Can Quantitative CT Texture Analysis be used to Differentiate Subtypes of Renal Cell Carcinoma?

Introduction

Renal cell carcinoma (RCC) is a common malignancy with an increasing mortality rate [1,2]. It is a heterogeneous disease with different histological subtypes. Clear cell, papillary and chromophobe RCC are the most common subtypes[2]. The histological classification of RCC is important as clear cell RCC (ccRCC) generally has a worse prognosis compared to other subtypes[3,4]. As the available targeted agents of metastatic RCC (mRCC) mainly relate to ccRCC[5-7], the optimal treatment for mRCC with non-clear cell histology is still under investigation. A tumor biopsy is indicated to provide histological information before commencing systemic treatment, but its invasive nature and unsatisfactory accuracy have limited its clinical application in certain patients[8]. It would be helpful if there is a safer and much less invasive method to characterize RCC subtypes.

Previous studies have focused on the use of enhancement of lesions at multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) to differentiate

ccRCC from papillary RCC (pRCC) or chromophobe RCC (chRCC)[9-12]. But it's still

challenging to make the right diagnosis of RCC subtype as the interpretation of imaging

findings is a subjective process and an accurate prediction of histological RCC subtype

strongly depends on the experience and expertise of radiologists. Besides, due to lack

of validation on a larger scale, clinical application of these methods is limited. We need

a more objective method to help us improve diagnosis of RCC subtype.

Texture analysis (TA) is a emerging imaging tool to quantify tissue heterogeneity

that may not be perceived by the naked eye. It involves an objective computer-aided

measurement of gray-level patterns within the lesions. A few studies have reported that

TA could accurately differentiate renal fat-poor angiomyolipoma from RCC[13-16].

However, whether TA could discriminate RCC subtypes has been controversial. Raman

et al[16] and Yan L et al[13] demonstrated that CT texture analysis (CTTA) could

differentiate ccRCC from pRCC, but Hodgdon et al[14] showed there was no difference

between ccRCC, pRCC and chRCC on unenhanced CT images. Further studies are

needed to investigate the potential value of CTTA in characterizing RCC subtypes. As

stated earlier that non-clear cell RCC (non-ccRCC) is not recommended for targeted

therapies, discriminating non-ccRCC from ccRCC is far more clinically relevant, which

could help patients with non-ccRCC avoid possible side effects and enormous cost of

targeted agents. To our knowledge, the potential of CTTA has not been explored in this

context of differentiating non-ccRCC from ccRCC.

The primary aim of this study was to retrospectively evaluate the diagnostic

performance of CTTA to differentiate non-ccRCC from ccRCC and secondary aim was

to investigate whether CTTA could differentiate non-ccRCC subtypes of pRCC and

chRCC on multiphasic images.

Materials and Methods

Patient Selection

The institutional review board of our institution approved this retrospective study

and waived the requirement for informed consent. Between June 2014 to August 2015,

165 patients with histologically confirmed diagnosis of RCC on entire tumor resection

were identified. Twenty-nine patients were excluded for absence of preoperative

multiphasic CT images in our picture archiving and communication system (PACS),

including 24 patients with ccRCC, 3 patients with pRCC and 2 patients with chRCC.

Two radiologists with 10 and 13 years of experience in abdominal imaging reviewed all the images and excluded another 10 patients with ccRCC in whom there was almost no solid component in the lesions for TA. The final study population comprised 126 patients and the details are provided in Fig 1.

CT Examination

All the patients underwent a preoperative three-phasic abdominal CT examination (Somatom Definition Flash; Siemens Healthcare, Forchheim, Germany). Protocol details are provided in Table 1. After the unenhanced scanning, intravenous injection of 100mL contrast material (Ultravist 370, Bayer ScheringPharma AG, Germany) followed by a 100-mL saline chaser were administered at a rate of 4mL/s. A bolus-tracking algorithm (CareBolus, Siemens Medical Solutions) was used and a region of interest (ROI) was placed in the thoracoabdominal aorta junction. The corticomedullary phase was initiated 5 seconds after the bolus-triggering threshold of 120 HU was reached and the nephrographic phase occurred 50 seconds after the corticomedullary imaging acquisition.

CTTA

All the images were de-identified before being accessed by the researchers. Two radiologists with 10 and 13 years of experience in abdominal imaging reviewed all the images and disagreement was resolved by consensus. Both reviewers were blinded to clinical and histological information. For each lesion in each phase, only one axial image with the optimal representation of the largest cross-sectional tumor area was chosen for TA. One of the two reviewers measured the maximal diameter of each lesion on the selected axial images and repeated the measurement several months later to assess the intra-observer agreement. Another radiologist also measured the maximal diameter of each lesion to assess the inter-observer agreement. All the selected images were exported from PACS and uploaded to the TexRAD commercial research software (TexRAD Ltd, www.texrad.com, part of Feedback Plc, Cambridge, UK). A single trained operator carried out all the TA and repeated the process eight weeks later. The average value of two measurements for each texture parameter was calculated and recorded.

For each lesion, a ROI was manually delineated slightly within the lesion border

leaving an approximate distance of 1-2mm from the outline in order to minimize

volume averaging from surrounding perirenal fat or normal renal parenchyma.

Confounding factors such as air, dense calcification and necrosis without enhancement

were excluded when drawing the ROIs to minimize their impact on the CTTA (Fig 2A).

Furthermore, the CTTA-algorithm setting excluded pixels with values less than -50 and

greater than 200HU from inclusion in the texture analysis to increase the robustness in

the quantification. Since the outline of lesions could be difficult to define on

unenhanced images, the corresponding matched enhanced images of each lesion were

referenced during delineation. ROIs for each axial section for matched unenhanced,

corticomedullary and nephrographic CT images were then used for TA.

TA comprised a two-step process that involved selective scale image filtration to

extract features of different sizes followed by texture quantification by histogram

analysis. Image filtration utilized a Laplacian of Gaussian spatial band-pass filter to

produce a series of derived images highlighting features at different spatial scales. The

size of the image features highlighted by the filter is denoted by the Spatial Scaling

Factor (SSF), which ranges between object radii of 0, 2, 3, 4, 5 and 6 mm. SSF can be

considered as the width at which structures in the image will be highlighted while structures less than this width will become blurred. SSF 0 indicates used of no filtration (used as control), 2 indicates fine, 3-5 indicates medium and 6 indicates coarse texture scales respectively (Fig 2B-D). Six texture parameters were derived from histogram analysis: mean gray-level intensity (Mean, brightness), standard deviation (SD, degree of variation from the mean), entropy (irregularity of pixel intensity), mean of positive pixels (MPP), skewness (symmetry of the histogram distribution), and kurtosis (sharpness of the histogram distribution)[17]. For each lesion in each phase, all the six parameters across each SSF were recorded.

Statistical Analysis

Intra- and inter-observer agreement were calculated for the measurement of the maximum diameter of the lesions by using the intraclass correlation coefficient (ICC) test (0.00–0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; 0.81–1.00, excellent agreement). Papillary RCC and chRCC were classified together as non-ccRCC. Mann-Whitney U tests were used to compare the value of each texture parameter in each phase for the research

purposes (SPSS for Mac, version 20, SPSS Inc., Chicago, Ill). Although a two-sided

P<0.05 indicated a significant difference, to control for type I errors arising from

multiple comparisons, we adjusted the individual significance level as proposed by

Cross and Chaffin[17]: $p^*=p\times[k-x+1]^{-1}$, where p* is the adjusted significance level for an

individual test, p is the nominal significance level for the sequence of tests, k is the total

number of the tests, and x is the number of significant tests. Receiver operating

characteristic (ROC) curves and the area under the ROC curves (AUC) were calculated

for each texture parameter in each phase and Pearson's correlation coefficient (r)

between texture features at each SSF in each phase was evaluated so that only one of

the features that showed a high correlation (r>0.90) was selected to build the classifiers.

As an AUC≥0.8 generally indicates a good test, we selected all the texture features

with AUC≥0.8 as predictors. In cases when all the AUCs<0.8, only three texture

parameters with the top three AUC values were selected as predictors as to minimize

the likelihood of overfitting. Combinations of predictors were used to train multiple

support vector machine (SVM) classifiers, and ROC curves were computed by the

predicted values of regression of SVM for each SSF in each phase to determine the

optimal combination. An SVM with a nonlinear radial basis function kernel was implemented in the 'SVM' function in R Package 'e1071' (Version 1.6-7, R Software), using the Library for Support Vector Machines (or LIBSVM) library[19]. The stability of classification was evaluated through 10-fold cross-validation.

Results

General characteristics of the 126 patients with 127 RCC lesions (100 ccRCC, 12 pRCC, 15 chRCC) are summarized in Table 2. The mean time from preoperative CT evaluation to nephrectomy was 20 days for all RCC (range, 0-35 days). For the measurement of maximum diameter of the lesions, we found excellent intra-observer (intraclass correlation coefficient, ICC=0.95) and inter-observer agreement (ICC=0.91). The average size of all the RCC was (4.9±2.6) cm. There was no significant difference in the average size of lesions among ccRCC (4.5±2.1), pRCC (6.5±3.7) and chRCC (6.1±3.2) groups ($P>0.05$).

Differentiating non-ccRCC from ccRCC

The median and interquartile range (IQR) associated with each texture parameter,

the corresponding *P* and the area under the receiver operating characteristic (ROC)

curve (AUC) values for assessing the difference between non-ccRCC and ccRCC are

provided in Supplementary 1. Compared to ccRCC, all the six texture parameters

quantified from unenhanced images and skewness quantified from enhanced images

didn't show any significant differences in non-ccRCC (*P*>0.001 after Cross and Chaffin

correction). However, on enhanced images, kurtosis was significantly higher while

Mean, SD, entropy and MPP were significantly lower at all the texture scales (SSF 0-

6) in non-ccRCC (*P*<0.001 after Cross and Chaffin correction). As Mean and MPP

quantified from SSF0 on both unenhanced and enhanced images, SD and entropy

quantified from SSF2 on enhanced images, SD and MPP quantified from SSF2-5 on

enhanced images all had a Pearson's correlation coefficient over 0.90, only one of these

correlated features at each SSF in each phase was selected to build the classifiers.

Regression models produced by combining the optimal discriminative texture

features are summarized in Table 3. To identify non-ccRCC from ccRCC, all the models

resulted in AUCs greater than 0.7. On unenhanced images, the model incorporating

MPP, skewness and kurtosis at SSF0 produced the highest AUC of 0.82±0.05 (*P*<0.001)

with 78% sensitivity and 86% specificity (Fig 3A). On corticomedullary images, the

highest AUC of 0.94±0.03 (P<0.001) was reached at SSF6 by the model incorporating

SD, entropy, MPP and kurtosis with 89% sensitivity and 92% specificity (Fig 3B). On

nephrographic images, the model incorporating entropy, MPP and kurtosis at SSF0

yielded the highest AUC of 0.89±0.04 (P<0.001) with 89% sensitivity and 83%

specificity (Fig 3C). The 10-fold cross-validation support vector machine (SVM)

accuracy arranged from 76% to 88% for each combination of texture features (Table 3).

Differentiation between pRCC and chRCC

The median and IQR associated with each texture parameter, the corresponding P

and AUC values for differentiating between pRCC and chRCC are summarized in

Supplementary 2. Only Mean and MPP quantified from SSF0 on corticomedullary

images were significantly different (P=0.002) between the two subtypes. Mean and

MPP were both significantly lower in pRCC (Mean: median pRCC, 48.2; IQR, 38.1-

60.0; median chRCC,72.4; IQR, 54.1-101.5; P=0.02) (MPP: median pRCC, 49.6; IQR,

40.0-61.1; median chRCC, 74.6; IQR,58.3-101.6; P=0.002). The mean AUC ± standard

error associated with Mean (0.84 ± 0.08) and MPP (0.85 ± 0.07) were greater than 0.8.

As Mean and MPP quantified from SSF0 on both unenhanced and enhanced images,

SD and entropy quantified from SSF3-6 on unenhanced images, SD and MPP

quantified from SSF2 on enhanced images and SSF3, 4 on corticomedullary images all

had a Pearson's correlation coefficient over 0.90, only one of these correlated features

at each SSF in each phase was selected to build the classifiers.

The results of different regression models to differentiate between pRCC and

chRCC are summarized in Table 4. On unenhanced images, all the AUCs were

significantly greater than 0.7 and the model incorporating entropy, MPP and kurtosis

quantified from SSF6 produced an AUC of 0.84±0.08 (P=0.077) with 67% sensitivity

and 100% specificity (Fig 4A). On corticomedullary images at SSF0, SD combined

with MPP and Skewness yielded an AUC of 0.96±0.04 with 87% sensitivity and 92%

specificity (Fig 4B). On nephrographic images, the highest AUC of 0.93±0.05 (P<0.001)

with 93% sensitivity and 83% specificity (Fig 4C) was reached at SSF0 by

incorporating MPP, skewness and kurtosis. The 10-fold cross-validation SVM accuracy

arranged from 30% to 78% for each combination of texture features (Table 4).

Discussion

Our study results show that texture parameters of SD, entropy and MPP seem to be strong predictors of non-ccRCC while MPP and skewness are helpful texture features to further differentiate between pRCC and chRCC. Our results indicate that TA may serve as a non-invasive method to identify non-ccRCC and it could potentially help those patients avoid unnecessary drug toxicity and financial burden by predicting histological RCC subtype.

Our results showed that non-ccRCC had significantly lower Mean, SD, entropy, MPP and higher kurtosis compared to ccRCC on enhanced CT images. Specifically, MPP quantified from the coarse texture scale (SSF6) on corticomedullary images seems to be a valuable texture feature, and the combination of SD, entropy, MPP and kurtosis at SSF6 on corticomedullary images is the strongest classifier for non-ccRCC. Generally, our results were comparable to previous studies of renal, brain and lung neoplasms[20-24]. Greater heterogeneity is known to be likely related to higher histological grade of malignancy and poorer prognosis[5-26]. We can infer from this study that heterogeneity between RCC subtypes is likely linked to increasing number of

objects or features highlighted in the filtration step and their mean brightness difference

compared to the background of lesions resulting in higher Mean, SD, entropy, MPP and

lower kurtosis in ccRCC. Skewness tends to be zero with increasing number of objects

highlighted, which may be a general characteristic of RCC subtypes and hence did not

demonstrate to be a useful discriminator. Our results were consistent with previous

studies that higher entropy and lower degree of texture features related to uniformity

are characteristics of ccRCC[13-14]. As ccRCC is generally more aggressive than non-

ccRCC, it worth investigating the relationship between these texture characteristics and

the prognosis of RCC. As for MPP, it has been correlated negatively with angiogenesis

in non-small cell lung cancer [22]. To our knowledge, we were the first to show that lower

MPP on enhanced CT images may help to identify non-ccRCC. And MPP may be quite

a good parameter in addition to kurtosis in vascular tumors as shown previously in

treatment response studies of metastatic RCC [27]. Given that MPP only considers the

average intensity of pixels greater than zero and non-ccRCC tends to be generally hypo-

vascular, lower MPP in non-ccRCC appears to be consistent with hypo-vascular tumors

exhibiting fewer bright areas. Furthermore, amongst non-ccRCC, pRCC tends to be

even more hypo-vascular, which potentially explains the even lower value of MPP in pRCC compared to chRCC. We hypothesize that MPP on contrast-enhanced CT images may be positively correlated with the blood supply of RCC and MPP may be a better marker of treatment response compared to size, density and perfusion. When we compared our results to similar studies evaluating MR images for classifying RCC subtypes, Chandarana et al[28] found that Kurtosis and skewness were significantly lower in ccRCC. We had similar findings about Kurtosis, but we didn't find any difference of skewness among RCC subtypes. This could possibly be attributed to the differences between imaging modalities and physical properties being captured. The role of skewness on CT in discriminating RCC subtypes may need further investigation.

In our study, we analyzed both unenhanced and contrast-enhanced CT images. On unenhanced CT images, our results were slightly different from the results of previous studies. Hodgdon et al[14] reported that there was no texture difference between RCC subtypes on unenhanced CT images. In our study, individual texture parameter also showed no significant difference between RCC subtypes but combinations of different texture parameters could be used to help identify non-ccRCC from ccRCC and

differentiate between pRCC and chRCC. One possible explanation could be combinations of texture parameters may help to enhance the detection of subtle but potentially discriminating features that individual parameter may not be able to reflect. Although the effects of iodinated contrast material on TA are still unclear, differences in texture features between unenhanced and contrast-enhanced CT images were observed in previous studies[21,29]. More texture parameters on enhanced images showed significant differences between RCC subtypes and models integrating texture parameters quantified from enhanced images demonstrated higher diagnostic accuracies. Our findings seem to support that CTTA on enhanced images may provide more useful information, specifically corticomedullary images, to identify non-ccRCC from ccRCC.

In our study, before building the classifiers, Pearson's correlation coefficient between each feature was evaluated to make sure that the features selected to train SVM were not highly correlated. As an AUC≥0.8 generally indicates a good test, we defined the optimal discriminative texture features as those with AUC≥0.8 and they were combined to train SVM at each SSF in each phase. But there were some circumstances

that none of the texture parameters yielded an AUC≥0.8. In such situations and to

minimize the likelihood of overfitting, the optimal discriminative texture features were

selected as texture parameters with the top three AUC values. However, there are also

other strategies to select and define SVM classifiers[14,30]. In this study, most cross-

validation accuracies for identifying non-ccRCC from ccRCC were above 80% and

some model resulted in 96% sensitivity and 92% specificity. However, when

differentiating between pRCC and chRCC, cross-validation SVM accuracies were low

(30% to 78%). But yet there was a model incorporating SD, MPP and skewness

quantified from SSF 0 on corticomedullary images produced an AUC of 0.96±0.04

(*P*<0.001) with 87% sensitivity and 92% specificity. We think the low cross-validation

accuracy is likely related to the small sample size and it's possible that the increase in

sample size would improve cross-validation accuracy. Larger cohorts of pRCC and

chRCC are necessary to validate our results.

Our study had several limitations. First, the retrospective nature of our study may

lead to overestimation of the diagnostic accuracy. Second, although the sample size of

non-ccRCC was comparable to that of previous studies involving differentiation of

RCC subtypes by using CTTA, the small sample size may contribute to the low cross-validation accuracy. More data should be pooled together to confirm our results. Third, as we excluded 10 ccRCC which had almost no solid component, it's possible that texture characteristics of ccRCC reported in this study may not be comprehensive enough and our results may not be generalized directly to those primarily cystic or necrotic lesions. Fourth, as the main purpose of this study was to investigate whether CTTA could be used to discriminate RCC subtypes, we haven't evaluated the correlation between texture parameters and the histological grading within each subtype. But we think that our study results add to clinical adoption of TA for evaluating RCC besides standard morphological assessment, which would give clinicians more confidence in making the optimal therapeutic choice for RCC patients.

In conclusion, our results show that CTTA could potentially be used to accurately differentiate non-ccRCC from ccRCC, and further differentiate between pRCC and chRCC. Prospective studies in larger cohorts of patients are required to further validate our study results before implementing into clinical practice.

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Table 1. Scan parameters of CT examination

Parameter	
Tube potential, kV	120
Tube current, mAs	Variable tube current with automatic tube-current modulation activated
Pitch	0.9
Gantry rotation time, second	0.28
Collimation, mm	128×0.6
Kernel	B30f (medium smooth)
Acquisition slice thickness, mm	5
Field of view, mm	300

Table 2. Characteristics of patients and renal cell carcinomas.

Characteristic	All	ccRCC	non-ccRCC		
			All	pRCC	chRCC
Sex[*]					
Male	83(66)	66(67)	17(63)	10(83)	7(47)
Female	43(34)	33(33)	10(37)	2(17)	8(53)
Age (y)[**]	54±12	55±12	51±15	53±18	49±13
Side					
Left	66(52)	55(55)	11(41)	5(42)	6(40)
Right	61(48)	45(45)	16(59)	7(58)	9(60)

Data are numbers of lesions and data in parentheses are percentage, unless otherwise indicated. [*]Data are numbers of patients. There was no significant difference in the portion of male patients among ccRCC, pRCC and chRCC groups ($P>0.05$). [**]Data are mean ± standard deviation. There was no significant difference in mean age among ccRCC, pRCC and chRCC groups ($P>0.05$). Note: ccRCC=clear cell RCC, non-ccRCC=non-clear cell RCC, pRCC=papillary RCC, chRCC=chromophobe RCC.

Table 3. ROC Curves for Combinations of Texture Features for differentiating

non-ccRCC from ccRCC.

Phase	SSF	Model	AUC[*]	P	SVM[+]	Sen	Spe
UE	0	MPP+ skewness+ kurtosis[**]	0.82±0.05	<0.001	79	0.78	0.86
	2	Mean+ skewness+ kurtosis	0.79±0.06	<0.001	79	0.79	0.86
	3	Mean+ MPP+ kurtosis	0.73±0.06	<0.001	80	0.59	0.85
	4	MPP+ skewness+ kurtosis	0.80±0.06	<0.001	80	0.74	0.83
	5	entropy+ MPP+ kurtosis	0.74±0.06	<0.001	76	0.59	0.84
	6	entropy+ MPP+ kurtosis	0.76±0.06	<0.001	76	0.63	0.88
CM	0	entropy+ MPP+ kurtosis	0.92±0.04	<0.001	86	0.85	0.88
	2	Mean+ entropy+ MPP	0.92±0.03	<0.001	87	0.89	0.90
	3	entropy+ MPP+ kurtosis	0.93±0.03	<0.001	88	0.96	0.85
	4	entropy+ MPP+ kurtosis	0.92±0.03	<0.001	87	0.89	0.88
	5	entropy+ MPP+ kurtosis	0.92±0.03	<0.001	88	0.93	0.89
	6	SD+ entropy+ MPP+ kurtosis[**]	0.94±0.03	<0.001	87	0.89	0.92
N	0	entropy+ MPP+ kurtosis[**]	0.89±0.04	<0.001	85	0.89	0.83
	2	entropy+ MPP+ kurtosis	0.84±0.05	<0.001	81	0.74	0.89
	3	entropy+ MPP+ kurtosis	0.83±0.05	<0.001	83	0.74	0.90
	4	entropy+ MPP+ kurtosis	0.83±0.05	<0.001	87	0.70	0.90
	5	Mean+ entropy+ MPP	0.88±0.04	<0.001	82	0.93	0.78
	6	SD+ entropy+ MPP	0.89±0.03	<0.001	84	0.89	0.81

[*]Data are mean AUC ± standard error. [+]Accuracy of the SVM classifier after 10-fold cross-validation. [**]Model with the highest AUC in each phase. Note: AUC=area under the ROC curve, SSF=spatial scaling factor, SVM= support vector machine, Sen=sensitivity, Spe=specificity, Mean=mean gray-level intensity, SD=standard deviation, MPP=mean of positive pixels, UE=unenhanced, CM=corticomedullary, N=nephrographic.

Table 4. ROC Curves for Combinations of Texture Features for differentiating between pRCC and ccRCC.

Phase	SSF	Model	AUC[*]	P	SVM[+]	Sen	Spe
UE	0	entropy+ MPP+ skewness	0.76±0.10	0.025	41	0.53	0.92
	2	SD+ entropy+ skewness	0.83±0.08	0.003	59	0.93	0.58
	3	entropy+ MPP+ kurtosis	0.81±0.08	0.006	41	1.00	0.50
	4	entropy+ MPP+ kurtosis	0.79±0.09	0.010	48	0.53	1.00
	5	entropy+ MPP+ kurtosis	0.78±0.09	0.013	52	0.60	0.92
	6	entropy+ MPP+ kurtosis[**]	0.84±0.08	0.077	52	0.67	1.00
CM	0	SD+ MPP+ skewness[**]	0.96±0.04	0.000	78	0.87	0.92
	2	entropy+ MPP+ kurtosis	0.77±0.10	0.017	59	0.93	0.67
	3	entropy+ MPP+ kurtosis	0.76±0.10	0.025	44	0.87	0.58
	4	entropy+ MPP+ kurtosis	0.80±0.09	0.008	41	0.73	0.83
	5	SD+ entropy+ MPP	0.64±0.11	0.223	30	0.73	0.67
	6	SD+ entropy+ MPP	0.68±0.11	0.118	37	0.53	0.92
N	0	MPP+ skewness+ kurtosis[**]	0.93±0.05	0.000	70	0.93	0.83
	2	entropy+ MPP+ skewness	0.74±0.10	0.032	37	0.93	0.50
	3	entropy+ MPP+ skewness	0.78±0.09	0.013	44	0.60	1.00
	4	MPP+ skewness+ kurtosis	0.84±0.08	0.002	41	0.67	1.00
	5	Mean+ SD+ kurtosis	0.88±0.07	0.001	41	0.67	1.00
	6	SD+ entropy+ kurtosis	0.91±0.06	<0.001	63	0.87	0.92

[*]Data are mean AUC ± standard error. [+]Accuracy of the SVM classifier after 10-fold cross-validation. [**]Model with the highest AUC in each phase. Note: AUC=area under the ROC curve, SSF=spatial scaling factor, SVM= support vector machine, Sen=sensitivity, Spe=specificity，Mean=mean gray-level intensity, SD=standard deviation, MPP=mean of positive pixels, UE=unenhanced, CM=corticomedullary, N=nephrographic.

Fig 1. Flowchart of patient population and exclusion criteria.

Note: ccRCC=clear cell RCC, non-ccRCC=non-clear cell RCC, pRCC=papillary RCC, chRCC=chromophobe RCC.

Fig 2. Demonstration of ROI delineation within the lesion and corresponding texture images of different texture scales.

Corticomedullary CT image in a patient with right renal lesion shows region of interest (blue contour) drawn within lesion border (A). Corresponding texture analysis images display fine (B), medium (C) and coarse (D) textures obtained by using SSF 2,4,6 respectively.

Fig 3. ROC curves for SVM performances with the highest AUC value on (A) unenhanced, (B) corticomedullary and (C) nephrographic phase images to identify non-ccRCC from ccRCC.

Fig 4. ROC curves for SVM performances with the highest AUC value for differentiating between pRCC and chRCC on (A) unenhanced, (B) corticomedullary and (C) nephrographic phase images.

Supporting Information

Supplementary 1. The median, inter-quartile range, *P* value and AUC value for each texture parameter for discriminating non-ccRCC from ccRCC on multiphasic CT images.

Supplementary 2. The median, inter-quartile range, *P* value and AUC value for each texture parameter for differentiating between pRCC and chRCC on multiphasic CT images.

Note: SSF=spatial scaling factor, Mean=mean gray-level intensity, SD= standard deviation, MPP=mean of positive pixels, UE=unenhanced, CM=corticomedullary, N=nephrographic, pRCC=papillary renal cell carcinoma, non-chRCC= chromophobe renal cell carcinoma, AUC= area under the ROC curve.