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Original

Use of three-dimensional Choi criteria in assessing response to molecular targeted therapy in advanced renal cell carcinoma

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Abstract

Tumor necrosis with no significant decrease in size is a common response to molecular targeted therapy in advanced renal cell carcinoma (RCC). Therefore, the response evaluation criteria in solid tumors (RECIST) might be inaccurate in assessing treatment response. Choi criteria consider changes in computed tomography (CT) values in conjunction with two-dimensional tumor size to assess response to molecular targeted therapy in gastrointestinal stromal tumors. Here, we aimed to assess the feasibility and reliability of modified Choi criteria in advanced RCC, using three-dimensional (3D) volume (3D-Choi criteria), a more suitable parameter, given the irregular and complex tumor shape. Thirty-five patients with 58 pathologically confirmed advanced RCC lesions diagnosed at our institution between June 2008 and May 2011 were enrolled. Response to molecular targeted therapy was assessed using Choi criteria and RECIST. All lesions were measurable using 3D-Choi criteria. According to RECIST, 1 (3%), 3 (9%), 22 (63%), and 9 (26%) patients showed complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively. According to 3D-Choi criteria, 1 (3%), 11 (31%), 12 (34%), and 11 (31%) patients showed CR, PR, SD, and PD, respectively. The concordance rate between RECIST and 3D-Choi criteria was 71.4%. Ten cases classified as showing SD according to RECIST were classified as having a PR according to 3D-Choi criteria, reflecting the reduced CT value. Inter- and intra-observer agreements for Choi criteria were good (kappa coefficient 0.857 and 0.750, respectively). Furthermore, treatment response as determined by 3D-Choi criteria showed a significantly higher correlation with progression-free survival than did treatment response as determined by RECIST ($p=0.038$ vs. $p=0.958$). Thus, 3D-Choi criteria may be useful for the early prediction of response to targeted therapy in patients with advanced RCC.

Key words: *renal cell carcinoma, Choi criteria, 3D-CT, molecular targeted therapy*

I. Introduction

The response evaluation criteria in solid tumors (RECIST) were commonly used for determining the effectiveness of treatment in clinical trials of solid tumors. Currently, molecular targeted therapy is a standard treatment for advanced renal cell carcinoma (RCC), with tumor necrosis

being a characteristic response. However, tumor necrosis is not always associated with a decrease in tumor size, and therefore, treatment response could be underestimated if assessed by RECIST. Therefore, RECIST is not suitable for assessing prognosis in such cases.

Originally, RECIST were based on one-dimensional measurement[1, 2]. In the revised RECIST ver.1.1, although one-dimensional measurement is still considered standard, three-dimensional (3D) volume evaluation based on magnetic resonance (MR) imaging has been introduced for estimating prognosis [3-5]. Evaluation of the 3D volume is more suitable for advanced RCC because the tumor shape tends to be irregular and complex. However, the evaluation of 3D volume for determining treatment response in cases of advanced RCC has not been reported.

Choi et al. reported the validity of their criteria (Choi criteria), considering changes in computed tomography (CT) values in conjunction with tumor size, in determining response to molecular targeted therapy for gastrointestinal stromal tumors [6, 7]. Furthermore, the effectiveness of the Choi criteria in determining response to molecular targeted therapy in advanced RCC has been reported [8-13]. However, these studies used two-dimensional tumor measurements. We hypothesized that three-dimensional measurements may be more accurate than two-dimensional measurements for the Choi criteria.

Accordingly, the purpose of our study was to assess the feasibility and reliability of the 3D-Choi criteria and to evaluate its impact on predicting the survival of advanced RCC patients.

II. Material and Methods

1. Study design and endpoints

This study was a retrospective observational study. The two major endpoints were feasibility and reliability of the 3D-Choi criteria.

2. Patients

Patients with pathologically confirmed advanced RCC diagnosed at our institution between June 2008 and May 2011 were included in this study. All patients received more than once course of molecular targeted therapy alone and underwent CT with the intravenous administration of contrast material at least two times: before and after treatment. Patients with contraindications for contrast material, tumors unsuitable for assessment by RECIST ver.1.1, or a lack of follow-up data for at least three months were excluded.

Patients treated with sunitinib (Sutent; Pfizer, New York, US; daily oral dose of 50mg for 4 weeks followed by another course at a 2 week interval), sorafenib (Nexavar; Bayer HealthCare, Leverkusen, Germany; daily oral dose of 400 mg continuously), everolimus (Afinitor; Novartis Pharma, Basel, Switzerland; daily oral dose of 10 mg continuously), or temsirolimus (Torisel; Pfizer, New York, US; daily intravenous dose of 25 mg, once a week continuously). Treatment was continued until the occurrence of disease progression, severe adverse events, or consent withdrawal.

This study was approved by the institutional review board. Written informed consent for inclusion in the study was obtained from all patients.

3. The CT technique

Contrast-enhanced CT was performed according to a routine protocol in all patients,

Table1. RECIST and Choi Criteria

	RECIST ver.1.1	Choi Criteria
CR	Disappearance of all lesions No new lesions	Disappearance of all lesions No new lesions
PR	A decrease in size ≧ 30% on CT No new lesions No obvious progression of non-measurable disease	A decrease in size ≧ 10% or a decrease in tumor attenuation(HU) ≧ 15% on CT No new lesions No obvious progression of non-measurable disease
SD	Does not meet criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression	Does not meet criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size ≧ 20% and does not meet criteria of PR by tumor attenuation on CT New lesions	An increase in tumor size ≧ 10% and does not meet criteria of PR by tumor attenuation on CT New lesions

abbreviation: RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

using a 16-channel multislice CT scanner (Aquilion-16; Toshiba Medical Systems, Tokyo, Japan). Contrast material (90–100 mL) was injected into the antecubital vein at a rate of 1 mL/s using an automated injector. Images were acquired at 120 s after the start of injection.

3D-reconstruction and measurement of CT attenuation were performed on a workstation (Zio Station; Amin, Tokyo, Japan), using dedicated semi-automated volume-of-interest analysis software developed specifically for this study. We extracted 3D tumor measurements semi-automatically and calculated the 3D-CT value. The 3D-CT value was defined as follows:

$$\text{3D-CT value} = \frac{\text{sum of the CT value of each voxel}}{\text{total number of voxels}}$$

The 3D-CT value thus calculated was used in the Choi criteria.

4. Image evaluation

One urologist and one radiologist independently measured the 3D-CT value and the tumor volume based on CT imaging, blinded to information on patients. Tumor response was assessed according to RECIST ver.1.1 (five target lesions, maximum of two lesions per organ) and the 3D-Choi criteria on the basis of the findings of the first CT after treatment. The definitions of RECIST and the Choi criteria are summarized in Table1.

5. Study outcomes

Inter- and intra-observer agreements for the 3D-Choi criteria were evaluated as the reliability endpoint. The concordance rate between RECIST and the 3D-Choi criteria was also assessed.

6. Statistical analysis

Patients and tumors were analyzed using descriptive statistics. The Wilcoxon signed-

rank test was used to compare the changes in size and attenuation. Kaplan-Meier curves were plotted to calculate progression-free survival (PFS) according to response based on the 3D-Choi criteria and RECIST , and differences were evaluated using a non-parametric log-rank test. PFS was also analyzed in two groups of complete response (CR) + partial response (PR) and stable disease (SD) + progressive disease (PD). A significant difference was considered to exist at p values <0.05. Inter-observer and intra-observer agreements were evaluated using the kappa coefficient.

III. Results

1. Patient characteristics

A total of 35 patients were evaluated in this study: 20 treated with sunitinib, 11 with sorafenib, 3 with everolimus, and 1 with temsirolimus. Patient characteristics are presented in Table 2. According to the Memorial Sloan-Kettering Cancer Center risk criteria [14], 60% of patients were classified as being at intermediate or poor risk. A total of 58 measurable lesions were independently detected by both evaluators, with common lesion types being lung metastases (n=15), primary renal tumors (n=11), and lymph node metastases (n=10).

Table 2. Patients' characteristics (N=35)

	No. of patients (%)
Gender	
Male	23 (66)
Female	12 (34)
Age	
Median	63.3
Range	45-83
ECOG PS	
0	23 (66)
1	11 (31)
2	1 (3)
Nephrectomy	25 (71)
Histology	
Clear cell ca	21 (84)
Other	4 (16)
MSKCC risk groups	
0 (favorable)	14 (40)
1-2 (intermediate)	12 (34)
≧ 3 (poor)	9 (26)
	No. of lesion (%)
Primary	11 (19)
Metastases	47 (81)
Lung	15 (26)
Contralateral kidney	7 (12)
Liver	7 (12)
Lymphnode	10 (17)
Pancreas	6 (10)
Adrenal	2 (3)

2. Feasibility

All 58 lesions could be analyzed using the 3D-Choi criteria. A representative case of 3D-Choi criteria assessment is shown in Fig.1.

3. Tumor response and concordance rate

A decrease in the CT value after one course of molecular targeted therapy was observed in 45 out of 58 lesions. Primary renal tumors, lung metastases, and lymph node metastases showed significant decreases in the 3D-CT value, whereas the decrease in tumor diameter was not significant in these cases (Figs. 2 and 3).

According to RECIST ver.1.1, 1 (3%), 3 (9%), 22 (63%), and 9 (26%) patients showed CR, PR, SD, and PD, respectively. According to the 3D-Choi criteria, 1(3%), 11 (31%), 12 (34%), and 11(31%) patients showed CR, PR, SD, and PD, respectively. The concordance rate between RECIST and the 3D-Choi criteria was 71.4%. Responses according to

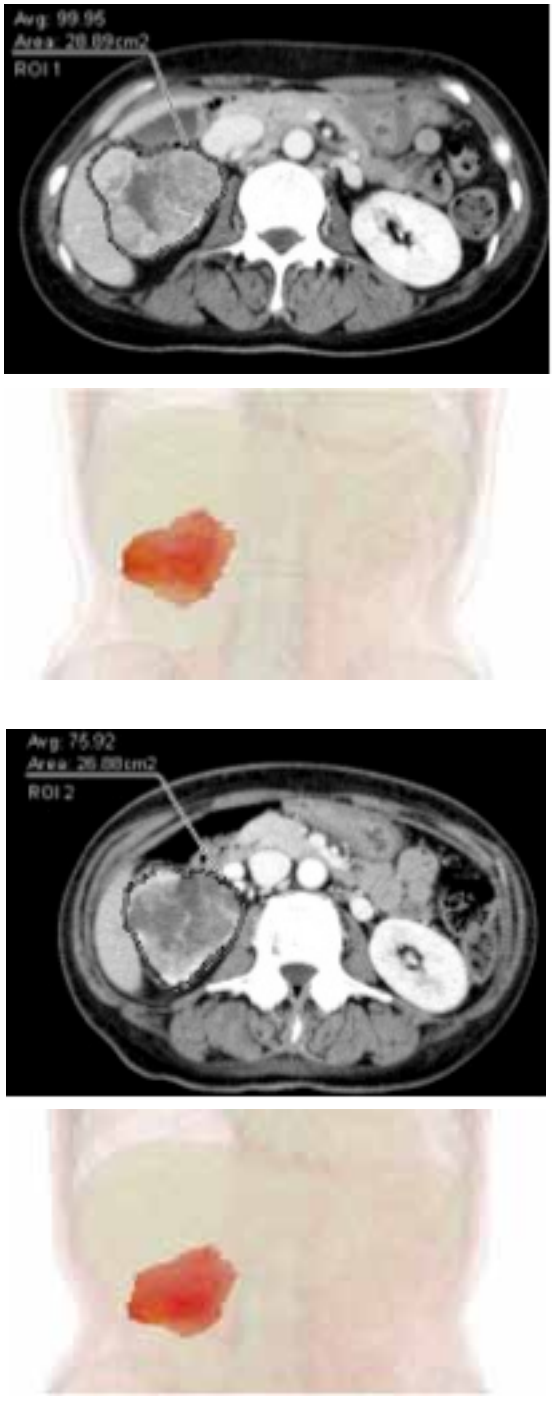

Fig. 1.
A: Pre-treatment 3D-CT value.
B: Post-treatment 3D-CT value.
3D-CT value measurement. After first course of sunitinib administration, tumor diameter reduced 2% (6.27cm → 6.14cm) and was classified as SD by RECIST ver.1.1. On the other hand, 3D-CT value reduced 27.0% (105.4HU → 76.9HU) and was classified as PR by 3D-Choi criteria.

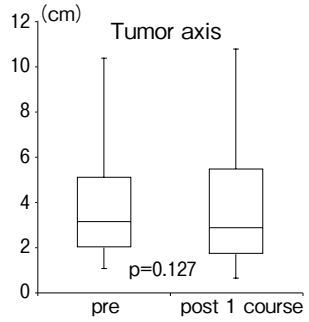

Fig. 2. Tumor size before and after the first course of treatment.

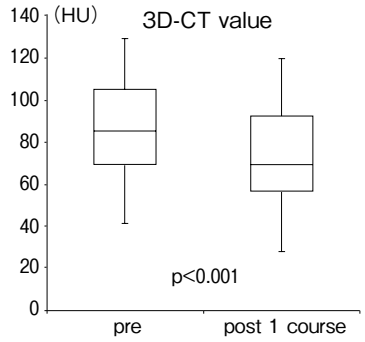

Fig. 3. 3D-CT value before and after the first course of treatment.

the two sets of criteria deferred in 10 cases; lesions classified as showing PR according to the 3D-Choi criteria were classified as showing SD according to RECIST (Table 3). Cases of tumor necrosis without a decrease in tumor size were classified as showing SD according to RECIST, and the qualitative response was not evaluated. Although the change in the tumor diameter was small, the 3D-CT value decreased considerably in response to molecular targeted therapy.

4. Reliability

For independent image evaluation, the kappa coefficient for inter-observer agreement was 0.857 and the rate of agreement between the two observers was 91.4%, whereas the kappa coefficient for intra-observer agreement

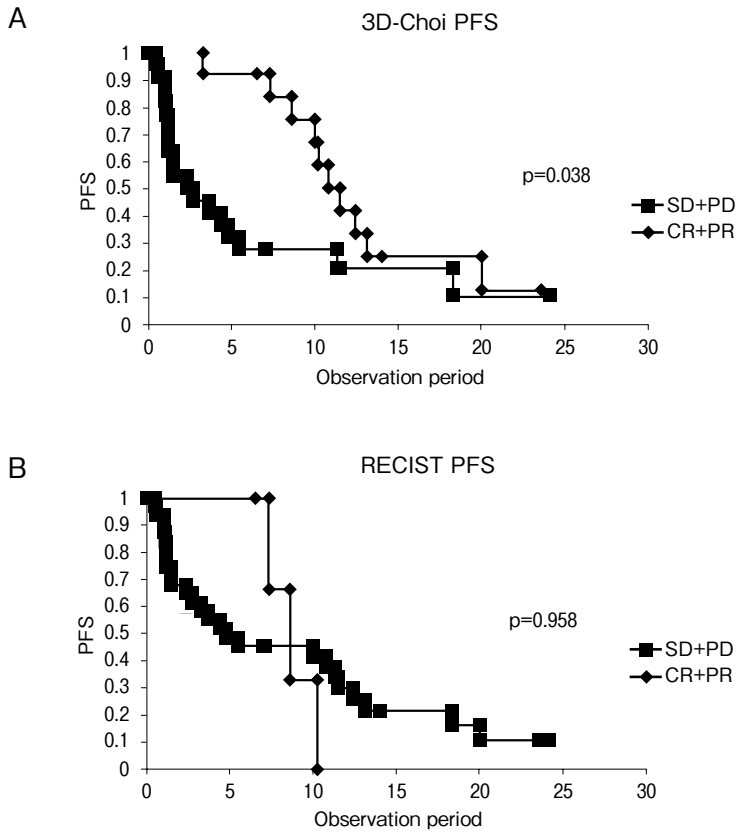

Fig. 4. Progression-free survival: 3D-Choi vs RECIST
A: 3D-Choi criteria. CR+PR (med 11.5 mo), SD+PD (med 2.2 mo). ($p=0.038<0.05$)
B: RESIST criteria. CR+PR (med 8.6 mo), SD+PD (med 4.8 mo).
A significant difference was considered to exist at p values <0.05.

was 0.750 and the rate of agreement was 88.5%.

5. Survival analysis

PFS was 8.6 months in the CR+PR group and 4.8 months in the SD+PD group, when these groups were classified according to RECIST ver.1.1 ($p=0.958$). When classified according to the 3D-Choi criteria, PFS was 11.5 months in the CR+PR group and 2.2 months in the SD+PD group ($p=0.038<0.05$) (Fig.4).

IV. Discussion

Although molecular targeted therapy is the standard treatment for advanced RCC, whether RECIST is suitable for evaluating tumor necrosis as a treatment response is debatable [15-17]. This is, to our knowledge, the first study to evaluate the relationship between the 3D-Choi criteria and RECIST for the evaluation of response to molecular targeted therapy in advanced RCC.

In our study, the most important finding was that response to treatment as determined by the 3D-Choi criteria showed a significantly higher correlation with PFS than did response to treatment as determined by RECIST. Randomized control trials of molecular targeted therapy for RCC reported a discrepancy between response rates, which

were as low as 10–31% according to RECIST, and survival, which was relatively high [18-21]. Because of this weakness, the Choi criteria have been used instead of RECIST in several studies [8-13]. Van der Veldt et al. [8] suggested that a PR status according to the Choi criteria has a significantly better predictive value for PFS and OS ($p<0.001$ for both) than does a PR status according to RECIST ($p=0.685$ and 0.191, respectively). Furthermore, the Choi criteria were more effective in identifying patients with advanced RCC who would benefit from sunitinib at an early stage.

As the second most important finding, inter- and intra-observer agreements in 3D-CT value measurement were adequately high. Theoretically, 3D volume measurement is ideal for the evaluation of advanced RCC, which is characterized by an irregular shape and internal structure. However, the use of 3D volume measurement has not been reported to date. Our results indicate that 3D-CT value measurement using multislice CT imaging was feasible and had the potential to replace the criteria for evaluating response to molecular targeted therapy.

Of note, patients classified as having a PR according to the 3D-Choi criteria and as having SD according to RECIST (Table 3) showed a significant decrease in the 3D-CT value compared to patients in whom there was no discrepancy between the two sets of criteria. This finding is consistent with previous reports of tumor necrosis being frequently seen as a treatment effect in advanced or metastatic RCC [22]. Since necrotic areas are usually irregular in shape, the 3D-Choi criteria were suitable for the evaluation of advanced RCC. With the increase in the number and complexity of molecular target therapies available for advanced RCC, evaluation of the effect of pharmacotherapy and determination of the need for a change in regimen is a major concern. Our results suggest that PR according to the 3D-Choi criteria that is classified as SD according to RECIST may be associated with prolonged PFS.

Table3. Comparison between 3D-Choi criteria vs RECISTver.1.1

		3D-Choi criteria				
		CR	PR	SD	PD	Total
RECISTver.1.1	CR	1	0	0	0	1
	PR	0	3	0	0	3
	SD	0	8	12	2	22
	PD	0	0	0	9	9
	Total	1	11	12	11	35

abbreviation: CR =complete response; PR =partial response; SD =stable disease; PD =progressive disease

There were two cases of PD according to the 3D-Choi criteria. In these patients, the sum of the tumor diameters was increased by 10.9% and 17.8% on treatment with sunitinib and sorafenib, respectively, with a short PFS of 1.5 and 2.7 months, respectively. Although the number of cases is limited, our findings suggest that PD according to the 3D-Choi criteria may be associated with poor PFS.

Our study was limited by its retrospective study design, small sample size, and short follow-up period. Therefore, a prospective study with a large number of patients and different molecular targeted therapies needs to be carried out.

In conclusion, the 3D-Choi criteria were

feasible for assessing the imaging response to molecular targeted therapy in advanced RCC, and high inter- and intra-observer agreements were noted. Furthermore, the 3D-Choi criteria may be useful in the early prediction of disease outcome in patients with advanced RCC receiving targeted therapy.

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Conflict of Interest: None to declare

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3D-Choi criteria を用いた進行性腎癌の治療効果判定

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要旨

進行性腎癌に対する分子標的治療薬を用いた治療においては，しばしば径の変化を伴わない腫瘍壊死を生じるため，response evaluation criteria in solid tumor (RECIST) のみで治療効果を完全に判定することは難しいとされる．進行性腎癌に対する分子標的治療薬の治療効果を，CT 値の変化を加味する Choi criteria に 3 次元画像解析を併用した 3D-Choi criteria を用いて判定し，RECISTver.1.1 と比較しその有用性を検討した．Choi criteria では CT 値を 2D 画像で計測するが，我々は 3D 評価法 (3D-Choi) を開発した．すなわち，腫瘍部分を 3D 処理にて半自動的に抽出し，ボクセル数と CT 値から 3D-CT 値を算出する (CT 値総和÷総ボクセル数＝3D-CT 値)．得られた 3D-CT 値を Choi criteria に当てはめ 3D-Choi とした．画像評価は，35 症例 58 病変全例で可能であった．3D-CT 値算出の信頼性は高く，本研究の評価者内一致割合 91.4%，カッパ係数 0.85，評価者間一致割合 88.5%，カッパ係数 0.75 であった．complete response + partial response,stable disease+progressive disease の 2 群に分けた PFS は，RECIST で中央値 8.6 か月，4.8 か月 (p=0.958)，3D-Choi で中央値 11.5 か月，2.7 か月 (p=0.038) であり，3D-Choi 評価が治療成績により強く相関した．進行性腎癌の分子標的治療における 3D-Choi 評価では，分子標的薬治療早期に予後を予測できる可能性が示唆された．