VALUE OF DIFFUSION – WEIGHTED AND CONTRAST ENHANCED MAGNETIC RESONANCE IMAGING IN DIFFERENTIATION OF RENAL MASSES

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ABSTRACT

AIM: to evaluate the role of contrast enhanced magnetic resonance imaging and the usefulness of diffusion weighted magnetic resonance imaging in differentiating benign from malignant renal masses and to assess the diffusion characteristics as well as ADC values of different renal masses.

MATERIALS AND METHODS: Fifty patients with renal masses and normal contra-lateral kidneys (used as control) were enrolled in the study. DWI was performed with *b* values of 0 and 1000 s/ mm^2. Results of the histopathological evaluation were compared with the DWI and CE-MRI results. Apparent diffusion coefficient (ADC) values were calculated for each *b* value.

RESULTS: The mean ADC values of normal renal parenchyma with *b*= 0 and 1000 s/ mm^2 values were (3.7 ± 0.27) x 10^{-3} and (2.8 ± 0.21) x 10^{-3} mm^2/s, respectively. The mean ADC values of benign cystic renal lesions (n=18) with *b*= 0 and 1000 s/ mm^2 values were (3.73 ± 0.44) x 10^{-3} and (3.09 ± 0.46) x 10^{-3} mm^2/s, respectively. The mean ADC values of benign solid renal lesions (n=5) with *b*= 0 and 1000 s/ mm^2 values were (1.53 ± 0.44) x 10^{-3} and (1.797 ± 0.46) x 10^{-3} mm^2/s, respectively. The mean ADC values of malignant cystic renal lesions (n=4) with *b*= 0 and 1000 values were (3.09 ± 0.29) x 10^{-3} and (2.73 ± 0.10) x 10^{-3} mm^2/s, respectively. The mean ADC values of malignant solid renal lesions (n=23) with *b*= 0 and 1000 values were (1.63 ± 0.29) x 10^{-3} and (1.16 ± 0.25) x 10^{-3} mm^2/s, respectively. The sensitivity, and specificity of combined CE-MRI and DW imaging were 95.6 % and 96.3% respectively. We can differentiate malignant renal lesions from benign renal lesions using CE-MR imaging combined with DWI.

CONCLUSIONS: Combined CE-MRI and DWI with quantitative ADC measurements can be useful in differentiating benign from malignant renal lesions. Using high *b* values (b=1000 s / mm^2) had the best specificity and sensitivity.

INTRODUCTION

Accurate assessment of renal masses is important for establishing whether tumors require surgical intervention or not[1&2]. CT and MRI are the primary investigative tools for diagnosing, characterizing, and staging cystic or solid renal mass discovered incidentally by sonography. In many cases, the imaging tests still cannot easily differentiate benign from malignant lesions. Studies have shown that 16–33% of nephrectomies are performed on benign lesions [3-5]. With CE-MRI, the composition of renal lesions can be suggested and the differential diagnosis of the disease can be narrowed down[1].However, in view of recently reported concerns regarding the development of nephrogenic systemic fibrosis in patients with renal insufficiency who undergo CE-MRI[6-9]and given the risk of contrast material–induced nephropathy with contrast enhanced CT [10,11], there is increasing interest in assessing non enhanced imaging modalities that might be useful for characterizing renal lesions. DWI is an MRI technique used to show molecular diffusion, which is the Brownian motion of the spins in biological tissues. The ADC, is a quantitative parameter calculated from the DWI, combines the effects of capillary perfusion and water diffusion in the extracellular extravascular space ([12,13]. The application of DWI in the abdomen has been limited due to its susceptibility to respiratory motion, cardiac movement and bowel peristalsis that affect the image quality. Recently ultra-fast echo-planar breath-hold imaging (EPI) technique has been developed, and DWI of the abdomen has become possible. Acquisition time of EPI sequences is very fast (19sec); this minimizes the effects of gross physiologic motion [14]. Most tumors show restricted diffusion because of the higher cellularity of solid tumors and their increase in cell membranes per unit volume, resulting in restriction of water movement and corresponding high signal intensity on DWI [15]. The ADC value has been reported to be valuable for quantitatively distinguishing malignant from benign lesions [16,17]. When applying a high *b* value, the ADC value approximates the true diffusion. Low b values are influenced by both perfusion and diffusion [18]. While MRI is a useful modality as an investigative tool for diagnosing, characterizing and staging renal masses, DWI contributes additional value by promising differentiation benign from malignant renal tumors, even histologically subtyping of renal cell cancer [2].

MATERIALS AND METHODS

Patients

This study was performed in the period between October 2008 and April 2012 in Zagazig university hospitals and was conducted on fifty patients suffering from renal masses previously diagnosed with ultrasound or computed tomography , referred to the radiology , urology and oncology department .These patients included (26) females and (24) males , their age ranged from 21 months to 83 years old .

MRI STUDY TECHNIQUE

MRI examinations were performed using a 1.5 T whole-body superconducting MRI machine (Acheiva, Philips medical system). A body phased array coil was used for all images. The standard imaging protocol consisted of unenhanced T1- and T2-weighted images. Post contrast T1- weighted images was performed at three times (at corticomedullary, nephrographic, and excretory phases) after dynamic injection of 0.1-0.2 mmol of gadopentetate dimeglumine per kilogram of body weight. DWI axial single-shot spin echo, echo-planar imaging (EPI) were obtained before contrast medium administration using *b* values of 0 and 1000 s / mm^2 using the following parameters: TR 8000 ms , TE 58 ms and frequency 128. ADC maps were calculated automatically with the MRI system and ADC values were expressed in square millimeters per second. ADCs were measured from each lesion and the value was recorded for each *b* value. Necrotic portions were excluded from the ROIs. Circular ROIs were placed in the normal renal parenchyma for the measurement of ADC values. ADC values of the normal kidney parenchyma in different *b* values were measured and compared with ADC values of the renal lesions.

HISTOPATHOLOGICAL CORRELATION

The final diagnosis were obtained from the pathological results of the surgical specimen in patients with operable masses and follow up of the inoperable masses. Correlation of the findings obtained using conventional, CE- MRI and DWI , including the image with *b* values of 0 and1000 s / mm^2 with the results of the histopathological findings was done for each patient.

STATISTICAL ANALYSIS

Sensitivity and specificity for differentiating benign renal masses from malignant masses using DWI, including the image with *b* values of 0 and 1000 s / mm^2, were calculated. Mean ADC values of the contra-lateral healthy kidney were compared with the mean ADC values of the focal kidney lesions using a non-paired Student's *t* test. Analysis of variance (ANOVA) of mean ADC values of the different lesions was performed. Finally the results of MRI study were compared with the histopathological results of excised renal lesions, malignant or benign using a non-paired Student's *t* test . A value of $p<0.05$ was considered statistically significant for all tests.

RESULTS

Fifty renal masses were included in this study. They were (18) renal cell carcinoma (clear cell type RCC; No.= 12; chromophobe type RCC; No.=1; and papillary type RCC(solid); No.=1; and cystic RCC No.= 4; all are histologically proven); angiomyolipoma (AML; No.=3); adenoma; No.=1; peri-renal lymphoma (No.= 1; histologically proven); leukemia; No.=2 ; fibrosarcoma; No.=1 ; metastatic; No.=2;Wilm's tumour; No.= 3; simple cyst (category I; No.=5; autosomal dominant polycystic kidney disease; No.= 2; multicystic dysplastic kidney; No.=1 ;renal hematoma; No.=2; dromedary hump;No.=1; and renal abscesses No.=7. Mean diameter was 40 mm (range 20-100 mm).

Analysis of the ADCs of the renal masses revealed that the mean ADCs for malignant renal masses were significantly lower than those for benign renal masses at DW imaging performed with b values of 0 and 1000 sec/mm^2. For example, at b1000 sec/mm^2, the mean ADC was 1.35×10^{-3} mm2/sec ± 0.46 for malignant solid masses versus 2.05×10^{-3} mm^2/sec ± 0.25 for benign solid masses (P=0 .01) as shown in table (4).

Renal tumors had significantly lower ADCs compared with benign cysts (Bosniak category I and II lesions) that had the highest ADCs ; complex cystic lesions (Bosniak category III and IV lesions) had the second highest ADCs while AMLs had the lowest mean ADC.

This study results demonstrate that renal lesions with different tissue contents may have different diffusion characteristics. Solid tumor tissue has lower ADCs compared with necrotic or cystic tumor tissue, in which the ADCs are lower than those in benign cysts.

In this study there was significant difference between the ADCs of RCCs (1.95 x10-3 and 1.65 x 10-3 mm2/s at b 0 and b1000 s/mm2 respectively) and the ADCs of normal renal parenchyma (3.14 x10-3 and 2.41 x 10-3 mm2/s at b 0 and b1000 s/mm2 respectively) , simple cyst (3.65 x10-3 and 3.09 x 10-3 mm2/s at b 0 and b1000 s/mm2 respectively) and complex cysts (3.2 x10-3 and 2.37 x 10-3 mm2/s at b 0 and b1000 s/mm2 respectively).

In this study ,the mean ADC value of clear type RCC was (2.03 ± 0.10 &1.74 ± 0.6 x10-3 mm2/s) , chromophobe RCC (2.07 ± 0.17&1.80 ± 0.20 x10-3 mm2/s), papillary RCC (1.74 ± 0.7&1.41 ± 0.3 x10-3 mm2/s) and cystic RCC (3.01 ± 0.21&2.74 ± 0.10 x10-3 mm2/s) at (b0 & b1000 s/ mm2 respectively). Ther is significant difference among the ADC values of carcinomas and normal parenchyma, however there is no significant difference in the mean ADC value of the individual histological variants of renal carcinoma as shown in table(1).

All renal lesions and mean ADC values of benign (n =23) and malignant (n=27) renal masses are listed in tables.

Table 1: Mean (ADC) values of solid ma lignant renal masses

Final diagnosis	diffusion weighted images	ADC map	Mean ADC value b0 s/mm^2 (x10^{-3} mm^2/s	Mean ADC value b1000 s/mm^2 (x 10^{-3}mm^2/s)
Renal cell carcinoma				
clear cell RCC	Bright	Low	2.03 ± 0.10	1.74 ± 0.6
papillary RCC	Bright	Low	1.74 ± 0.7	1.41 ± 0.3
Chromophobe RCC	Bright	Low	2.07 ± 0.17	1.80 ± 0.20
Wilm's tumour	Bright	Low	2.74 ± 0.5	1.66 ± 0.5
FibroSarcoma	Bright	Low	2.37 ± 0.28	1.71± 0.3
Renal secondaries				
-lymphoma				
-leukemia				
-direct metastases	Bright	Low	1.18 ± 0.3	0.92 ± 0.71
	Bright	Low	1.87±0.20	1.26 ± 0.96
	Bright	Low	2.24	1.90

Table 2: Mean (ADC) values of solid benign renal masses

Final diagnosis	Angiomyolipoma	Dromedary hump	Metanephric adenoma
DWI	Bright	Isointense	Bright
ADC map	Low	Isointense	Low
Mean ADC value b0 s/ mm^2 (×10^{-3}mm^2/s)	1.65 ± 0.60	3.05 ± 0.5	2.80 ± 0.8
Mean ADC value b1000 s/ mm^2 (×10^{-3}mm^2/s)	0.89 ± 0.06	2.55 ± 0.06	2.13 ± 0.7

Table 3: Mean (ADC) values of cystic renal masses

	Category I	Category II&IIf	Category III	Category IV
DWI	Low	Intermediate	Low center&bright septae	Bright
ADC map	bright	Intermediate	Bright center& low septae	Low
Mean ADC value b0 s/mm^2(×10^{-3}mm^2/s)	3.65 ± 0.09	3.2 ± 0.22	3.20 ± 0.54	2.74 ± 0.10
Mean ADC value b1000 s/mm^2 (×10^{-3}mm^2/s)	3.09 ± 0.14	2.37 ± 0.37	2.80 ± 0.29	3.01 ± 0.21

Among the studied cystic renal masses, there was a case of multicystic dysplastic kidney that displayed low signal intensity on DWI at b1000s/mm^2, bright SI on ADC map, mean ADC value equal (3.18 ± 0.49 &2.84 ± 0.10 x10^{-3} mm^2/s) at b0 & b1000 s/mm^2.

Also two cases of AD polycystic kidney disease were examined that harbors multiple variable sized cysts some of which are complicated (displayed high SI on T1WIs & bright SI on DWI at b1000 s/mm^2 .Mean ADC value equal (3.11 ± 0.49 & 2.21 ± 0.10 x10^{-3} mm^2/s) at *b*0 & *b*1000 s/mm^2 .

Two cases of perinephric hematoma following ESWL were examined displayed mixed SI on all examined pulse sequences. Mean ADC value equal (2.84 & 1.63 ± 0.60 x10^{-3} mm^2/s) at b0 & b1000 s/mm^2 .

Six cases of renal abscesses were included in this study that all displayed bright SI on DWI and low SI on ADC map. mean ADC value equal (1.58 ± 0.78 & 0.45 ± 0.14 x10^{-3} mm^2/s) at b0 & b1000 s/mm^2 .

Table 4: Mean (ADC) values of solid benign and malignant renal masses

Lesions	**ADC values (× 10^{-3} mm^2/s)**	
	B = 0 s/mm^2	**b = 1000 s/mm^2**
Benign lesions	2.44 ± 0.44	2.05 ± 0.46
Malignant lesions	2.37 ± 0.28	1.35 ± 0.25
***p*-Value**	**0.03****	**0.01****

Table 5: Mean (ADC) values of cystic benign and malignant renal masses

Cystic masses	**ADC values (× 10^{-3} mm^2/s)**	
	b = 0 s/mm^2	**b = 1000 s/mm^2**
Benign cystic	3.2 ± 0.22	2.43 ± 0.23
Malignant cystic	2.47 ± 0.35	2.07 ± 0.26
***P* = value**	0.26	0.34

Table (6): Threshold apparent diffusion coefficient (ADC) values for differentiating malignant renal lesions from benign renal lesions

Pair wise comparison	***b*-value s / mm^2**	**ADC cut-off value**	**Sensitivity %**	**Specificity %**	***p*-value**
Malignant solid lesions versus benign lesions	0	≤2.2	**85.2**	**85.2**	0.05*
	1000	≤1.9	**79.4**	**69.6**	**0.01****

It is found that the apparent diffusion coefficient [ADC] cutoff value was less than or equal to (2.2 and 1.53 × 10^{-3} mm^2/sec for *b* values of 0 and 1000 sec/mm^2) with Sensitivity equal to 56.5% and specificity equal to 80%(p value=0.01) for malignant solid masses.

Table (7): Correlation between imaging diagnosis and histopathological diagnosis of the examined cases

Nature of the lesion	Imaging results	Histopathological and follow up results
Benign	22	23
Malignant	28	27

The sensitivity is equal to 95.6 % and specificity is equal to 96.3%.The only mis-diagnosed case as a malignant cystic neoplasm and proved to be benign was a multilocular cystic nephroma that appeared as a well defined multilocular cystic lesion with multiple septa and small peripherally located soft tissue component that significantly enhanced on
post Gd-DTPA series.

DISCUSSION

Renal cell carcinoma represent 85% of all renal tumours. Differentiation between renal cell carcinomas and other renal masses as angiomyolipomas, oncocytomas, and complex cysts is not always easy. ADC values have been reported to be related to the cellular density of a tumour, and a reduced ADC value has been reported for most malignant tumors [18,19].

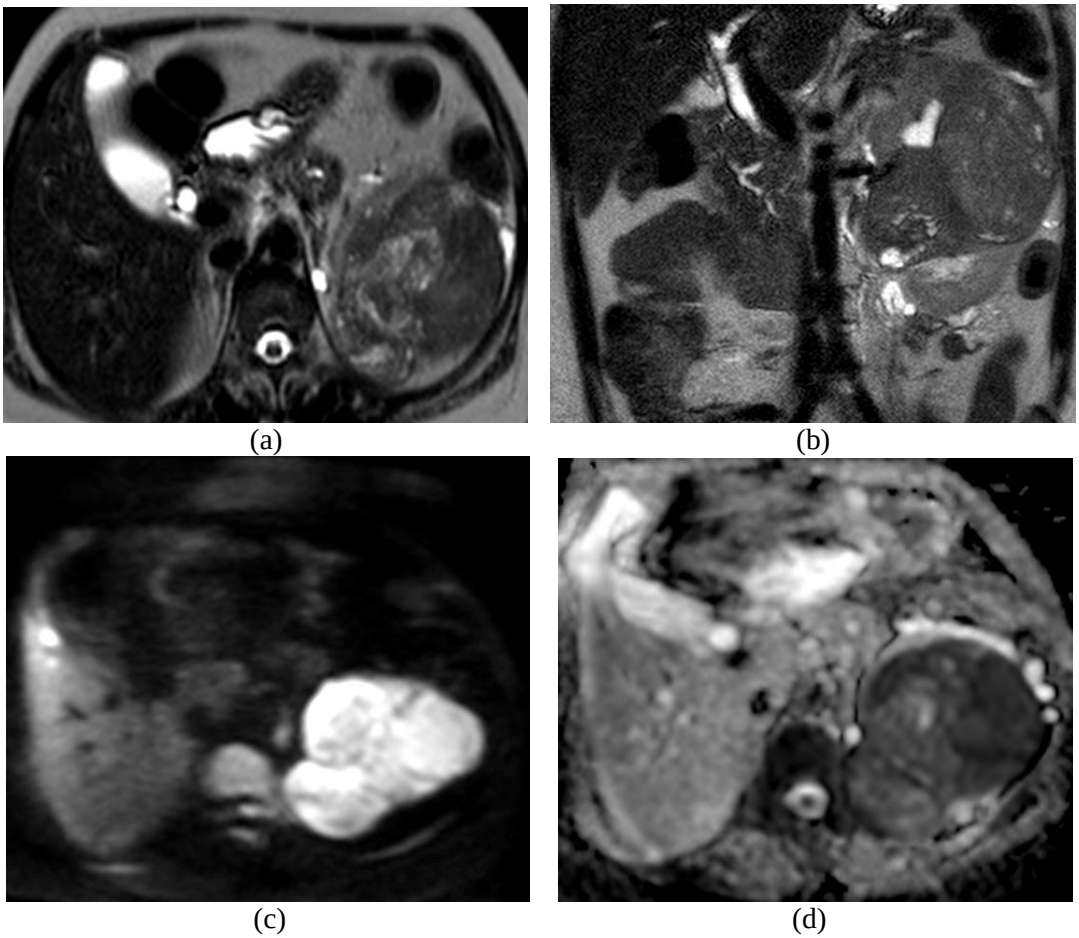


Fig 1: Left papillary type RCC. (A&b) Axial and coronal T2WI shows low signal intensity mass with hyperintense small cystic areas at the upper pole of Lt. kidney extending to the renal sinus . It displays high signals at DWI (c) and low signals at ADC map (d).

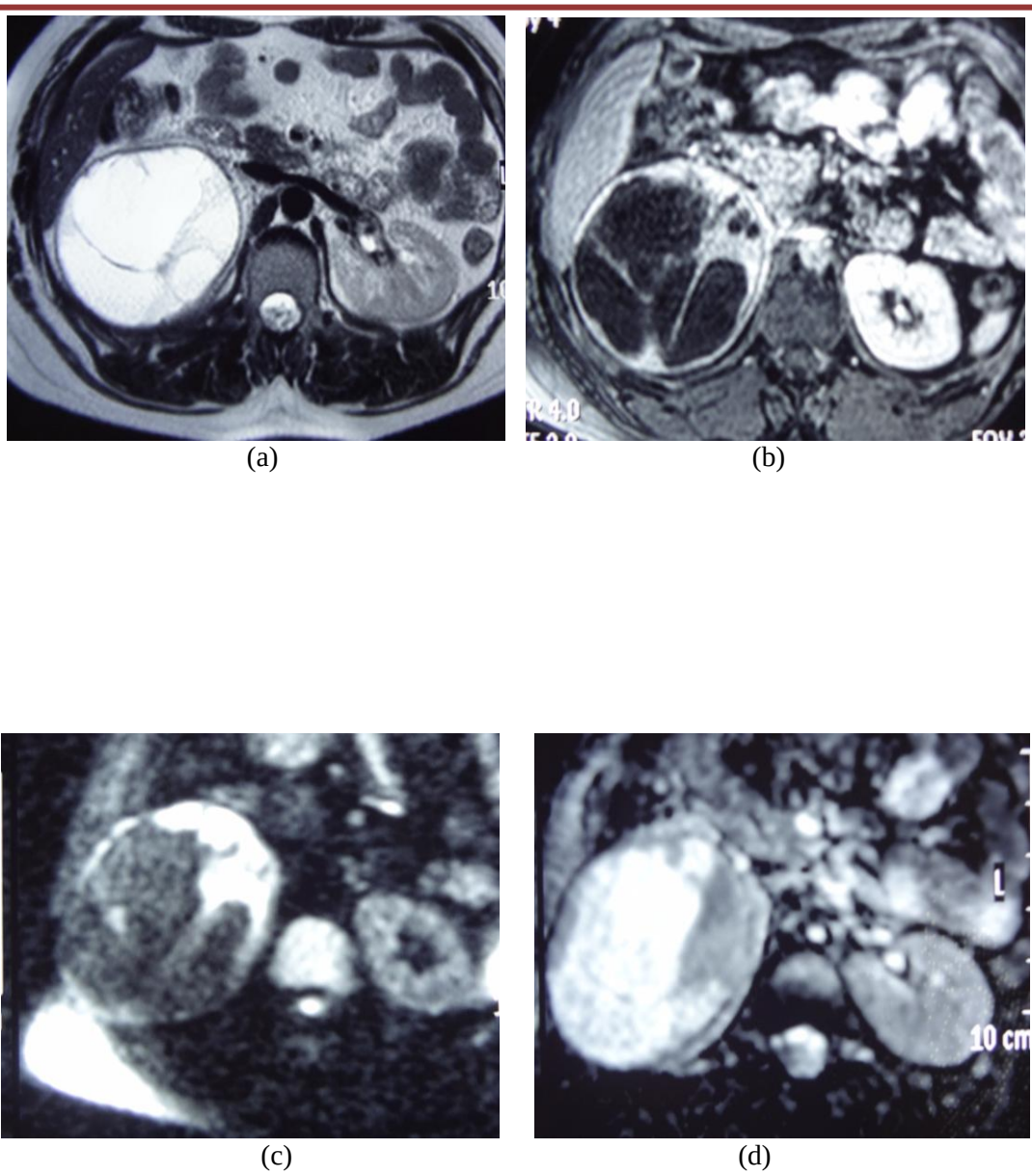
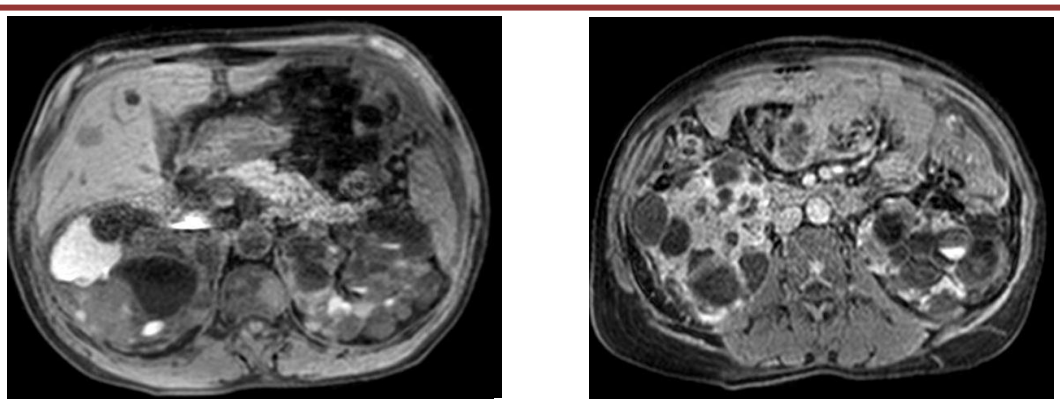
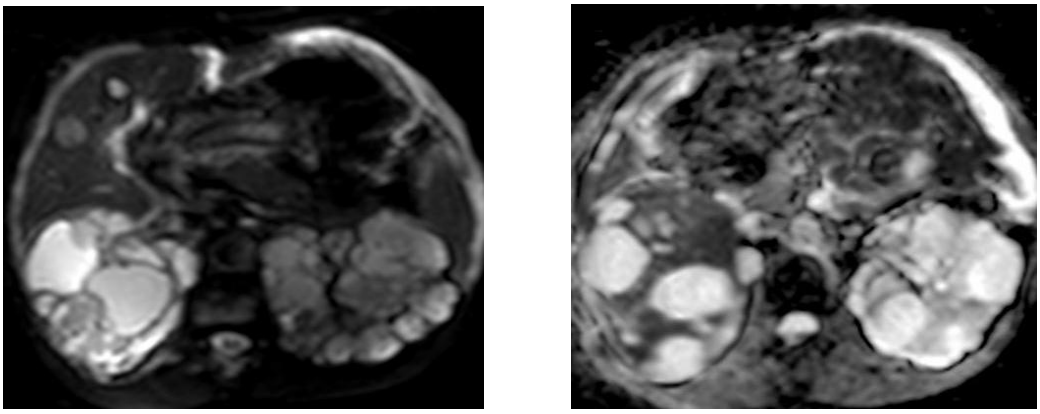


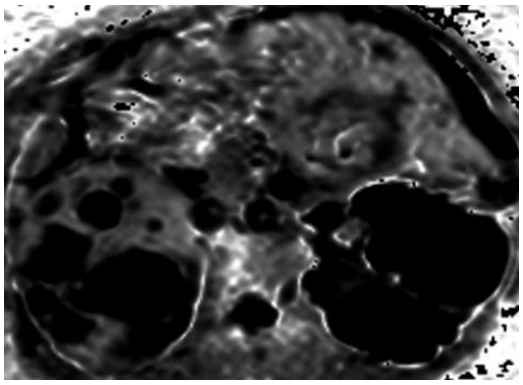
Fig 2: Right multilocular cystic nephroma (A)Axial T2WI shows large multilocular cystic mass with thick wall and septae displayed post contrast marginal and septal enhancement at (b). Wall and septae display high signals at DWI (c) and low signals at ADC map (d).



(a) (b)

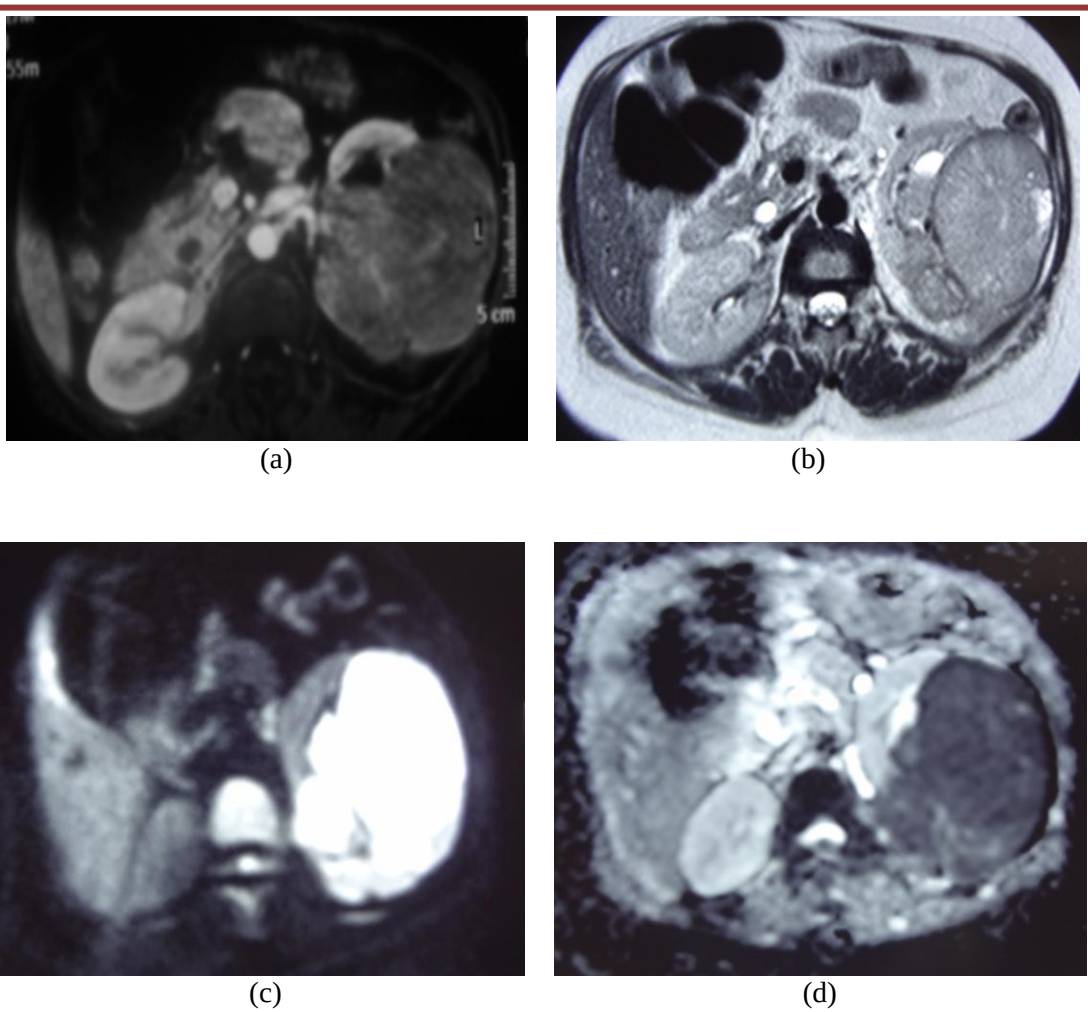


(b) (d)



(e)

Fig. 3: Autosomal-dominant polycystic kidney disease (a) Axial unenhanced fat-suppressed T1-weighted gradient-echo MR image reveals many of the cysts to be hemorrhagic.(b) Axial T1WI post-contrast (delayed phase) reveals no internal enhancement in any of the cystic lesions.The cysts display high signals at DWI at bo (c) and b1000 (d)and low signals at ADC map (e).



(a) (b)

(c) (d)

Fig4: Left clear cell RCC. (a) Axial enhanced T1-fat saturated image shows heterogenous enhanced left renal mass. (b) Axial T2WI shows large isointense signal mass at Lt. kidney . It displays high signals at DWI (c) and low signals at ADC map (d).

Thus DWI using b values of 0 and 1000 s/mm^2 was included in the routine MRI examination to differentiate benign and malignant kidney masses. Some investigators have recommended a b value >400 s/mm^2 because it can reduce ‘‘T2 shine-through’’ and intravoxel perfusion effects[20&21].Conversely, a higher b value leads to a lower signal to noise ratio (SNR) and anatomic distortion occurs at such high b values. In the present study, the malignant kidney lesions had lower ADCs than benign kidney lesions and normal renal parenchyma.

There was a statistically significant difference between benign and malignant kidney masses using b values of 0 and 1000s/mm^2. This was more apparent using b= 1000 s/mm^2 images than b=0 s/mm^2 images (P-value =0.01 using b =0 s/mm^2, P-value =0.03 using b= 1000 s/mm^2). Low b value is composed of both diffusion and perfusion and these insignificant results may be related to perfusion effects of the low b value. More importantly, we have shown that the ADC of benign cystic lesions is significantly higher than that of cystic RCCs. This finding is particularly useful in diagnosing cases in which gadolinium cannot be given or the contrast bolus is suboptimal, leading to difficulty in identifying an enhancing mural nodule. Repeated measurements of all regions of a cystic tumor, particularly of the peripheral regions showing nodularity, may help determine the malignant potential of a cystic mass. The angiomyolipomas are benign tumours, composed of blood vessels, muscle tissue and adipose tissue. In the study of Zhang et al.[23] there was a case of AML that had an ADC value of 1.23 mm^2/s, that was lower than the mean ADC value of RCC in the same study (2.03± 0.10). The findings of this study are in concordance with those of the study by Zhang et al.[24] and the ADC values of angiomyolipomas were lower than the ADC values of malignant lesions . In the present study a statistically significant difference was found among the ADCs of the AMLs and RCCs with using b values of 0 and 1000 s/mm^2. b =1000 s/mm^2 was more significant than other b values for differentiation between AMLs and RCCs . In the

study by Taouli et al.[21] the mean ADC of the AMLs (n= 3) were lower than the RCCs as found in the present study. Yoshikawa et al.[20]also found significantly lower ADCs in AMLs than the RCCs. They considered that the decreased ADC of AMLs may be explained by restricted diffusion caused by the muscle and fat components. Conversely, Kilickesmez et al.[16], found higher ADCs in AMLs than RCCs with the AML ADCs were gradually decreasing as the fat contents increased. AMLs with obvious fat content may be diagnosed easily using CT or conventional MRI. In the present study results also show that DW imaging is currently a reasonable alternative to contrast-enhanced MR imaging and contrast-enhanced CT for the diagnosis of malignant renal neoplasms in patients who have renal dysfunction and/or are at risk for nephrogenic systemic fibrosis or contrast material–induced nephropathy.

This study had some limitations. A major limitation was the relatively small patient sample, which was due in part to our attempt to limit the study population to patients with histopathologically confirmed findings. Also the relatively small patient sample in each category didn't allow accurate study of each lesion diffusion charachteristics , However, even though the patient sample was relatively small, we were able to demonstrate significant differences in ADCs among the different types of renal lesions and lesion areas. Another limitation of DWI include its poor anatomic localization and relatively poor spatial resolution. Particularly, using a high b value resulted in a lower SNR(signal-noise ratio) and increased anatomic distortion.. Further studies with larger patient populations and larger varieties of tumors are needed to confirm our preliminary findings.

Two important facts were learned from this study results: First, benign cysts and necrotic or cystic tumor areas have significantly different ADCs, even though they may have a similar appearance on conventional (T1-weighted, T2-weighted, and contrast-enhanced) MR images. This is presumably because although the nonviable soft tissue in necrotic tumors does not enhance, unlike cystic fluid, it is solid and does lead to restricted water diffusion. Therefore, the ADC potentially can be used as an additional parameter for characterizing renal lesions. Second the T1 signal characteristics of a lesion might need to be taken into account when ADCs are interpreted to evaluate a disease process.

In conclusion, DWI with quantitative ADC measurements could be easily added to a routine renal MR imaging protocol. It is an accurate method for renal lesion characterization . It can be useful in the differentiation of benign and malignant renal lesions. High b value (b 1000 s/mm^2) had the best specificity and sensitivity. DWI also had the advantage of being fast and not requiring a contrast agent. It can contribute to accurate diagnosis when the discrimination of benign and malignant renal lesions cannot be accomplished by conventional MRI sequences.We recommend using high b values for better results, a bigger number of cases is required for subsequent studies for more data to be retrieved.

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قيمة مرجح الإنتشار وتباين الصبغة بالرنين المغناطيسى فى التفرقة بين الكتل الكلوية

الهدف : تقييم دور مرجح الإنتشار وتباين الصبغة بالرنين المغناطيسى فى التفرقة بين الكتل الكلوية الحميدة و الخبيثة وتحديدخصائص انتشارها فضلا عن قياس قيم معامل الانتشار الظاهري لكل منها.

المواد والطرق : أجريت هذه الدراسة على خمسين مريض مصاب بالكتل الكلوية مع استخدام الكلى السليمة (كعنصر تحكم).تم عمل مرجح الانتشار مع القيم ب 0 و 1000 ثانية/مم2 و قورنت نتائج الفحص النسيجي مع نتائج التصوير بالرنين المغناطيسي وحسبت قيم معامل الانتشار الظاهري لمختلف الكتل الكلوية.

النتائج : توصلت هذه الدراسة الى أن متوسط قيم معامل الانتشار الظاهري للكلى السليمة باستخدام ب = 0 و 1000 ثانية/مم2 هو (3.7 ± 0.27)و (0.21± 2.8) . بينما كان متوسط قيم معامل الانتشار الظاهري في الآفات الكلوية الكيسية الحميدة (n =18) مع ب = 0 و 1000 ثانية/مم2 هو (0.44 ± 3.73) و (0.46± 3.09)متوسط قيم معامل الانتشار الظاهري في الآفات الكلوية الحميدة الصلبة (n = 5) مع ب = 0 و 1000 ثانية/مم2 هو (0.44 ± 1.53) و (0.46 ± 1.79) . متوسط قيم معامل الانتشار الظاهري للكتل الكلوية الكيسية الخبيثة (n = 4) مع ب = 0 و 1000 ثانية/مم2 هو (0.29 ± 3.09) و (0.10 ± 2.73) . متوسط قيم معامل الانتشار الظاهري للكتل الكلوية الخبيثة الصلبة الآفات (n = 23) مع ب = 0 و 1000هو (0.29 ± 1.63) و (0.25 ± 1.16) x 3- 10 مم2/ثانية ، على التوالي. وكانت الخصوصية و الحساسية للتصوير باستخدام مرجح الإنتشار مع قياس قيم معامل الانتشار الظاهري بالاضافة الى تباين الصبغة بالرنين المغناطيسى مجتمعة تعادل 95.6 و 96.3 في المائة على التوالي. علينا التفريق بين الكتل الكلوية الخبيثة من الكتل الكلوية الحميدة باستخدام تباين الصبغة بالرنين المغناطيسى جنبا إلى جنب مع مرجح الإنتشار .

الاستنتاجات : استخدام مرجح الإنتشار مع قياس قيم معامل الانتشار الظاهري بالاضافة الى تباين الصبغة بالرنين المغناطيسى مجتمعة يفيد فى التفرقة بين الكتل الكلوية الحميدة والخبيثة –كما وجد أن استخدام قيم عالية من ب (ب = 1000ثانية/مم2) كان الأفضل خصوصية وحساسية في التشخيص.