Prognostic Value of The Ratio of Maximum To Minimum Diameter of Primary Tumor In Metastatic Clear Cell Renal Cell Carcinoma

Hongzhe Shi

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital

Chuanzhen Cao

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital

Li Wen

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital

Lianyu Zhang

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital

Jin Zhang

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital

Jianhui Ma

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital

Jianzhong Shou (✉ shoujzh2021@163.com)

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital

Changling Li

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital

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Abstract

Background: Several models and markers were developed and found to predict outcome of advanced renal cell carcinoma. This study aimed to evaluate the prognostic value of the ratio of maximum to minimum tumor diameter (ROD) in metastatic clear cell renal cell carcinoma (mccRCC).

Methods: Patients with mccRCC (n=213) treated with sunitinib from January 2008 to December 2018 were identified. Cut-off value for ROD was determined using receiver operating characteristic. Patients with different ROD scores were grouped and evaluated. Survival outcomes were estimated by Kaplan-Meier method.

Results: The optimal ROD cutoff value of 1.34 was determined for progression free survival (PFS) and overall survival (OS). Patients in $ROD \geq 1.34$ group had shorter PFS (9.6 versus 17.7 months, $p < 0.001$) and OS (25.5 versus 32.6 months, $p < 0.001$) than patients in $ROD < 1.34$ group. After adjustment for other factors, multivariate analysis showed $ROD \geq 1.34$ was an independent prognostic factor for PFS ($p < 0.001$) and OS ($p = 0.006$). Patients in $ROD \geq 1.34$ group presented higher proportions of T3/4 stage (92.9% versus 7.1%, $p = 0.012$), WHO/ISUP grade III/IV (72.0% versus 28.0%, $p = 0.010$), tumor necrosis (71.0% versus 29.0%, $p = 0.039$), sarcomatoid differentiation (79.1% versus 20.9%, $p = 0.007$), poor MSKCC risk score (78.4% versus 21.6%, $p < 0.001$) and poor IMDC risk score (74.4% versus 25.6%, $p < 0.001$) than $ROD < 1.34$ group.

Conclusion: Primary tumor with higher ROD was an independently prognostic factor for both PFS and OS in patients with mccRCC who received targeted therapy. Higher ROD was also associated with high T stage, high WHO/ISUP grade, sarcomatoid features, tumor necrosis, poor MSKCC and IMDC risk score.

Background

Renal cell carcinoma (RCC) accounts for approximately 3% of malignant tumors in adults and 20–30% of them are diagnosed as advanced diseases with poor prognosis(1, 2). Targeted therapy has been the standard metastatic RCC treatment since 2005(3, 4). Several risk score models, such as the Memorial Sloan Kettering Cancer Center (MSKCC) system and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, have been found and validated to predict the prognosis of different patients with metastatic RCC(5, 6). However, MSKCC and IMDC classification mostly focus on the state of the performance status and laboratory values while the primary tumor status has not been involved in.

Several studies have reported primary tumor size may be associated with prognosis of metastatic RCC(7, 8). It is still controversial and cannot completely reflect the role of primary tumor. The ratio of maximum to minimum tumor diameter (ROD), a specific primary tumor feature, has not been mentioned. Previously, we have investigated the utility of ROD in predicting pathologic subtypes of RCC before surgery and found its association with adverse pathological factors(9). We used ROD to quantify tumor irregularity. The more irregular the tumor, the higher the degree of malignancy was discovered. To further demonstrate the prognostic value of the ROD, in this study, we retrospectively analyzed the records of

clear cell RCC (ccRCC) patients treated by surgery and followed sunitinib due to subsequent or simultaneous metastasis.

Patients And Methods

Patient selection

This is a retrospective study focusing on patients with metastatic ccRCC (mccRCC), which was approved by the Domain-Specific Review Board Ethics Committee. Patient consent for treatment and follow-up was included in each medical record. Patients diagnosed as ccRCC after surgery and treated with sunitinib for metastasis between January 2008 and December 2018 were collected. Metastasis was confirmed by imaging examination. Sunitinib was initially administered 50 mg once daily, on a 4/2 schedule. Patients received other systematic therapies after sunitinib treatment failure, including pazopanib, everolimus, axitinib, immune checkpoint inhibitors, or other free second-line therapy trials. Clinicopathological features, such as age, gender, Karnofsky performance status, presenting symptom, tumor size, World Health Organization/International Society of Urologic Pathologists (WHO/ISUP) grade, tumor necrosis, sarcomatoid differentiation, MSKCC and IMDC criteria were used to evaluate.

Radiological Assessment

Patients had contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) examination within 2 weeks before surgery for primary tumor diagnosis and clinical staging. CT scans were undertaken every 4-8 week since taking sunitinib, and the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 were used to evaluate(10). The best response of treatment, including complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD) was recorded.

The diameters of the tumor were measured including coronal, sagittal and axial view, including a maximum diameter, a sub maximum diameter and a minimum diameter in clinical staging before surgery (Figure 1). Tumor's three diameters were recorded separately by 2 independent radiologists. The ratio of the maximum diameter to the minimum diameter (ROD) was calculated to quantify tumor irregularity.

Statistical analysis

Chi-square test, Fisher's exact test or Student's t-test were used to analyze the relationship of different groups. The optimal cutoff value of ROD in prediction of survival outcomes was determined by Receiver Operating Characteristic (ROC) curve analysis. To investigate the survival outcome of patients with mccRCC, progression-free survival (PFS) and overall survival (OS) from the initiation of sunitinib were determined using the Kaplan-Meier method and were analyzed using the log-rank test. Cox proportional hazards regression models were used to assess the significant factors unadjusted and adjusted for

covariates. Statistical analysis was performed using SPSS 23.0 software, and differences were considered statistically significant if p values were < 0.05.

Results

Patients' characteristics

A total of 213 patients with a median age of 55.0 years (range, 17-76 years) were identified. Patients included 139 (65.3%) males and 74 (34.7%) females. Median primary tumor size measured in CT or MRI was 6.1 cm (range, 1.1-15.6 cm). The number of patients in T1a, T1b, T2a, T2b, T3 and T4 stage was 23 (10.8%), 117 (54.9%), 45 (21.1%), 14 (6.6%), 8 (3.8%), and 6 (2.8%) respectively. All patients were received nephrectomy before systemic therapy. Patients consisted of 96 (45.1%) cases of synchronous RCC and 117 (54.9%) cases of metachronous RCC. The most common site of metastasis was pulmonary in 164 cases (77.0%), followed by lymph node metastasis in 86 cases (40.4%). Other metastases included bone, adrenal, liver, brain, spleen, and pancreas. There were 152 patients (71.4%) harboring more than 2 metastatic organs. Twenty-two patients (10.3%) had responders including CR (n=5, 2.3%) and PR (n=17, 8.0%) during the treatment of sunitinib. Patients' characteristics were summarized in Table 1.

Table 1
Correlation between ROD and the clinicopathological features of patients with metastatic renal cell carcinoma.

Characteristics	Total	ROD < 1.34 (n=83)	ROD ≥ 1.34 (n=130)	p value
Age at sunitinib (mean ± SD)	53.3 ± 9.8	52.1 ± 10.7	54.1 ± 9.2	0.139
Gender, n (%)				0.961
Man	139 (65.3)	54 (38.8)	85 (61.2)	
Woman	74 (34.7)	29 (39.2)	45 (60.8)	
KPS score < 80, n (%)	15 (7.0)	5 (33.3)	10 (66.7)	0.643
Presenting symptom, n (%)	19 (8.9)	7 (36.8)	12 (63.2)	0.842
Tumor size (mean ± SD)	6.3 ± 2.2	6.7 ± 2.1	6.1 ± 2.2	0.089
Tumor location, n (%)				0.182
Left	102 (47.9)	35 (34.3)	67 (65.7)	
Right	111 (52.1)	48 (43.2)	63 (56.8)	
Type of metastasis				0.908
Synchronous	96 (45.1)	37 (24.0)	59 (76.0)	
Metachronous	117 (54.9)	46 (51.3)	71 (48.7)	
T stage, n (%)				0.012
T1/2	199 (93.4)	82 (41.2)	117 (58.8)	
T3/4	14 (6.6%)	1 (7.1)	13 (92.9)	
WHO/ISUP grade, n (%)				0.010
I/II	131 (61.5)	60 (45.8)	71 (54.2)	
III/IV	82 (38.5)	23 (28.0)	59 (72.0)	
Tumor necrosis, n (%)	69 (32.4)	20 (29.0)	49 (71.0)	0.039

Abbreviations: ROD, Ratio of maximum to minimum tumor diameter; KPS, Karnofsky performance status; WHO/ISUP, World Health Organization/International Society of Urologic Pathologists; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

Characteristics	Total	ROD < 1.34 (n=83)	ROD ≥ 1.34 (n=130)	p value
Sarcomatoid differentiation, n (%)	43 (20.2)	9 (20.9)	34 (79.1)	0.007
MSKCC risk classification				< 0.001
Good	102 (47.9)	59 (57.8)	43 (42.2)	
Intermediate and poor	111 (52.1)	24 (21.6)	87 (78.4)	
IMDC risk classification				< 0.001
Good	92 (43.2)	52 (56.5)	40 (43.5)	
Intermediate and poor	121 (56.8)	31 (25.6)	90 (74.4)	
Number of metastatic organs				0.943
< 2	61 (28.6)	24 (39.3)	37 (60.7)	
≥ 2	152 (71.4)	59 (38.8)	93 (61.2)	
Response to sunitinib, n (%)				0.844
Responder	22 (10.3)	9 (40.9)	13 (59.1)	
Non-responder	191 (89.7)	74 (38.7)	117 (61.3)	
Abbreviations: ROD, Ratio of maximum to minimum tumor diameter; KPS, Karnofsky performance status; WHO/ISUP, World Health Organization/International Society of Urologic Pathologists; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.				

The Association Between Rod And Clinicopathological Features

ROC curves were constructed to determine the appropriate cut-off point of ROD (Supplementary figure 1). The most discriminative ROD cutoff value of 1.34 was selected for both PFS (sensitivity=79.3%, specificity=74.0%; Area Under Curve, AUC=0.810, 95% confidence interval, CI:0.752–0.869, $p<0.001$) and OS (sensitivity=84.9%, specificity=83.8%; AUC=0.932, 95% CI:0.899–0.966, $p<0.001$). The patients were divided into two groups including ROD<1.34 group (n=83) and ROD≥1.34 group (n=130). Comparison between ROD and the Clinicopathological features were showed in Table 1. Patients in ROD≥1.34 group presented higher proportions of T3/4 stage (92.9% versus 7.1%, $p=0.012$), WHO/ISUP grade III/IV (72.0%

versus 28.0%, $p=0.010$), tumor necrosis (71.0% versus 29.0%, $p=0.039$), sarcomatoid differentiation (79.1% versus 20.9%, $p=0.007$), poor MSKCC risk score (78.4% versus 21.6%, $p<0.001$) and poor IMDC risk score (74.4% versus 25.6%, $p<0.001$) than $ROD<1.34$ group.

The Evaluation Of Rod In Clinical Outcomes

After 32.0 months (range, 2.6-125.8 months) median follow-up, patients in $ROD\geq 1.34$ group experienced significantly shorter PFS (median, 9.6 versus 17.7 months, $p<0.001$) and OS (median, 25.5 versus 32.6 months, $p<0.001$) than patients in $ROD<1.34$ group (Figure 2).

The univariate survival analysis revealed that $ROD\geq 1.34$ ($p<0.001$), WHO/ISUP grade ($p<0.001$), tumor necrosis ($p=0.032$), sarcomatoid differentiation ($p<0.001$), MSKCC score ($p<0.001$) and IMDC score ($p<0.001$) appeared as significant prognostic factors for PFS (Table 2). After adjustment for WHO/ISUP grade ($p<0.001$), tumor necrosis ($p=0.118$), sarcomatoid differentiation ($p=0.035$), MSKCC score ($p=0.008$) and IMDC score ($p<0.001$), the multivariate Cox regression analysis revealed that $ROD\geq 1.34$ (adjusted hazard ratio, $HR=3.068$, 95% CI: 2.102-4.478, $p<0.001$) was an independent prognostic factor for poor PFS (Table 3). In addition, presenting symptom ($p=0.007$), $ROD\geq 1.34$ ($p<0.001$), WHO/ISUP grade ($p<0.001$), tumor necrosis ($p=0.007$), sarcomatoid differentiation ($p=0.016$), MSKCC score ($p<0.001$) and IMDC score ($p<0.001$) were prognostic factors for OS (Table 2). After adjustment for presenting symptom ($p=0.009$), WHO/ISUP grade ($p<0.001$), tumor necrosis ($p<0.001$), sarcomatoid differentiation ($p=0.621$), MSKCC score ($p=0.002$) and IMDC score ($p<0.001$), $ROD\geq 1.34$ (adjusted $HR=1.774$, 95% CI: 1.175-2.676, $p=0.006$) was still an independent prognostic factors for OS (Table 3).

Table 2

Univariate Cox regression analysis of clinical factors in patients with metastatic renal cell carcinoma

Variable	Progression free survival			Overall survival		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.003	0.988-1.019	0.653	1.001	0.985-1.018	0.871
Gender, male	0.936	0.677-1.293	0.688	0.829	0.586-1.173	0.290
KPS, < 80	1.064	0.520-2.177	0.864	0.577	0.212-1.569	0.281
Presenting symptom	1.292	0.770-2.168	0.332	2.256	1.247-4.082	0.007
Tumor location, left	1.027	0.753-1.400	0.867	1.073	0.769-1.497	0.678
ROD, ≥ 1.34	3.974	2.784-5.673	< 0.001	2.783	1.927-4.018	< 0.001
T stage, 3/4	1.116	0.774-1.628	0.052	1.059	0.927-1.253	
WHO/ISUP grade, III/IV	2.308	1.684-3.165	< 0.001	3.164	2.249-4.415	< 0.001
Tumor necrosis	1.438	1.031-2.007	0.032	1.677	1.167-2.410	0.007
Number of metastatic organs, ≥ 2	1.053	0.728-1.547	0.468	0.459	0.592-1.426	0.584
Sarcomatoid differentiation	2.131	1.455-3.120	< 0.001	1.722	1.107-2.680	0.016
MSKCC score, intermediate and poor	2.624	1.895-3.634	< 0.001	3.125	2.174-4.493	< 0.001
IMDC score, intermediate and poor	3.342	2.116-6.528	< 0.001	4.317	2.383-6.657	< 0.001
Abbreviations: KPS, Karnofsky performance status; ROD, Ratio of maximum to minimum tumor diameter; WHO/ISUP, World Health Organization/International Society of Urologic Pathologists; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.						

Table 3
Independent prognostic factors analyzed using a multivariable Cox model in patients with metastatic renal cell carcinoma

Variable	Progression free survival			Overall survival		
	HR	95% CI	p value	HR	95% CI	p value
Presenting symptom				2.219	1.220-4.037	0.009
ROD, ≥ 1.34	3.068	2.102-4.478	< 0.001	1.774	1.175-2.676	0.006
WHO/ISUP grade, III/IV	2.102	1.512-2.922	< 0.001	2.699	1.880-3.874	< 0.001
Tumor necrosis	1.315	0.933-1.854	0.118	2.046	1.395-3.002	< 0.001
Sarcomatoid differentiation	1.529	1.031-2.268	0.035	1.123	0.710-1.776	0.621
MSKCC score, intermediate and poor	1.619	1.137-2.305	0.008	1.901	1.261-2.864	0.002
IMDC score, intermediate and poor	2.315	1.427-4.438	< 0.001	2.004	1.258-4.062	< 0.001
Abbreviations: ROD, Ratio of maximum to minimum tumor diameter; WHO/ISUP, World Health Organization/International Society of Urologic Pathologists; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.						

Discussion

From published papers, intratumor heterogeneity is a key factor contributing to the survival of cancer, therapeutic failure, and drug resistance(11, 12). The scale of heterogeneity within a tumor has also been found and proved in RCC(13, 14). Studies have showed that intratumor heterogeneity may contribute to the polyclonal growth pattern of tumors(15). In addition, polyclonal growth commonly accompanies with corresponding change of tumor microenvironment, which is also thought to play an important role for tumor growth and progression and to be involved in the treatment outcome of targeted therapy(16). We considered that the intratumor heterogeneity evolved to the asymmetric tumor morphology. From the clinical practice, we observed that the ROD could be used to quantify the tumor irregularity. The higher the intratumor heterogeneity, the more irregular tumor and the higher ROD would achieve, which was likely to reveal the efficacy of later treatment.

The ROD, a specific feature of primary tumor, has not been investigated before. In this study, the most optimal ROD cutoff value of 1.34 was determined. Patients in $ROD \geq 1.34$ group accounted for 61.0% (130/213). In this study, we were not surprised to find that more cases of metastatic renal cell carcinoma

were in the group with larger ROD. This finding suggested a new hypothesis that the stronger tumor heterogeneity have more chances of metastasis.

We found that the $ROD \geq 1.34$ was also significantly associated with prognosis. Compared with patients in $ROD \geq 1.34$ group, patients in $ROD < 1.34$ group achieved longer PFS (17.7 versus 9.6 months, $p < 0.001$) and OS (32.6 versus 25.5 months, $p < 0.001$). Variable pathology factors including WHO/ISUP grade, tumor necrosis, and sarcomatoid differentiation were also associated with outcome of RCC, which were confirmed in previous studies(17–19). In this study, these features were also investigated. WHO/ISUP grade, sarcomatoid differentiation, MSKCC score and IMDC score were independent prognostic factors for PFS, and presenting symptom, WHO/ISUP grade, tumor necrosis, MSKCC score and IMDC score were independent prognostic factors for OS. Interestingly, we found that patients in $ROD \geq 1.34$ group were more likely to present high WHO/ISUP grade, high T stage, tumor necrosis, sarcomatoid differentiation, poor MSKCC risk score, and poor IMDC score. Besides above findings, after adjustment for significant variables, we also found that $ROD \geq 1.34$ was an independent prognostic factor for both poor PFS and OS.

In addition, $ROD \geq 1.34$ was associated with high T stage (3/4), high WHO/ISUP grade, sarcomatoid features, tumor necrosis, poor MSKCC risk score and poor IMDC score. This showed that as an index to quantify tumor irregularity, ROD had a strong relationship with tumor malignancy.

Our study includes several limitations that need to be acknowledged. It was a retrospective study including limited cases, which still needed to accumulate data, and we will carry out prospective studies to confirm. In addition, we will further explore the possible molecular mechanism of poor outcome associated with irregularity of primary tumor.

Conclusions

Primary tumor with $ROD \geq 1.34$ was an independently prognostic factor for both PFS and OS in patients with mcrRCC who received targeted therapy and also associated with high T stage, high WHO/ISUP grade, sarcomatoid features, tumor necrosis, poor MSKCC and IMDC risk score. Further prospective validation is required to confirm these findings.

Abbreviations

AUC: Area Under Curve

CI: confidence interval

CR: complete response

CT: computed tomography

HR: hazard ratio

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

mccRCC: metastatic clear cell renal cell carcinoma

mRCC: metastatic RCC

MRI: magnetic resonance imaging

MSKCC: Memorial Sloan Kettering Cancer Center

NCC/CHCAMS: National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences

OS: overall survival

PD: progression disease

PFS: progression-free survival

PR: partial response

RCC: Renal cell carcinoma

RECIST: Response Evaluation Criteria in Solid Tumors

ROC: Receiver Operating Characteristic

ROD: ratio of maximum to minimum tumor diameter

SD: stable disease

WHO/ISUP: World Health Organization/International Society of Urologic Pathologists

Declarations

Ethics approval and consent to participate

The research study was reviewed and approved by the Domain-Specific Review Board, Cancer Hospital Chinese Academy of Medical Sciences (ID: NCC2016YJC-08). Patient details were anonymized before analysis. Patient written informed consent for treatment and follow-up was included in each medical record. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to individual privacy could be compromised but are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interests.

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Authors' contributions

All authors listed in this manuscript contributed significantly to the study. Shi HZ and Cao CZ contributed to writing the manuscript. Wen L contributed to clinical data collection and analysis. Zhang LY and Zhang J contributed to reviewing CT or MRI data. Ma JH contributed to conception of the study. Li CL and Shou JZ contributed to the study design and reviewed the manuscript for critical revisions. All authors read and approved the final manuscript.

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Figures

Figure 1

Example of measuring the three diameters: one maximum, one sub maximum, and one minimum.

Figure 2

Patients with $ROD \geq 1.34$ had shorter progression free survival (A) and overall survival (B) than patients with $ROD < 1.34$.

Supplementary Files

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