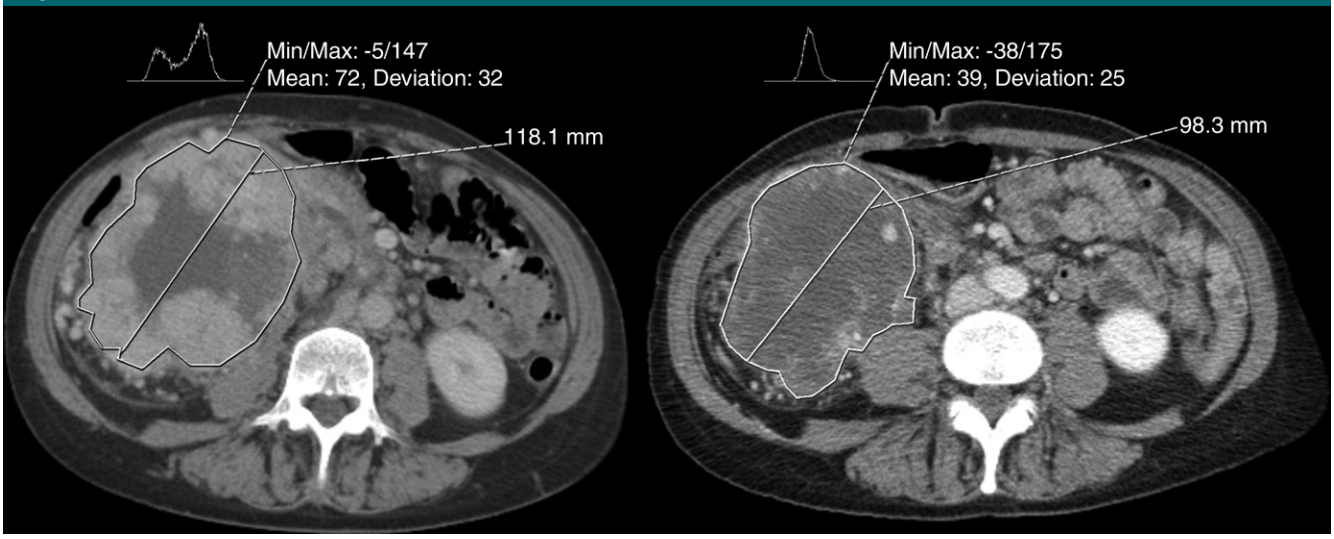

Figure 1: Method of target lesion analysis that incorporates size and attenuation measurements. Longest dimension of each target was measured in axial plane at baseline (left) and follow-up (right). Attenuation measurements were made by drawing regions of interest around the tumor margin. In this example of a target renal lesion in a 63-year-old woman with mRCC treated with sunitinib, dramatic decrease in CT attenuation was seen, although size reduction was less marked. Patient was a nonresponder according to RECIST, but responder according to Choi and revised Choi criteria. She is still alive after 4 years of follow-up.

revised Choi criteria considered patients with a 30% or greater decrease in the sum of diameters of target lesions to be PRs.

Statistical Analysis

All statistical analyses were performed by using statistical software (Stata 12; StataCorp, College Station, Tex). The two main outcome measures were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from initiation of sunitinib therapy to death from any cause or censorship at the date of last follow-up. PFS was defined as the time from initiation of sunitinib therapy to the date of clinically documented tumor progression or death (whichever occurred first) or censorship at the date of last follow-up. For OS and PFS analyses, data collection was closed on June 25, 2013. The relationship of the RECIST, Choi, and revised Choi response criteria after two cycles of treatment and the two primary outcome measures were assessed by using Kaplan-Meier analysis. The median follow-up time was calculated by using the reverse Kaplan-Meier method. Differences between Kaplan-Meier curves were evaluated by using a nonparametric log-rank test. Multivariate Cox regression analysis was performed to determine the hazard ratios of responders to nonresponders for each set of criteria. The proportional hazard assumption was verified with the log-minus-log plot. Weighted Cohen κ value was calculated to compare the degrees of agreement in response categorization by using the different criteria. Cohen κ value was used to evaluate the agreement between the two radiologists who assigned the response categories according to each set of response criteria. A P value of .05 was considered to indicate statistical significance. For measures of strength of agreement, we stratified κ statistics as follows: 0.81–1.00, very good; 0.61–0.80, good; 0.41–0.60, moderate; 0.20–0.40, fair; and <0.20, poor (21).

Results

Baseline Characteristics

Of the 118 patients who were identified in the institution database, 49 patients were excluded and 69 patients were included in the final analysis (Fig 2). The baseline characteristics of the patient population are summarized in Table 2. For tumor diameter measurement, 170 target lesions in 69 patients were eligible. Of these, 22 lung lesions were excluded from attenuation analysis and 148 lesions in 63 patients were eligible for CT attenuation measurements. The first response assessment scan was performed an average of 79.2 days (range, 56–130 days) after initiation of therapy. The median follow-up time was 29.7 months (95% confidence interval [CI]: 18.9, 45.9).

Response Assessment

Response according to RECIST.—By using RECIST, 12 patients (17.4%) reached PR, 46 patients (66.7%) had SD, and 11 patients (15.9%) had PD, which resulted in 12 responders (17.4%) and 57 nonresponders (82.6%). Among responders, the average change in summated lesion diameter was −40% (95% CI: −35.2%, −45.6%). Among nonresponders, the average change in summated lesion diameter was 4.3% (95% CI: −2.6%, 11.3%).

Response according to Choi criteria.—By using original Choi criteria,

Figure 2

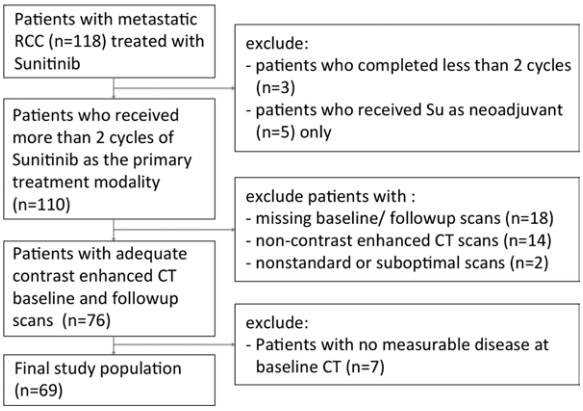

Figure 2: Flowchart of study population selection. *Su* = sunitib.

Table 2

Patient Characteristics

Characteristic	Data
Mean age (y)	60.3 (19–83)*
Women	56.7 (41–78)*
Men	61.6 (19 –83)*
Sex	
Female	19 (27.5)
Male	50 (72.5)
Previous nephrectomy	51 (73.9)
Line of treatment	
First	55 (79.7)
Second	13 (18.8)
Third	1 (1.5)
Start dose	
25 mg	1 (1.5)
37.5 mg	11 (15.9)
50 mg	57 (82.6)
Histologic analysis	
Clear cell	48 (69.6)
Papillary	3 (4.4)
Chromophobe	2 (2.9)
Sarcomatoid	1 (1.5)
Mucinous tubular and spindle cell	1 (1.5)
Xp11.2 translocation-TFE3	1 (1.5)
Subtype not available	13 (18.8)
Heng risk category	
Favorable risk	8 (11.6)
Intermediate risk	46 (66.7)
Poor risk	15 (21.7)
ECOG performance status	
0	28 (40.6)
1	32 (46.4)
2	7 (10.1)
3	2 (2.9)

Note.—Data are number of patients except where indicated. Data in parentheses are percentages except where indicated. There were 69 patients total. ECOG = Eastern Cooperative Oncology Group.

* Data in parentheses are range

42 patients (60.9%) reached PR, 17 patients (24.6%) had SD, and 10 patients (14.5%) had PD, which resulted in 42 responders (60.9%) and 27 nonresponders (39.1%). Among responders, the average change in summated lesion diameter and mean attenuation was −14.1% (95% CI: −5.1%, −23.0%) and −29.6% (95% CI: −23.8%, −35.5%), respectively. Among nonresponders, the average change in summated lesion diameter and mean attenuation was 13.0% (95% CI: 4.0%, 22.0%) and 4.4% (95% CI: −1.1%, 9.8%), respectively.

Response according to revised Choi criteria.—According to revised Choi criteria, 24 patients (34.8%) had PR, 30 patients (43.5%) had SD, and 15 patients (21.7%) had PD, which resulted in 24 responders (34.8%) and 45 nonresponders (65.2%). Among the 24 patients who had PR, in 22 patients categorization of PR was based on a decrease in tumor size and attenuation, and in two patients with no suitable lesions for attenuation analysis, categorization of PR was made because of a decrease in tumor size only (of more than 30%). Among responders, the average change in summated lesion diameter and mean attenuation was −26.5% (95% CI: −20.3%, −32.7%) and −35.7% (95% CI: −29.9%, −42.4%), respectively. Among nonresponders, the average change in summated lesion diameter and mean attenuation was 8.8% (95% CI: 0.4%, 17.3%) and −6.5% (95% CI: −12.9%, −0.1%).

Among six patients with size measurements only, there was no difference between RECIST, Choi, and revised Choi categories in five patients; one patient had SD by using RECIST, PR by using Choi, and SD by using revised Choi criteria.

OS data.—The revised Choi categories had significantly better discriminatory value for stratifying OS (P = .012) compared with RECIST (P = .082) and Choi criteria (P = .127) (Fig 3). When considering responders and nonresponders within each set of criteria, only revised Choi criteria correlated with OS (P = .023) compared with RECIST (P = .424) and Choi (P = .140) criteria (Fig 4). The median OS for responders and nonresponders according to revised Choi criteria was 39.4 months and 12.8 months, respectively. Responders according to revised Choi criteria had a hazard ratio of 0.47 (95% CI: 0.23, 0.99).

PFS data.—When the cohort was stratified by individual category (complete response, PR, SD, or PD), all three sets of radiologic response criteria were correlated with PFS (RECIST, P = .005; Choi, P = .007; revised Choi, $P < .001$). When the cohort was dichotomized to responders and nonresponders within each set of criteria, only revised Choi criteria was shown to have correlation with PFS (P = .022) compared with RECIST (P = .687) and Choi (P = .076) criteria. The median PFS for responders and nonresponders according to revised Choi was 13.7 and 5.3 months, respectively. Responders according to revised Choi criteria had a hazard ratio of 0.53 (95% CI: 0.29, 0.99).

Tables 3 and 4 summarize the multivariate hazard ratios and median OS and PFS times for responders

Figure 3

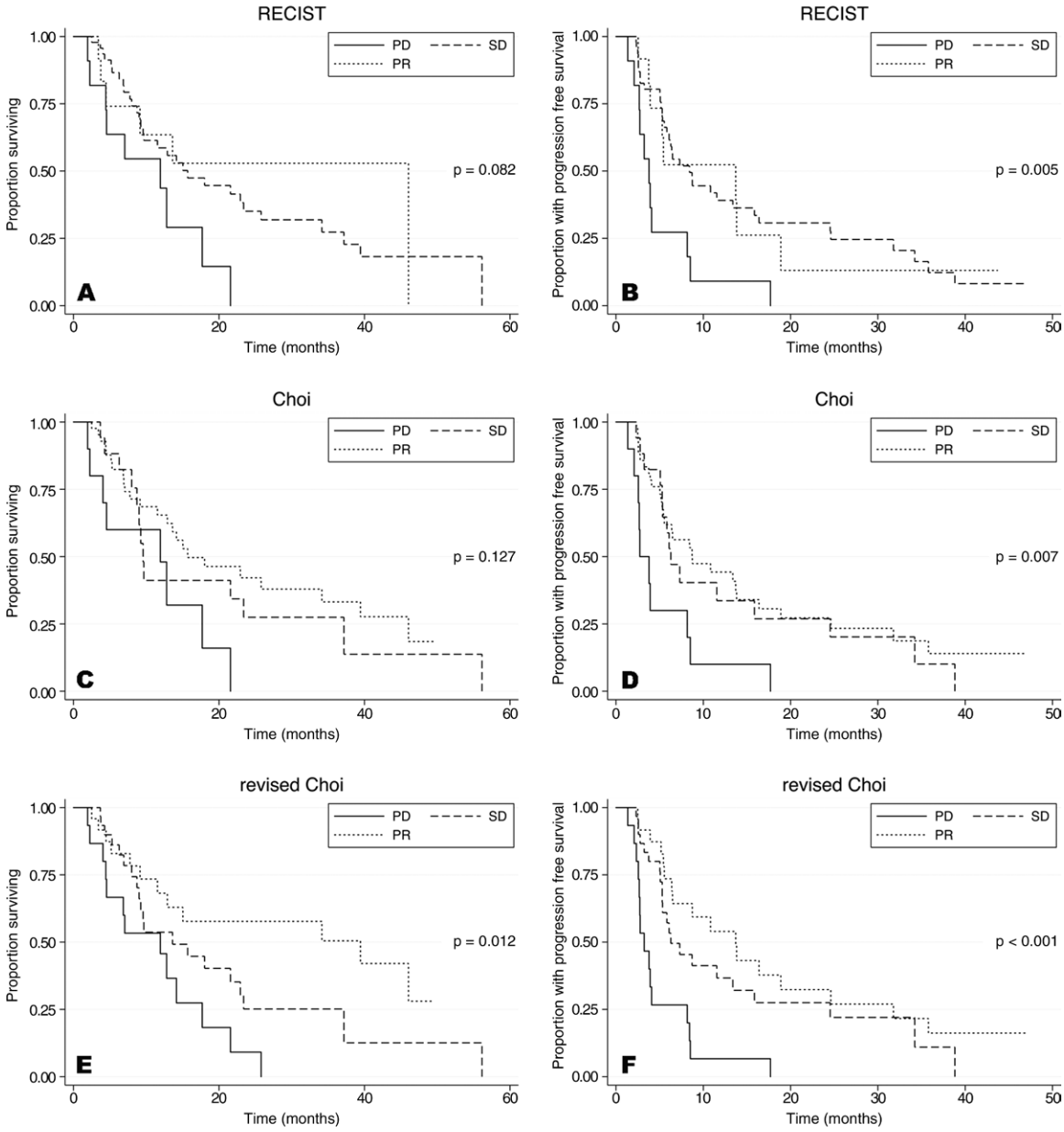

Figure 3: Revised Choi criteria improved stratification of clinical outcomes by Kaplan-Meier analysis. Kaplan-Meier plots for OS and PFS of patients with mRCC grouped by category: PD, SD, and PR as classified according to the RECIST *(A, B)*, Choi *(C, D)*, and revised Choi *(E, F)* criteria.

and nonresponders according to RECIST, Choi, and revised Choi criteria. The original Choi criteria reclassified 30 RECIST-defined nonresponders as responders and did not reclassify any patients who were RECIST responders. Of these 30 reclassified patients, the median OS and PFS were 15.7 and 8.7 months, respectively. Revised Choi criteria reclassified 14 RECIST-defined nonresponders as responders and two RECIST-defined responders as nonresponders. Among 14 reclassified responders, the median OS and PFS were 34.1 and 10.8 months, respectively; in two reclassified nonresponders, the median OS and PFS were 3.8 and 3.8 months, respectively.

Agreement between Response Categories and between Observers

Agreement between response categories was moderate for RECIST and Choi

Radiology

Figure 4

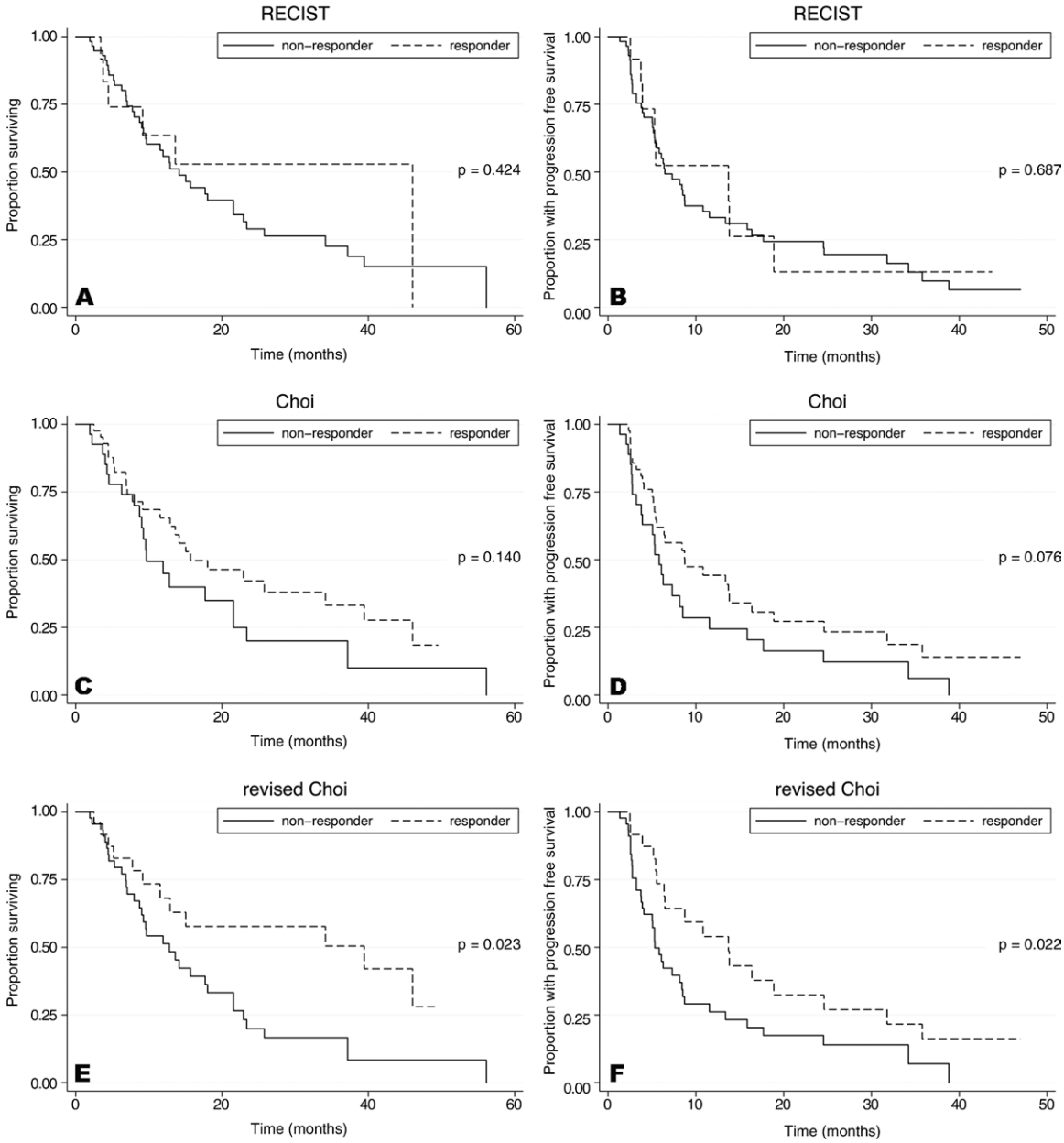

Figure 4: Kaplan-Meier plots for OS and PFS of patients with mRCC dichotomized to responder and nonresponder categories as classified by the RECIST *(A, B)*, Choi *(C, D)*, and revised Choi *(E, F)* criteria.

(κ = 0.423), RECIST and revised Choi (κ = 0.591), and Choi and revised Choi (κ = 0.600). Interobserver agreement with respect to the assignment of response categories was good for RECIST (κ = 0.743), Choi (κ = 0.739), and revised Choi (κ = 0.731) criteria.

Discussion

Among the three sets of response criteria applied to our study population, only the revised Choi response category assigned at CT after two cycles of treatment was able to stratify patients for both OS and PFS. For responders and nonresponders who were assigned according to each set of response criteria, only revised Choi criteria correlated with OS and PFS. Responders according to the revised Choi criteria also had lower hazard ratios and longer

Table 3

Multivariate Hazard Ratios for Death (OS) and Progression (PFS)

Parameter	OS Hazard Ratio	*P* Value	PFS Hazard Ratio	*P* Value
RECIST 1.1 responder	0.65 (0.27, 1.58)	.344	0.89 (0.42, 1.91)	.768
Choi responder	0.60 (0.32, 1.11)	.106	0.59 (0.34, 1.02)	.060
Revised Choi responder	0.47 (0.23, 0.99)	.046	0.53 (0.29, 0.99)	.047

Note.—Data in parentheses are CIs.

Table 4

Median Times for OS and PFS in mRCC Patients Dichotomized to Responders and Nonresponders according to RECIST, Choi, and Revised Choi Criteria

Response Category	Median OS (mo)	Median PFS (mo)
RECIST		
Responder	46.1 (3.75, ULND)	13.7 (3.75, 18.9)
Nonresponder	14.1 (9.2, 21.6)	6.5 (5.3, 10.8)
Choi		
Responder	15.7 (11.5, 39.4)	8.8 (5.4, 13.8)
Nonresponder	9.7 (8.0, 21.6)	5.8 (3.2, 8.5)
Revised Choi		
Responder	39.4 (9.1, ULND)	13.7 (6.4, 24.6)
Nonresponder	12.8 (8.7, 18.0)	5.3 (3.9, 8.4)
Total cohort	14.1 (9.6, 21.6)	6.5 (5.3, 10.8)

Note.—Data in parentheses are CIs. According to RECIST criteria, there were 12 responders and 57 nonresponders; according to Choi criteria, there were 42 responders and 27 nonresponders; and, according to the revised Choi criteria, there were 24 responders and 45 nonresponders. ULND = upper limit not defined.

OS and PFS times compared with responders who were classified by using the other two response criteria.

Our findings show that the revised Choi response criteria were superior to discriminate the clinical outcomes defined by OS and PFS compared with RECIST 1.1 and Choi criteria when applied after two cycles of treatment to mRCC patients who were treated with sunitinib. The interobserver agreement for response categorization was good for all three criteria, which is important for wider clinical application.

Our results are consistent with those of Nathan et al (16), who observed in a smaller cohort of 20 patients that response defined by concomitant 10% size reduction and 15% attenuation reduction provided superior correlation with time to progression compared with RECIST and original Choi criteria. However, there are several key differences in our methodology. We included only patients treated with sunitinib, whereas Nathan et al included patients who were on two different types of antiangiogenic agents (sunitinib and cediranib), which can be confounding in evaluation of clinical outcomes. We measured CT attenuation on portal venous phase scans instead of on arterial phase scans as in the study by Nathan et al. Arterial phase attenuation measurements are potentially superior for assessing tumor vascularity, but are more vulnerable to cardiovascular output and injection factors (22). Moreover, portal venous phase imaging is more commonly performed in routine clinical practice, and our study suggests that the revised Choi criteria can be robustly applied in institutions that do not routinely perform arterial phase imaging for mRCC follow-up.

Our proposed revised Choi criteria make provision for scans on which no lesions are suitable for attenuation analysis by categorizing patients with a 30% reduction in size only as having PR. This gives allowance for patients with no lesions suitable for attenuation analysis to be categorized as having PR in clear-cut cases of dramatic size reduction, which thereby allows extension of the criteria to all patients with measurable disease.

One of the criticisms of RECIST is its poor sensitivity for identifying responders who would derive clinical benefit from antiangiogenic therapy (6–9). In our study cohort, revised Choi criteria identified twice as many responders as RECIST (24 of 69 patients who were responders compared with 12 of 69 patients who were responders, respectively), and responders identified by revised Choi criteria had comparable median OS and PFS times compared with RECIST responders. Therefore, revised Choi criteria appear more sensitive than RECIST in identifying patients with favorable outcome.

In our study, the original Choi criteria categorized more patients as responders (42 of 69) compared with RECIST and revised Choi criteria. However, Choi responders and nonresponders did not show significant differences in OS and PFS, which indicated a lack of discriminatory value. This is consistent with the results of previous investigators (15–18). One study by Schmidt et al (12) found that Choi criteria stratified prognostic groups better than did RECIST, although the study was based on a smaller cohort of 35 patients treated with different targeted therapies. The conflicting results in the literature indicate that the original Choi criteria have yet to be validated in mRCC.

The median OS and PFS times for RECIST and Choi responders and nonresponders in our cohort are comparable to that of previously published data by other investigators (11,18). However, we note that the OS and PFS ranges for the entire cohort are slightly lower than results of a large phase-III clinical trial of mRCC patients treated with sunitinib (2). This difference may be attributed to

our exclusion of all patients with no measurable disease, which conceivably excludes a portion of patients with favorable outcome. Our study population also included patients with nonclear-cell pathologic subtypes and those on sunitinib as second- and third-line therapies, who may derive less benefit from sunitinib (23,24), versus the selected population in the phase III trial of Motzer et al (2).

Our study shows that PR defined by concurrent size and attenuation reduction demonstrated better correlation with clinical outcomes compared with both the original implementation of the Choi criteria and RECIST 1.1. We hypothesize that the original Choi criteria, in which only slight decrease in one of the parameters was sufficient to define response, may overestimate response in some cases of mRCC. The proposed criteria, in which contemporaneous reduction in both size and attenuation are necessary to define response, could be more specific, and that may account for its superior performance. As with any form of prognostication tool that uses defined thresholds, exceptions to this rule exist, and instrumental to resolving uncertainties of response to treatment in clinical practice are the experience of the radiologist and, if necessary, follow-up imaging.

Our study had limitations. First, this was a retrospective study and we excluded 42% (49 of 118) of the patients in our database. We excluded patients who completed fewer than two cycles of sunitinib because these were patients who had severe toxicities from therapy and therefore discontinued use of the drug. The clinical outcomes of these patients would not reflect the therapeutic effect of sunitinib treatment. Patients without appropriate imaging that was performed at baseline or follow-up also had to be excluded. Second, attenuation measurements on portal venous scans are vulnerable to differences in the scan parameters and cardiovascular dynamics of each patient. However, all scans obtained at our institution followed a strict and well-established CT imaging protocol. Although more direct measurements of tumor vascularity (eg, perfusion CT) exist (25), these involve changes in scan protocols and complex analyses that are more difficult to implement in clinical practice. Third, we excluded lung lesions from attenuation analysis. This approach was chosen a priori because sunitinib frequently induces air-filled necrotic cavitations in responding lung metastases (which would include voxels with markedly negative Hounsfield units), which renders attenuation measurements of lung lesions unreliable. This pitfall has been reported by previous groups (11,12,20). Fourth, the baseline CT scans were obtained up to 4 weeks before treatment, and there was variability in the timing of the first response CT scan in this study. However, this could not be avoided because of its retrospective design. Fifth, this study evaluated only patients who received sunitinib treatment, and our findings should be validated in patients receiving other types of antiangiogenic therapy. Finally, attenuation measurements performed in this study cannot be applied to patients in whom intravenous contrast material administration is contraindicated, such as in patients with impaired renal function.

In summary, our study demonstrates that the proposed revised Choi criteria show better correlation with clinical outcomes in patients with mRCC on sunitinib at early follow-up imaging compared with RECIST and original Choi criteria. These criteria should be validated prospectively in an independent group of patients.

Acknowledgments: We acknowledge the support of the National Institute for Health Research Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research.

Disclosures of Conflicts of Interest: Y.T. No relevant conflicts of interest to disclose. **A.G.** No relevant conflicts of interest to disclose. **D.M.K.** No relevant conflicts of interest to disclose. **R.F.** No relevant conflicts of interest to disclose. **H.L.** No relevant conflicts of interest to disclose. **J.L.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: author receives money from grant and personal fees from Pfizer and Novartis, author receives personal fees from GlaxoSmithKline. Other relationships: none to disclose. **A.S.** No relevant conflicts of interest to disclose.

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