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ORIGINAL PAPER

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Diffusion weighted imaging in differentiation of the clear cell RCC from the major non-clear cell RCC subtypes

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ABSTRACT

Introduction. Renal cell carcinoma (RCC) is the most common malignant renal tumor in adults accounting for 80-90% of primary malignant adult renal neoplasms. RCC represents a very heterogenous groups of tumors with a number of distinct histological varieties, of which the major 3 subtypes are clear cell RCC (70-80%), papillary RCC (13-20%), and chromophobe RCC (5%). Imaging features are varied from solid and relatively homogenous appearance to markedly heterogenous appearance with cystic changes, hemorrhage and necrosis. The use of diffusion weighted imaging (DWI) for RCC subtyping and also for differentiation of high grade and low grade tumors has been showed to be useful in many studies in the literature.

Aim. In this study, we aimed to determine the comparative contribution of DWI in differentiation of the clear cell RCC from the major non-clear cell RCC subtypes at standard high b-value (1000 s/mm^2) versus low b-value (500 s/mm^2). In addition, we also aimed to assess the diagnostic performance of DWI for differentiating high grade clear cell RCC from low grade clear cell RCC based on Fuhrman grades in our patients.

Material and methods. 62 cases with a prediagnosis of RCC according to MRI findings including DWI sequence with histological verification and subtyping of renal cortical tumor following a total or partial nephrectomy were included in the study.

Results. Among 62 cases, 46 were male and 16 were female, with mean age of 59.5±15.7. Pathological diagnoses of 62 cases were as follows, clear cell RCC, (44) papillary cell RCC (14) and chromophobe cell RCC (4). They were divided into two groups as clear cell RCC group (44 cases) and non-clear cell RCC group (18 cases). There was no statistically significant difference between the mean ADC values of clear cell and non-clear cell groups at b-value of 1000 s/mm^2 ($p>0.05$). However, the mean ADC level for clear cell RCC group at b-value of 500 s/mm^2 were significantly higher than for non-clear cell RCC group ($p<0.05$). When a value of 0.99x10^{-3} mm^2/s was set as cut-off for ADC at b-factor of 500 s/mm^2, differentiation was achieved with a high sensitivity (91%) and specificity (56%). Regarding the diagnostic performance of DWI for differentiating high from low Fuhrman grades clear cell RCCs, there was no statistically significant difference between the ADC values of Grade I-II clear cell RCC cases and Grade III-IV clear cell RCC cases at b-factor of 1000 s/mm^2 ($p>0.05$). However, ADC values for grade III-IV group was statistically significantly lower than ADC values for Grade I-II group at b-factor of 500 s/mm^2 level.

Conclusion. ADC measurements at moderate b-value of 500 s/mm^2 were more sensitive in subtyping and grading of RCC cases. This technique can be used in clinical practice as a fast and additional sequence in abdominal MRI.

Keywords. apparent diffusion coefficient, diffusion weighted imaging, renal cell carcinoma

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Introduction

Renal cell carcinoma (RCC) is the most common malignant renal tumor in adults accounting for 80-90% of primary malignant adult renal neoplasms.[1,2] The age of presentation is typically 50-70 years and there is a moderate male predilection of 2:1.[3,4] Macroscopic hematuria, flank pain and palpable flank mass are typical clinical findings.[5] However, due to the widespread use of imaging, incidental detection of asymptomatic lesions have been increased. RCC represents a very heterogenous groups of tumors with a number of distinct histological varieties, of which the major 3 subtypes are clear cell RCC (70-80%), papillary RCC (13-20%), and chromophobe RCC (5%).[1,6] Imaging features are varied from solid and relatively homogenous appearance to markedly heterogenous appearance with cystic changes, hemorrhage and necrosis. The main forms of RCC subtypes can often be non-invasively differentiated by imaging characteristics on dynamic contrast enhanced MRI. While clear cell RCC is typically heterogenous secondary to necrosis, cystic change or hemorrhage, and has high signal intensity on T2w images atributable to clear cytoplasms of large uniform cells, most papillary RCCs show low signal intensity on T2w MRI. Chromophobe RCCs may have a homogeneous solid appearance even when large. On dynamic contrast-enhanced images, while clear cell RCCs are highly vascular masses, papillary RCCs are hypovascular and chromophobe RCCs may exhibit a central stellate scar and spoke-wheel enhancement.[6] In addition to that, the use of diffusion weighted imaging (DWI) for RCC subtyping and also for differentiation of high grade and low grade tumors has been showed to be useful in many studies in the literature.

Aim

In this study, we aimed to determine the comparative contribution of DWI in differentiation of the clear cell RCC from the major non-clear cell RCC subtypes which are papillary RCC and chromophobe RCC at standard high b-value (1000 s/mm^2) versus low b-value (500 s/mm^2). In addition, we also aimed to assess the diagnostic performance of DWI for differentiating high grade clear cell RCC from low grade clear cell RCC based on Fuhrman grades in our patients.

Material and methods

Patients

62 cases with a prediagnosis of RCC according to MRI findings including DWI sequence with histological verification and subtyping of renal cortical tumor following a total or partial nephrectomy between February 2011 and November 2012 were included in the study. The study was approved by the institutional ethics committee and written informed consent was taken from all patients prior to be included in the study.

Sample cases are presented below (Figure 1-3).

MRI technique

Conventional MRI and DWI examinations were performed with Siemens Avanto 1.5 Tesla MR scanner (Siemens Erlangen, Germany). DWI echo-planar images (TR: 4000, TE: 76, FOV of 400 mm, matrix: 156 x 192, NEX: 3, sectional thickness: 5 mm with a 1 mm intersection gap) were obtained in the axial plane before the contrast administration. DWI were obtained by diffusion gradients between, 500 and 1000 s/mm^2 b-values. An ADC map was automatically constructed in the workstation. Mean ADC values of all lesions were automatically measured by using the ADC maps according to the formula ADC = (lnS0 – lnS)/b (signal intensity values are measured as S0 at b = 0 s/mm^2, b=500 s/mm^2, at b = 1000 s/mm^2).

ADC measurement

Measurements were performed by placing a region of interest (ROI) of 1 cm diameter on the solid parts that enhances in postcontrast images and shines in DWI images. The ROI did not include normal parenchymal tissue, or haemorrhagic or necrotic areas The lowest one of three consecutive measurements were included in the analyses.

Statistical analysis

Differences of ADCs of lesions and normal parenchyma were assessed with paired samples t-test. Differentiability of clear-cell RCC from non-clear cell RCC by ADC values was evaluated by ROC curve analysis. Moreover, a mean of 3 different ADC values from normal renal parenchyma were taken for comparing with the ADC values of lesions. A p value < 0.05 was considered as statistically significant.

Results

62 cases, of whom 46 were male and 16 were female, with an age range between 26 to 86 years (mean 59.5±15.7 years) were recruited for the study. Pathological diagnoses of 62 cases were as follows, 44 cases of clear cell RCC, 14 cases of papillary cell RCC and 4 cases of chromophobe cell RCC. They were divided into two groups as clear cell RCC group (44 cases) and non-clear cell RCC group (18 cases). There was no statistically significant difference between the mean ADC values of clear cell and non-clear cell groups at b-value of 1000 s/mm^2 ($p>0.05$) (Table 1).

However, the mean ADC level for clear cell RCC group at b-value of 500 s/mm^2 were significantly higher than for non-clear cell RCC group ($p<0.05$). When a

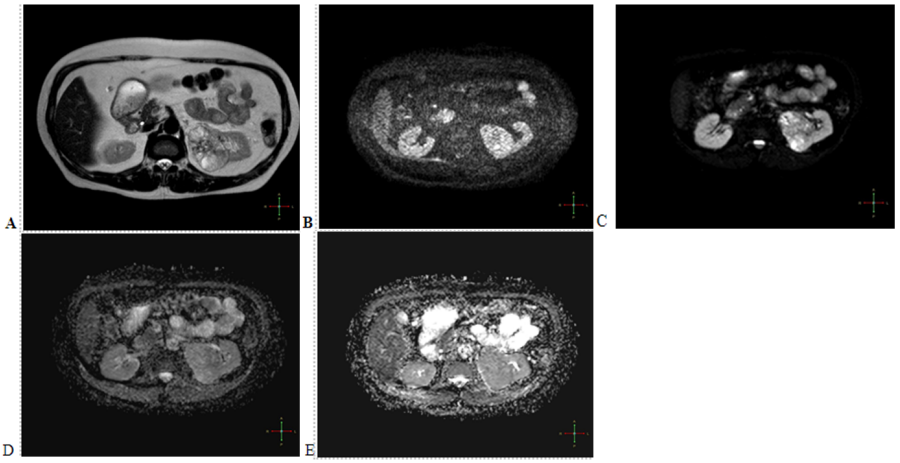

Fig. 1. Case 1: Clear cell RCC in a 56 years-old male patient: (A) heterogeneous hyperintense lesion with cystic necrosis fields in T2WI of left kidney; (B-C) restriction in diffusion series; (D-E) b-factor 1000 s/mm^2 ADC: 1.68x10^{-3} mm^2/s, b-factor 500 s/mm^2 ADC: 2.05x10^{-3} mm^2/s.

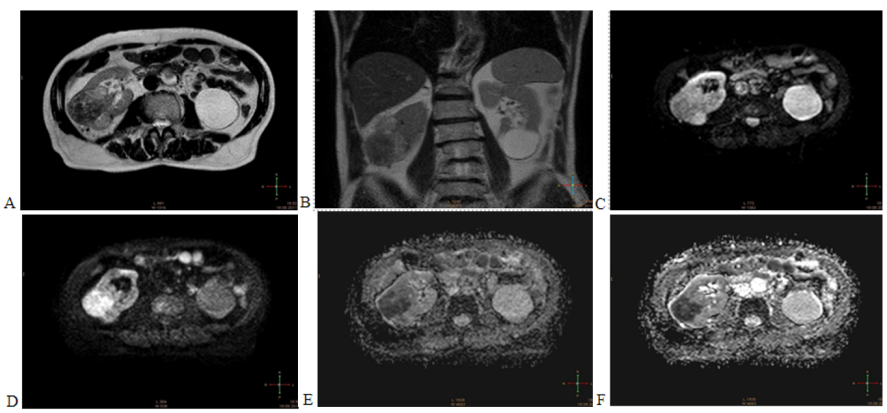

Fig. 2. Case 2: Papillary cell RCC in right kidney, and simple cyst in left kidney of an 80 years-old male patient. (A-B) hypointense heterogeneous lesion with exophytic extent in right kidney, and hyperintense cystic lesion with exophytic extent from left kidney in T2WI; (C-D) restriction in solid lesion at right kidney in diffusion series (T2 shining effect on simple cyst in left kidney at b-factor of 1000 s/mm^2); (E-F) b-factor 1000 s/mm^2 ADC: 0.61x10^{-3} mm^2/s, b-factor 500 s/mm^2 ADC: 0.93x10^{-3} mm^2/s for lesion in right kidney, and b-factor 1000 s/mm^2 ADC: 2.53x10^{-3} mm^2/s, b-factor 500 s/mm^2 ADC: 2.79x10^{-3} mm^2/s for cyst in left kidney

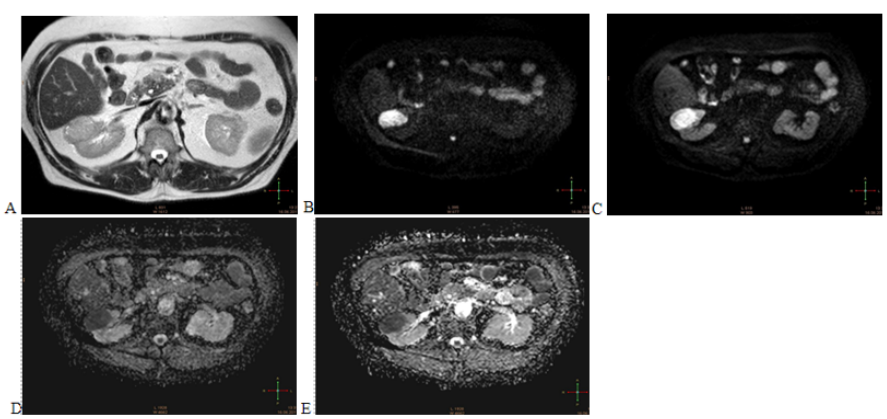

Fig. 3. Case 3: chromophob cell RCC in right kidney of a 63 years-old male patient. (A) heterogeneous hypointense lesion in T2WI of right kidney; (B-C) overt restriction in lesion in diffusion series; (D) b-factor 1000 s/mm^2 ADC: 0.68x10^{-3} mm^2/s, (E) b-factor 500 s/mm^2 ADC: 0.94x10^{-3} mm^2/s.

Table 1. RCC subtypes

	Clear cell (n=44)		Non-clear cell (n=18)		p
	Mean	SD	Mean	SD	
ADC at b-factor of 1000 s/mm^2	1.292	0.371	1.017	0.388	0.117
ADC at b-factor of 500 s/mm^2	1.536	0.421	1.129	0.389	**0.030***
NP of ADC at b-factor of 1000 s/mm^2	1.893	0.202	2.000	0.080	**0.017***
NP of ADC at b-factor of 500 s/mm^2	2.214	0.278	2.276	0.195	0.727

**: p<0.05*

Difference between ADC values of clear cell and non-clear cell groups at b-factor of 1000 s/mm^2 was not statistically significant (p>0.05).

ADC values of clear cell group at b-factor of 500 s/mm^2 were significantly higher than the non-clear cell group (p<0.05).

Table 2. Fuhrman grades in clear-cell subtype

	I-II clear cell (n=24)		III-IV clear cell (n=20)		p
	Mean	SD	Mean	SD	
ADC at b-factor of 1000 s/mm^2	1.413	0.363	1.147	0.343	0.075
ADC at b-factor of 500 s/mm^2	1.738	0.383	1.293	0.338	**0.018***
NP of ADC at b-factor of 1000 s/mm^2	1.918	0.236	1.864	0.161	0.643
NP of ADC at b-factor of 500 s/mm^2	2.241	0.254	2.181	0.314	0.792

**: p<0.05*

In cases with a clear-cell pathology; difference between ADC values of grade I-II clear cell and grade III-IV clear cell groups at b-factor of 1000 s/mm^2 was not statistically significant (p>0.05).

In cases with a clear-cell pathology; ADC values of grade I-II clear cell group at b-factor of 500 s/mm^2 were significantly higher than the grade III-IV cell group (p<0.05).

value of 0.99x10^{-3} mm^2/s was set as cut-off for ADC at b-factor of 500 s/mm^2, differentiation was achieved with a high sensitivity (91%) and specificity (56%). Regarding the diagnostic performance of DWI for differentiating high from low Fuhrman grades clear cell RCCs, there was no statistically significant difference between the ADC values of Grade I-II clear cell RCC cases and Grade III-IV clear cell RCC cases at b-factor of 1000 s/mm^2 (p>0.05). However, ADC values for grade III-IV group was statistically significantly lower than ADC values for Grade I-II group at b-factor of 500 s/mm^2 level (Table 2).

Discussion

RCC which is the most frequent malignant renal tumor in adults arises from tubular epithelium and represents a number of distinct histological variants associated with different metastatic potential, prognosis and management. Many studies showed that as compared to clear cell RCC, chromophobe and papillary RCC have better prognoses and may be treated with kidney sparing approaches rather than radical nephrectomy.[7] Therefore, preoperative discrimination of clear cell RCC from non-clear cell subtypes is very important. DWI is a method that provides characterization of biological tissues based on irregular diffusion motion of water molecules, which can be integrated easily into a conventional MRI providing more detailed information at the cellular. The diffusion of free water in tissues is restricted basically by cell membranes and therefore, by the increased cellularity of the tissue, as in tumoral processes. [8] Diffusion weighted images are obtained from T2w images with the addition of diffusion weighting gradient, that is the b-value which shows the extent to which the sequence is sensitive to the diffusion.[9] ADC is the mathematical expression of diffusion as a result of marking the signal loss on the map, which occurs after applying diffusion gradient. The ADC value of free water molecules at 37°C is reported to be 3.0×10^{-3} mm^2/s. This value is taken as the reference point, and it is the value at which the diffusion is maximum. When there is restriction to diffusion, the ADC value decreases.[8] When the b value is low, the diffusion weight of the sequence decreases and it is affected by T2 time and perfusion. The perfusion of malignant tumours is markedly higher than that of the benign ones, and so at low b values the ADC of malignant lesions are measured as higher than it is artifactually from capillary perfusion effect.[10] It has been postulated that the b-value gradients between 0 and 200 s/mm^2 primarily measure perfusion, whereas gradient strengths greater than 200 s/mm^2 primarily measure diffusion.[11,12] In a study performed for discriminating malignant from benign vertebral compression fracturesMore pronounced difference in the mean ADC value in the group of low b-value (<500) than in the group of b-value (≥500) was reported. The authors concluded that, low b-value (<500) is a more valuable parameter than standard b-value (≥500) to show mean

ADC differences.[13] Wang et al. tried to determine the subtypes of 85 RCCs observed in 83 patients (49 clear cell tumors, 22 papillary tumors and 14 chromophobe tumors) at 3T MRI at b-value of 500 and 800 s/mm^2. They found that papillary RCCs (1.1 x 10^{-3} mm^2/s) and chromophobe RCCs (1.3 x 10^{-3} mm^2/s) had significantly lower mean ADC values than clear cell RCCs (1.8 x 10^{-3} mm^2/s).No significant differences were found between papillary and chromophobe RCCs. However, at b-value of 800 s/mm^2, they could be able to differentiate all subtypes, and concluded that this b-value is more sensitive.[14] On the other hand, in a meta analysis conducted to determine the comparative diagnostic performance of standard b-value (800–1000 s/mm^2) versus low b-value (400–500 s/mm^2) DW-MRI in the detection of RCC. The study concluded that the standard b-value DW-MRI showed a superior specificity but an approximately equivalent sensitivity to low b-value DW-MRI in detecting RCC. However, low b-value DW-MRI displayed an overall superior diagnostic accuracy over standard b-value DW-MRI.[15] Because, when the b value increases the spatial resolution decreases significantly, and when the b value decreases then the perfusion effect appears, in our study the b value was taken as 500 and 1000 s/mm^2. Similar to this study, significant difference in terms of mean ADC value between clear cell and non-clear cell groups was not observed when b-value was chosen as 1000 s/mm^2, but ADC level of non-clear cell group was significantly lower at b-value of 500 s/mm^2 in our study. Although it was reported that for the b value equal to or higher than 600 s/mm^2, the effect of perfusion is minimal and can be ignored, the appearance of significant difference between two groups when the b-value was decreased to 500 s/mm^2, in our study can be explained to some extent by explicitness of perfusion effect.[16] In addition, the papillary cell RCC group had the lowest ADC values in our patients, as in the study of Wang et al. and Taouli et al. [14,17]

In a study conducted to assess the value of DWI in differentiating the various subgroups of renal masses, it was found that ADC values higher than 2.12x10^{-3} mm^2/s were only observed in low-grade cancers, and ADC values lower than 1.50x10^{-3} mm^2/s were only observed in high-grade cancers.[17] In various studies, it was also found that high grade clear cell RCCs have significantly lower mean ADC values than low grade clear cell RCCs.[10,14,18] In our study, we also tried to discriminate the preoperative histological grades of clear cell RCC cases. These tumors were graded as Fuhrman grade I-II (low-grade) and Fuhrman grade III-IV (high-grade) according to postoperative pathological findings. There was also no significant difference between groups at b-value of 1000 s/mm^2, but there was a statistically significant difference when b-value was selected as 500 s/mm^2. ADC values at b-value of 500 s/mm^2 were lower in Fuhrman grade III-IV clear cell RCC cases, when compared with Fuhrman grade I-II group. This finding can be explained by explicit limiting in diffusion due to increased cellularity.

The main limitations of our study includes the limited number of patients and the validity of the cut-off ADC value only for the imaging protocols performed with the b values defined for our MRI device.

Conclusion

ADC measurements at moderate b-value of 500 s/mm^2 were more sensitive in subtyping and grading of RCC cases. This technique can be used in clinical practice as a fast and additional sequence in abdominal MRI. Completion period is as short as 17 seconds, and it can provide both qualitative and quantitative findings for diagnosis.

References

1. Ng CS, Wood CG, Silverman PM, et al. Renal cell carcinoma: diagnosis, staging, and surveillance. *AJR Am J Roentgenol.* 2008;191(4):1220-1232.
2. Sheth S, Scatarige JC, Horton KM, et al. Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector ct and three-dimensional CT. *Radiographics.* 2001;21(1):237-254.
3. Federle MP, Jeffrey RB, Woodward PJ, et al. *Diagnostic Imaging: Abdomen.* Amirsys®, Lippincott Williams & Wilkins; 2009. ISBN:1931884714.
4. McPhee SJ, Papadakis MA. *Current Medical Diagnosis and Treatment 2009.* McGraw-Hill Professional; 2008. ISBN:0071591249.
5. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst.* 2006;98:1331-1334.
6. Oliva MR, Glickman JN, Zou KH, et al. Renal cell carcinoma: t1 and t2 signal intensity characteristics of papillary and clear cell types correlated with pathology. *AJR Am J Roentgenol.* 2009;192(6):1524-1530.
7. Hötker A, Mazaheri Y, Wibmer A, et al. Use of DWI in the Differentiation of Renal Cortical Tumors. *American Journal of Roentgenology.* 2016;1:100-105.
8. Woodhams R, Ramadan S, Stanwell P, et al. Diffusion-weighted imaging of the breast: principles and clinical applications. *Radiographics.* 2011.31:1059-1084.
9. Li Y, Chen Z, Wang J. Differential diagnosis between malignant and benign hepatic tumors using apparent diffusion coefficient on 1.5-T MR imaging: a meta analysis. *Eur J Radiol.* 2012;81:484-490.
10. Rosenkrantz AB, Niver BE, Fitzgerald EF, Babb JS, Chandarana H, Melamed J. Utility of the apparent diffusion coefficient for distinguishing clear cell renal cell carcinoma of low and high nuclear grade. *AJR Am J Roentgenol.* 2010;195:W344-351.

11. Iima M, Le Bihan D. Clinical intravoxel incoherent motion and diffusion MR imaging: past, present, and future. *Radiology.* 2016;278:13-32.
12. Kim HS, Suh CH, Kim N, Choi CG, Kim SJ. Histogram analysis of intravoxel incoherent motion for differentiating recurrent tumor from treatment effect in patients with glioblastoma: initial clinical experience. *AJNR Am J Neuroradiol.* 2014;35:490-497.
13. Luo Z, Litao L, Gu S, et al. Standard-b-value vs low--b-value DWI for differentiation of benign and malignant vertebral fractures: a meta-analysis. *Br J Radiol.* 2016;89(1058):20150384.
14. Wang H, Cheng L, Zhang X, et al. Renal Cell Carcinoma: Diffusion-weighted MR Imaging for Subtype Differentiation at 3.0 T. *Radiology*. 2010;257:135-143.
15. Tang Y, Zhou Y, Du W, et al. Standard b-value versus low b-value diffusion-weighted MRI in renal cell carcinoma: a systematic review and meta-analysis. *BMC Cancer.* 2014;14:843.
16. Baron P, Dorrius MD, Kappert P, et al. Diffusion-weighted imaging of normal fibroglandular breast tissue: influence of microperfusion and fat suppression technique on the apparent diffusion coefficient. *NMR Biomed.* 2010.23:399-405.
17. Taouli B, Thakur RK, Manelli L, et al. Renal lesions: characterization with diffusion-weighted imaging versus contrast-enhanced MR imaging. *Radiology.* 2009;251:398-407.
18. Goyal A, Sharma R, Bhalla AS, Gamanagatti S, Seth A, Iyer VK, Das P. Diffusion-weighted MRI in renal cell carcinoma: a surrogate marker for predicting nuclear grade and histological subtype. *Acta Radiol.* 2012;53:349-358.