Differentiation of Renal Oncocytoma and Renal Clear Cell Carcinoma Using Relative CT Enhancement Ratio

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Abstract

Background: The difference between renal oncocytomas (RO) and renal clear cell carcinomas (RCCs) presents the greatest diagnostic challenge. The aim of this study was to retrospectively determine if RO and RCCs could be differentiated on computed tomography (CT) images on the basis of their enhancement patterns with a new enhancement correcting method.

Methods: Forty-six patients with a solitary renal mass who underwent total or partial nephrectomy were included in this study. Fourteen of those were RO and 32 were RCCs. All patients were examined with contrast-enhanced CT. The pattern and degree of enhancement were evaluated. We selected the area that demonstrated the greatest degree of enhancement of the renal lesion in the corticomedullary nephrographic and excretory phase images. Regions of interest (ROI) were also placed in adjacent normal renal cortex for normalization. We used the values of the normal renal cortex that were measured at the same time as divisors. The ratios of lesion-to-renal cortex enhancement were calculated for all three phases. The Student's t-test and Pearson's Chi-square test were used for statistical analyses.

Results: All RCCs masses showed contrast that appeared to be better enhanced than RO on all contrast-enhanced phases of CT imaging, but there was no significant difference in absolute attenuation values between these two diseases ($P > 0.05$). The ratio of lesion-to-cortex attenuation in the corticomedullary phase showed significantly different values between RO and RCCs. The degree of contrast enhancement in RCCs was equal to or greater than that of the normal renal cortex, but it was less than that of the normal cortex in RO in the corticomedullary phase. The ratio of lesion-to-cortex attenuation in the corticomedullary phase was higher than the cut off value of 1.0 in most RCCs (84%, 27/32) and lower than 1.0 in most RO (93%, 13/14) ($P < 0.05$). In the nephrographic phase, the ratio of lesion-to-cortex attenuation was higher than that in the corticomedullary phase in most RO (71%, 10/14), showing a prolonged enhancement pattern; and was lower than that in most RCCs (97%, 31/32), showing an early washout pattern ($P < 0.05$). In the differentiation of RO from RCCs, the sensitivity was 93%, specificity 84%, positive predictive value 72%, negative predictive value 84%, and accuracy for RO was 87, if the ratio of lesion-to-cortex attenuation in a cortex phase was lower than the cutoff value of 1.0. The sensitivity was 71%, specificity was 97%, positive predictive value was 91%, negative predictive value was 91%, and accuracy for RO was 89%, if the ratio of lesion-to-cortex attenuation in nephrographic phase was higher than that in the corticomedullary phase.

Conclusions: The ratios of renal lesion-to-cortex attenuation ratios may be helpful in differentiating RO from RCCs.

Key words: Clear Cell Renal Cell Carcinomas; Ratio of Renal Lesion Enhancement to Cortical Enhancement; Renal Oncocytoma; Tomography; X-ray Computed

INTRODUCTION

Renal clear cell carcinomas (RCCs) which account for approximately 70% of renal cortical tumors and 90% of metastases, have the greatest metastatic potential. Renal oncocytomas (RO) are virtually benign. Since clinical implications and therapeutic strategies may differ for RCCs and RO, preoperative identification of RCCs and RO would be of great clinical interest. Computed tomography (CT) remains the standard modality to use in diagnosing and staging renal neoplasms. Thus, it would be helpful to have CT criteria that could differentiate among solid renal masses and allow the radiologist to differentiate RO from RCCs. Several studies[1-3] have described imaging features of RO. However, these findings overlapped considerably with those for RCCs. Therefore, no specific imaging findings that suggested a diagnosis of RO could be identified in these studies. The purpose of our study was to retrospectively determine if RCCs and RO depicted on CT images could be differentiated on the basis of their enhancement patterns.

METHODS

Fourteen patients with RO were selected at two institutions (China-Japan Friendship Hospital and Beijing Union Hospital) during a 3-year period. As a control group, 32

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consecutive patients seen with RCCs during an 8-month period were included in this retrospective study. A total of 46 cases of patients with a solitary renal mass constituted the basis of our study. All patients were pathologically confirmed after surgery. The study population consisted of 29 men and 17 women, and the mean age was 58 years with an age range of 31–79 years.

CT examination

All CT examinations were performed with 128-or 64-detector row helical scanners (Philips Brilliance, Siemens Somatom Sensation 64). CT images were obtained during breath hold with the following parameters; 120 kV, 250 mA, and section thickness and reconstruction interval of 2.5 mm through the kidneys and 5.0 mm through the rest of the abdomen. A 80–100 ml dose of nonionic intravenous contrast material (Ultravist 370, Schering) was administered with a power injector at a rate of 3.0 ml/s. Time delay to scanning was determined on the basis of the typical time to the renal corticomedullary (30 s) and parenchymal (60 s) and excretory (360 s) phases. All images were sent to a picture archiving and communication system (PACS) to be interpreted on workstations.

CT image analysis

The CT studies were independently reviewed by two radiologists. Each renal mass was assessed according to: Absolute attenuation values and the degree of enhancement in each phase of CT measured and evaluated. We selected the area that demonstrated the greatest degree of enhancement of the renal lesion in the images from the three phases. Matching elliptical regions of interest (ROI) approximately 8–15 mm^2 in size were placed in these areas. The ROI was also placed in the adjacent normal renal cortex. The location of the ROI was consistent in the images obtained during all scan phases. At least two measurements were obtained for each parameter with a cursor of the same size and configuration for the two measurements. A single consensus measurement was made for each lesion in each imaging phase to record mean attenuation in the measurements of attenuation (Hounsfield unit (HU)). To normalize the variations due to individual patient factors and technical factors, the relative enhancement ratio (the ratio of lesion-to-cortex attenuation) was calculated by the absolute measurement of the lesion dividing that of adjacent normal renal cortex. The enhancement pattern over time was classified as follows: An early washout pattern was considered present when the ratio of lesion-to-cortex attenuation in the nephrographic phase was lower than that in the corticomedullary phase. A prolonged enhancement pattern was considered present when the ratio of lesion-to-cortex attenuation in the nephrographic phase was higher than that in the corticomedullary phase.

Statistical analysis

All calculations were performed using Statistical Package for Social Sciences (SPSS) 17.0 software (SPSS Inc, Chicago, USA). The mean enhanced CT attenuation value and the ratio of lesion-to-cortex attenuation of RO and RCCs in all phases were calculated and analyzed with an unpaired t-test. Comparative analyses were obtained by using the Pearson's Chi-square test for the distribution of the ratio-to-lesion attenuation across the two groups of diseases. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of the ratio of lesion-to-cortex attenuation for the RO and RCCs were obtained. P-values less than 0.05 were considered to indicate a statistically significant difference.

RESULTS

The mean diameter of the RO and RCCs was 3.6 cm (1.3–5.9 cm) and 4.3 cm (1.2–9.7 cm), respectively.

Comparison of the CT direct measurements of the attenuation and the degree of contrast enhancement between the RO and RCCs are listed in Table 1 and shown in Figure 1. There was no significant difference in absolute attenuation value between these two types of tumors ($P > 0.05$). In the corticomedullary phase in 13 RO (93%), the enhancement of the lesion was hypodense to the renal cortex; the ratio of lesion-to-cortex attenuationwas less than 1.0 [Figure 2]. Twenty-seven (84%) of the RCCs lesions were hyperdense to the renal cortex; the ratio of lesion-to-cortex attenuation was over 1.0 ($P < 0.05$) [Figure 3]. In the nephrographic phase, the ratio of the lesion/cortex attenuation was higher than that of the corticomedullary phase in most RO (71%, 10/14), showing a prolonged enhancement pattern, and was lower thanthat in most RCCs (97%, 31/32) and showing an early washout pattern ($P < 0.05$).

The ratio of lesion-to-cortex attenuation showed considerable overlap between RO and RCCs in the excretory phase ($P < 0.05$). In the differentiation of RO from RCCs, the sensitivity was 93%, specificity 84%, positive predictive value 72%, negative predictive value 84%, and accuracy 87%, if the ratio of lesion-to-cortex attenuation

Table 1: Comparison of CT direct measurements of the attenuation and the degree of contrast enhancement between RO and RCCs

| Phase	Measurements of the attenuation (HU)			Ratio of lesion-to-cortex attenuation		
	RO	RCCs	P	RO	RCCs	P
Corticomedullary phase	143 ± 33.9	121 ± 37.8	0.057	1.14 ± 0.2	0.73 ± 0.19	0.000
Nephrographic phase	120 ± 27.9	118 ± 29.5	0.086	0.7 ± 0.08	0.72 ± 0.13	0.264
Excretory phase	78.9 ± 11.4	85.6 ± 17.2	0.126	0.5 ± 0.07	0.61 ± 0.10	0.568

CT: Computed tomography; RO: Renal oncocytoma; RCC: Renal clear cell carcinoma; HU: Hounsfield unit.
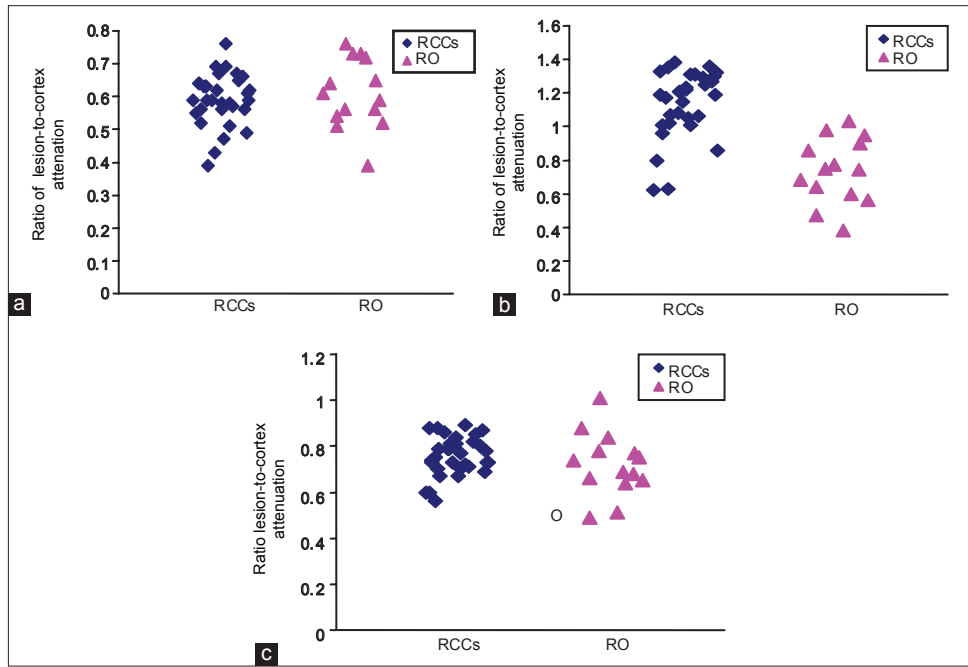
Figure 1: The distribution of the ratio-to-lesion attenuation between RO and RCCs. Scatter plots shows the ratios of lesion-to-cortex attenuation in three phases. (a) In corticomedullary phase, most RCCs have a ratio lower than 1.0, whereas nearly all RO have a ratio higher than 1.0. (b) In nephrographic phase, the ratio of lesion-to-cortex attenuation is higher than in the corticomedullary phase in most RO, showing a prolonged enhancement pattern, whereas, nearly all RCCs show an early washout pattern. (c) In excretory phase, image phase, the ratios of lesion-to-cortex attenuation of RO and RCCs are largely overlapping, lacking clinical significance. RO = Renal oncocytoma, RCC = renal clear cell carcinoma.
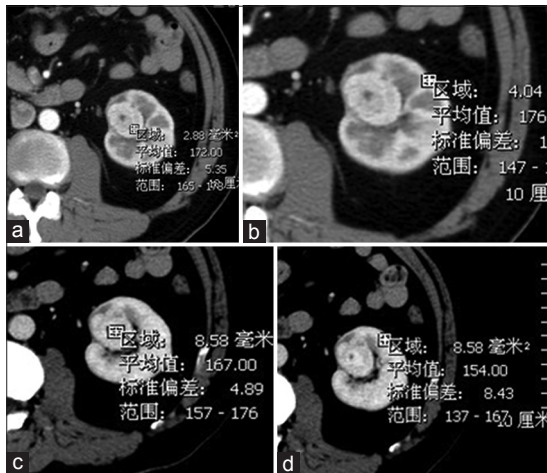
Figure 2: A 53-year-old-man with RO. (a) The attenuation value of the lesion is 172 HU in the corticomedullary phase. (b) The attenuation value of the renal cortex is 176 HU in the corticomedullary phase, giving the ratio of lesion to cortex of 0.98. (c) In the nephrographic phase, the attenuation value of the lesion is 167 HU. (d) In the nephrographic phase the attenuation value of the renal cortex is 154 HU, giving a ratio of lesion-to-cortex of 1.08, showing a prolonged enhancement pattern compared with the corticomedullary phase, which indicates the high likelihood of RO.
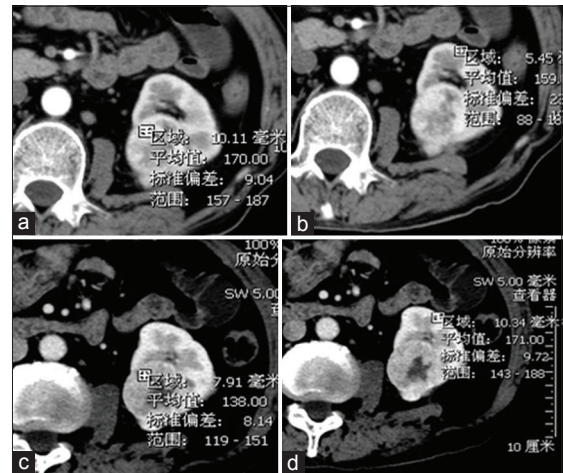
Figure 3: A 63-year-oldman with RCCs. (a) The attenuation value of the lesion is 170 HU in the corticomedullary phase. (b) The attenuation value of the renal cortex is 159 HU in the corticomedullary phase, giving the ratio of lesion to cortex of 1.07, revealing a RCCs. (c) In the nephrographic phase, the attenuation value of the lesion is 138 HU. (d) In the nephrographic phase, the attenuation value of the renal cortex is 171 HU, giving a lesion-to-cortex ratio of 0.81, showing an early washout pattern compared with that in the corticomedullary phase, which indicates the high likelihood of the RCCs.

in the cortex phase was lower than the cutoff value of 1.0. The sensitivity was 71%, specificity 97%, positive predictive value 91%, negative predictive value 91%, and the accuracy for RO was 89%, if the ratio of lesion-to-cortex attenuation was higher in the nephrographic phase than in the corticomedullary phase.

Discussion

RO account for 3%–7% of all renal lesions.[4] They are the most common benign solid renal neoplasm with distinct pathological characteristics. Radiological differentiation of RO from RCCs would be invaluable prior to surgery as small RO could be managed conservatively. Nephron-sparing

surgery can be used for larger tumors and there is no requirement for chemotherapy of radiation therapy after surgery.[5,6]

It has been found[7] that when comparing benign and malignant renal lesions on contrast-enhanced CT, RCCs and RO are greatly enhanced in the parenchymal phase, whereas chromophobe carcinoma and lipid-poor angiomyolipoma are moderately enhanced and papillary tumors are the least enhanced. RO may overlap considerably with RCCs in terms of imaging features and the degree of enhancement. Therefore, the differentiation between RO and RCCs presents the greatest diagnostic challenge. Because there are no imaging characteristics and CT enhancement criteria that distinguish a small RO from a small RCCs, RO remains the most commonly excised benign solid renal mass.

Previous studies tried to describe and differentiate RO according to morphologic criteria. Quinn et al.,[2] suggest that a central, sharply defined, stellate scar is present on CT in 33% of large oncocytomas and strongly suggests the diagnosis. This scar was originally considered as a good predictor of oncocytoma,[3] but the presence of a central stellate scar is relatively uncommon in RO, and other studies[8] have shown that it is not a specific finding. The present study demonstrates that this imaging feature is found only in a small proportion of these tumors. Only 7% (1/14) of the RO had a central stellate scar in our study. In a recently published article,[9] investigators suggest that segmental enhancement inversion at biphasic multidetector CT (MDCT) is helpful in identifying RO. Contrary to this report, McGahan et al.,[10] reported that they found the segmental enhancement inversion pattern to be present in only one of 16 small RO. The reason for this controversial outcome is unclear at this time. No tumors showed distinct segmental enhancement inversion in our study group. Review of available literaturesupports the view that it is not possible to distinguish RO reliably from RCCs on imaging alone.[10,11] A histopathological diagnosis (fine-needle aspiration or core biopsy) remains the reference standard.[12]

Numerous studies[13-16] have shown that the degree of enhancement is the most valuable parameter for differentiation of RCC subtypes. Absolute attenuation measurement is considered to be accurate for differentiating renal lesions, however, a large number of intrinsic and extrinsic factors can affect organ perfusion and the quantity, time, and rate of delivery of contrast material to organs such as the kidneys, influencing the attenuation values, and the types of contrast enhancement of lesions in contrast phases.[17] The intrinsic factors are anatomic and physiologic characteristics that vary from patient to patient and can vary temporally within the same patient. They include, for example, the patient's weight, cardiac function, state of hydration, and renal function. Extrinsic factors are mechanical variables that are dictated by the CT protocol. They include the quantity, rate, and length of injection of contrast material and delay from the injection of contrast material to the beginning of image acquisition. All these factors influence enhancement dynamics of organs or lesions after contrast administration and make attenuation measurements variable.[18] As suggested previously,[13] the measure attenuation of the renal lesions should be normalized by using the measured attenuation of either the renal cortex or the aorta to ensure that attenuation is independent of technical or patient variables. The influence of the extrinsic factors can be excluded when they are equalized for all patients using a standard CT protocol, but it is not possible to control the intrinsic factors under natural conditions. Therefore, in our study we used a ratio rather than an absolute enhancement to attempt to correct for differences in each patient's body habitus and cardiac output.

Different from previous investigations, our methods can be summarized as follows: (1) Since renal tumors are often heterogeneous, we decided to measure the areas of greatest enhancement in the lesion rather than the entire tumor. Measurements obtained with this approach minimize volume averaging effects from areas of cystic or necrotic changes and truly reflect the vascularity of the tumor. (2) Our study used a new method to standardize enhancement measurement in lesions not being influenced by intrinsic factors mentioned above. To our knowledge, this is the first study to focus on the ratio of lesion-to-cortex attenuation of CT enhancement for differentiating RO from RCCs.

Our study showed that all RCCs masses showed contrast that appeared to be better enhanced than RO on all contrast enhanced phases of CT imaging, but there was no significant difference in absolute attenuation measurement values between these two diseases ($P > 0.05$) [Table 1]. Our observation was in accordance with the results of Other investigator,[7,18,19] and absolute attenuation and the quantitative amount of the enhancement were not strong predictors for differentiating benign and malignant renal lesions.

Our study results also showed that the ratio of lesion-to-cortex attenuation in the corticomedullary phase was significantly higher than the cutoff value of 1.0 in most RCCs (27/32, 84%) and lower than 1.0 in most RO (13/14, 93%). Most RCCs showed a significantly higher degree of enhancement than RO in the corticomedullary phase. This could be explained by the higher microvessel density of RCCs vs RO. In a study of small renal parenchymal tumor angiogenesis, Jinzakim et al.,[20] found that the degree of enhancement in the corticomedullary phase was considered to reflect the vascularity of the tumor and correlated with the microvessel density. The mean microvessel density of RCCs (653/mm^2) was significantly higher than that of RO (315/mm^2). Therefore, microvessel density and the degree of enhancement in the corticomedullary phase is different between RO and RCCs. Consequently, it is not surprising that the ratio of lesion-to-cortex attenuation in the corticomedullary phase is more reliable than direct attenuation measurements for differentiation of the two lesions that have similar attenuation.

We found that in the nephrographic phase, the ratio of lesion/cortex attenuation was higher than in the corticomedullary phase in most RO. Ten (71%) of the lesions were hyperdense or isodense to the renal cortex, and showed a prolonged enhancement pattern. This finding seems to be consistent with the results from Millet et al.[21] In that study, the renal lesions with gradual enhancement were more likely to be benign. There has been no sufficient explanation for this phenomenon in the literature. In another study, Roy et al.,[22] assessed the role of contrast-enhanced ultrasound in renal tumors and found that RO showed a prolonged enhancement pattern, similar to our results using CT scans.

The present finding suggests that in the nephrographic phase, the ratio of lesion-to-cortex attenuation is lower than that of in the corticomedullary phase in most RCCs. Thirty-one (97%) of the lesions showed decreased density compared with the surrounding cortex and showed a faster washout pattern. The main reason for an early washout pattern is considered to be the existence of abundant arteriovenous shunting within the RCCs that allows contrast material to easily flow through the lesion resulting in fast washout.

Our study results demonstrate that the ratio of lesion-to-cortex attenuation is more sensitive and accurate for differentiation of RO from RCCs, than are the absolute attenuation values. The method can be applied not only to renal lesions but also to differentiate lesions in other organs after contrast-enhanced CT.

This study has several limitations. First, this study was performed retrospectively and had some selection bias. A prospective study might be needed to support these results. Second, the number of RO patients was relatively small compared with the number of RCCs patients. Third, it might be interesting to compare the results with other correcting attenuation methods.[23] We plan to do this in a future study.

In conclusion, our enhancement correcting method is a simple way to deal with the influence of intrinsic factors on quantitative enhancement patterns in renal lesions. It may be helpful in differentiating RO from RCCs. Further evaluation of this method is ongoing.

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