Potential of application of the apparent diffusion coefficient as the imaging biomarker of the clear cell renal cell carcinoma of different Fuhrman grades

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Abstract

Objectives. The purpose of the study was to assess the potential of the ADC of the DWI as the imaging biomarker in diagnosis of RCC of different Fuhrman degrees of its differentiation. **Materials and methods.** The study involved 62 adult patients with pathologically verified clear cell subtype of the renal cell carcinoma (ccRCC) and 15 healthy volunteers. All patients underwent renal magnetic resonance imaging (MRI) which included diffusion-weighted imaging (DWI) with subsequent apparent diffusion coefficient (ADC) measurement. **Results.** We observed significant difference in mean ADC value of the normal renal parenchyma and ccRCC – $1.82 \pm 0.16 \times 10^{-3}$ mm^2/s vs $2.15 \pm 0.12 \times 10^{-3}$ mm^2/s, respectively ($p < 0,05$). Statistically reliable difference in ADC values in patients with high and low ccRCC grades was obtained ($p<0.05$): in patients with the I grade the mean ADC value was $1.92 \pm 0,12 \times 10^{-3}$ mm^2/s, in patients with the II grade this value was $1.84 \pm 0.14 \times 10^{-3}$ mm^2/s, in patients

Key words:

renal cell carcinoma, apparent diffusion coefficient, diffusion-weighted imaging, biomarker

with the III grade the mean ADC value was 1.79 ± 0.12 × 10^{-3} mm^2/s, and in patients with the IV grade of nuclear polymorphism the mean ADC value was 1.72 ± 0.11 × 10^{-3} mm^2/s. **Conclusions.** The data obtained in the survey show a significant restriction of diffusion of hydrogen molecules in tissues of ccRCC compared to the healthy renal parenchyma due to the greater density of tumor. We observed a statistically significant difference in a mean ADC values of ccRCC tumors with different degrees of nuclear atypia by Fuhrman: tumors with a low grade of differentiation demonstrated higher mean ADC value compared to highly differentiated tumors. Calculation of ADC of DWI is useful for the diagnosis of ccRCC of different grades of differentiation.

Introduction

RCC is the most common primary tumor of the kidney and is found in 3% of all malignancies and in 90% of cases of the renal malignant neoplasms [1,2]. Among various histological subtypes of RCC clear-cell (ccRCC) is the most common which appears in 70-80% of pathological conclusions [3]. The degree of malignancy of ccRCC is determined on the background of various histological classifications, Fuhrman grading system being the most commonly used, which is based on 4 morphologic criteria of the nuclei [4]. Along with significant progress in understanding the mechanisms of RCC, an active survival option in selected patients was suggested; the degree of malignancy being a major criterion in the decision making process regarding treatment options [5].

Computed tomography (CT) is still the «golden standard» in imaging of RCC allowing to accurately perform staging of the tumors, to determine the nature of its growth and detect the presence of necrotic areas. Researchers had achieved promising results in the differentiation of histological subtypes of RCC and tumors with various degrees of nuclear atypia [6,7]. However, the use of CT is always associated with radiation exposure and consequently a significant increase in the risk of malignancy in patients with aplastic processes [8,9]. In recent years, MRI is increasingly attracting the attention of clinicians as a method of choice for the diagnosis and staging of the RCC, due to several advantages over CT: excellent image quality, high information content, the absence of any radiation exposure to the patients and staff, the ability to obtain three-dimensional images, assessment of renal function using contrast, etc [10]. According to studies of the sensitivity and specificity of MRI with contrast enhancement in the differential diagnosis of RCC, it is quite comparable by these parameters to CT [11].

The application of DWI representing the MRI modality which uses strong bipolar gradients to enhance sensitivity to thermally induced Brownian motion of hydrogen molecules allows to measure molecular diffusion in tissues in vivo [12]. To date, DWI is mainly used for differential diagnosis of tumors of the central nervous system, but in recent years encouraging data has been received on the use of this technique in the diagnosis of diseases of other organs, including kidneys [13,14,15]. ADC is a quantitative parameter which is measured from DWI images and used for the assessment of diffusion in healthy and affected tissues [16].

Given the above, the assessment of the efficacy of DWI modality of MRI and subsequent measurement of ADC in order to determine the parameters of the tumor and the degree of its differentiation in RCC is vitally important issue.

Objectives

The purpose of the study was to assess the potential of the ADC of the DWI as the imaging biomarker in diagnosis of RCC of different Fuhrman degrees of its differentiation.

Material and methods

Research was allowed by Ethics Committee of Lviv National Medical University named after Danylo Halytsky and was conducted on the basis of clinics of the Department of Urology and at the medical center "Euroclinic" (Lviv, Ukraine) during 2013-2017.

Retrospective study was conducted among 62 adult patients with ccRCC (32 men and 30 women) with 65 renal tumors aged 42-73 years old (mean age 59.5 ± 1.2 years). The control group consisted of 15 healthy volunteers with no renal disease according to clinical and radiological examinations (9 men and 6 women) aged from 23 to 46 years (mean age 22.2 ± 1.8 years). All patients with RCC and healthy volunteers were performed an MRI, which included DWI, followed by ADC measurement.

The study involved patients exclusively with clear cell histological subtype of RCC. Patients with renal insufficiency, metal objects in the body, cystic renal disease, low image quality, DWI with obvious artifacts were excluded from the study. All patients with ccRCC had undergone partial or radical nephrectomy with subsequent pathological verification of diagnosis. According to the grading system of nuclear polymorphism in ccRCC according to Fuhrman patients were randomized as follows: I grade – 12 patients, II grade – 18 patients, III grade – 21 patients, IV grade – 11 patients. Anticancer therapy in patients prior to the MRI and surgical treatment was not performed.

MR imaging was executed with a 1.5 T body scanner (Signa HDxt, General Electric, USA) using an eight-channel phased-array body coil. In addition to standard abdominal MR imaging protocol for renal masses it included axial DWI series with following parameters: b-values 0 and 800 mm2/s, TR=12000 ms, TE=90 ms, FOV=40×40 cm; matrix=200×192; NEX=3; bandwidth=250 kHz, diffusion direction=slice, slice thickness=6.0 mm, interscan gap=1.0 mm, acquisition time=17 s. DWI was conducted before contrast administration, using single-shot echo-planar imaging sequence with parallel imaging and fat-saturation during 1 breathhold. Apparent diffusion coefficient was measured from color ADC-maps generated automatically at the workstation (Advantage Windows, GE Healthcare). ADC value was recorded within ROI using described earlier technique [17]. For the statistical data analysis SPSS 22.0 software was used. The ADC value was expressed as mean + standard deviation, statistical significance was considered when P value was <0.05.

Discussion

On MRI images renal lesions had irregular shape with indistinct outlines. All tumors had a diameter exceeding 3 cm, with an average size of 5.6 ± 2.2 cm (range from 3.0 to 13.5 cm). 3 of 62 (4.8%) patients had multifocal tumors, the remaining 59 (95.2%) – monofocal. Patients with ccRCC in 49 (79%) cases demonstrated homogeneous signal; the remaining 13 patients (21%) had marked heterogeneous signal due to the presence of necrotic component of the tumor. On MRI images ccRCC was characterized by hyperintense signal in regard to renal parenchyma on T2-weighted images and hypointense signal on T1-weighted images. On DWI the tumor area was always represented by hyperintense signal while on the ADC-maps corresponding zone appeared to be hypointense compared to the unaffected renal parenchyma.

We found that the average ADC value of RCCs was statistically reliably lower compared to normal renal parenchyma and was $1.82 \pm 0.16 \times 10^{-3}$ mm²/s vs $2.15 \pm 0.12 \times 10^{-3}$ mm²/s, respectively ($p < 0.05$), due to significantly higher density of the ccRCC tissue and consequently due to the limitation of the diffusion of hydrogen molecules within the tumor.

Evaluation of the mean ADC value in patients with different degrees of ccRCC malignancy in accordance with classification by Fuhrman decrease in the mean ADC value along with the increase of the nuclear polymorphism was observed. Thus, in patients with the I grade the mean ADC value was $1.92 \pm 0{,}12 \times 10^{-3}$ mm²/s, in patients with the II grade this value was $1.84 \pm 0.14 \times 10^{-3}$ mm²/s, in patients with the III grade the mean ADC value was $1.79 \pm 0.12 \times 10^{-3}$ mm²/s, and in patients with the IV grade of nuclear polymorphism the mean

ADC value was $1.72 \pm 0.11 \times 10^{-3}$ mm²/s. Statistical comparison of the data obtained among patients of all 4 groups with different degrees of ccRCC differentiation had revealed a significant difference ($p < 0.05$). The mean ADC values of normal renal parenchyma and ccRCC of different degrees of malignancy are displayed in Table 1. These data suggest that tumors with a higher degree of malignancy are characterized by a restriction in the diffusion of hydrogen molecules in their tissue on DWI (Fig. 1).

Box diagram of ADC values of normal renal parenchyma and ccRCC and its grades of differentiation by Fuhrman (Fig. 2).

Table 1.
Mean ADC values of normal renal parenchyma and ccRCC

Pathologic type/stage (cases)	Mean ADC value (×10–3 mm2/s)	Groups comparison
Normal renal parenchyma (n=15)	2.15 ± 0,12	-
ccRCC (n=62)	1.82 ± 0,16	p <0.05 vs normal
Grade I (n=12)	1.92 ± 0,12	p <0.05 vs normal
Grade II (n=18)	1.84 ± 0,14	p <0.05 vs normal
Grade III (n=21)	1.79 ± 0,12	p <0.05 vs normal
Grade IV (n=11)	1.72 ± 0,11	p <0.05 vs normal
ccRCC, low grade (grade 1 + grade 2)	1.89± 0,18	p <0.05 vs high grade
ccRCC, high grade (grade 3 + grade 4)	1.74± 0,15	-

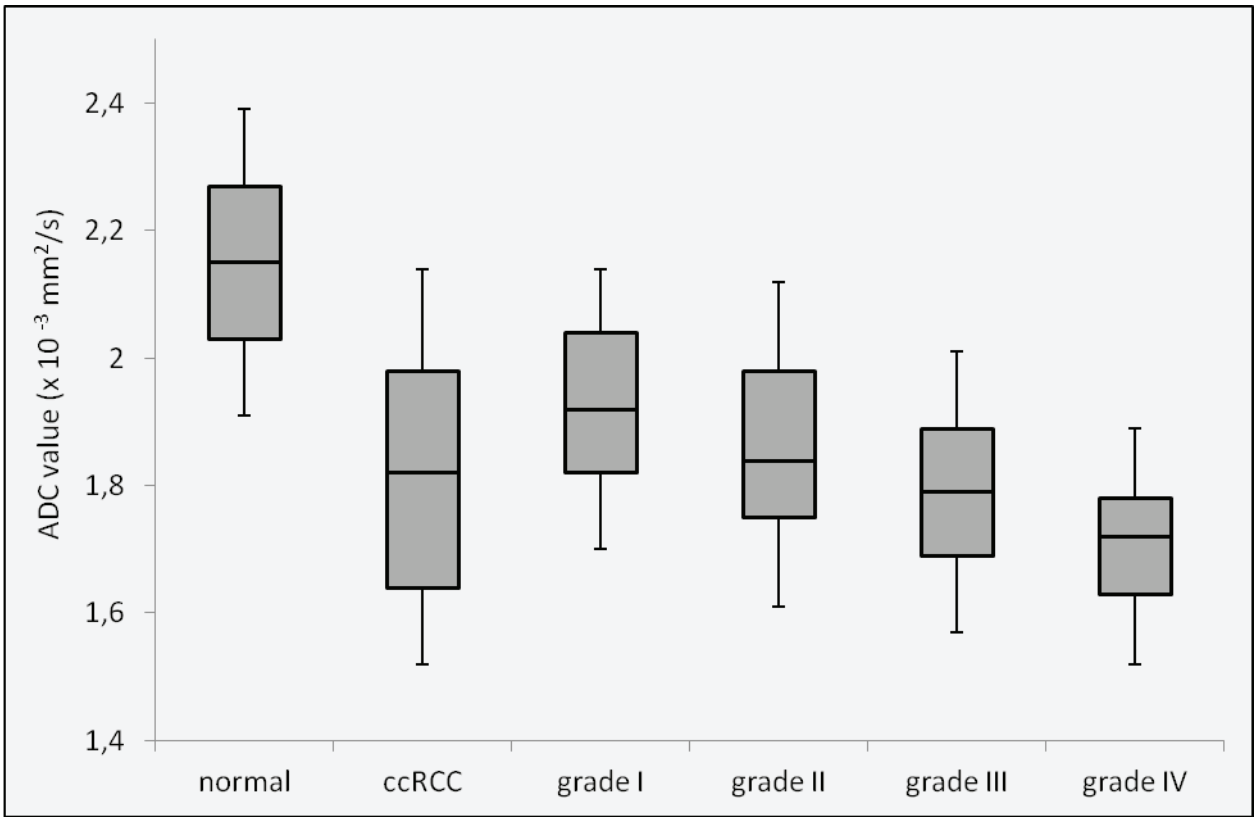
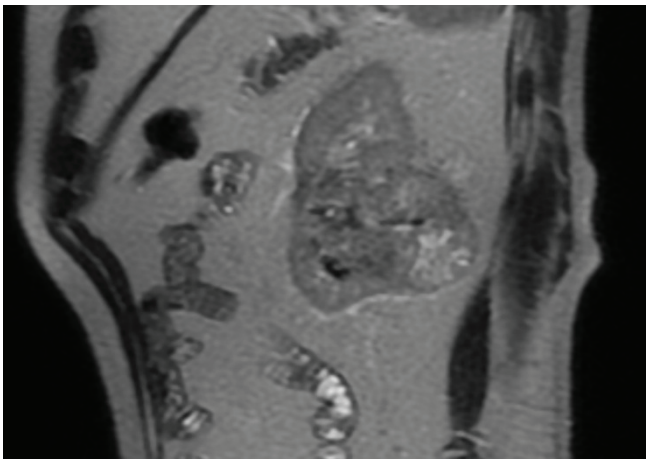


Fig. 1.
Box diagram of ADC values of normal renal parenchyma and ccRCC and its grades of differentiation by Fuhrman



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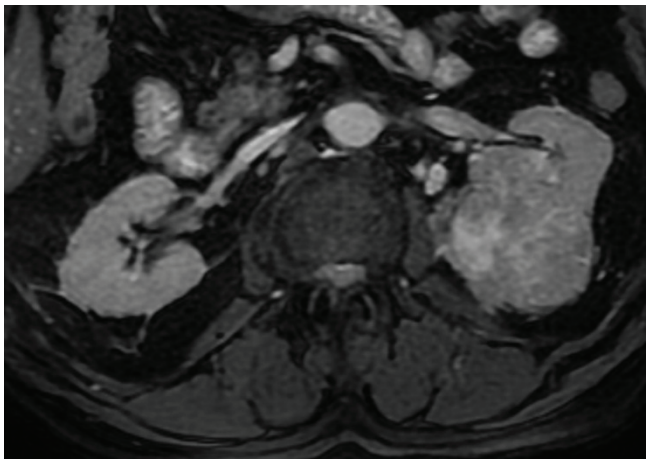

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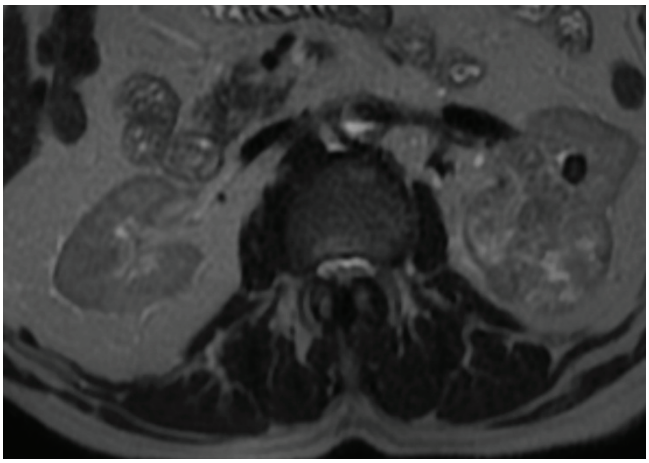

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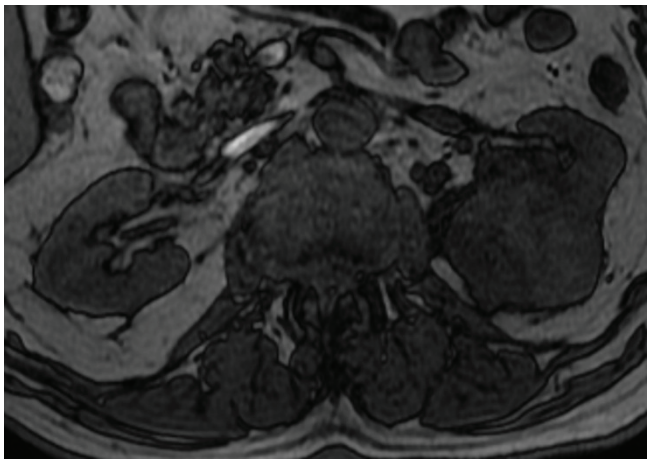

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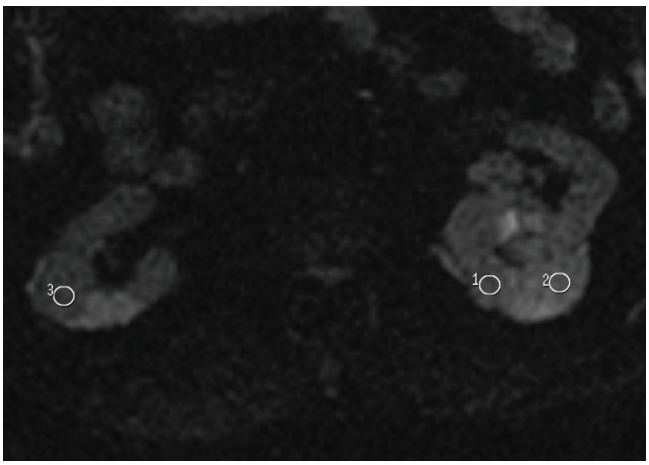

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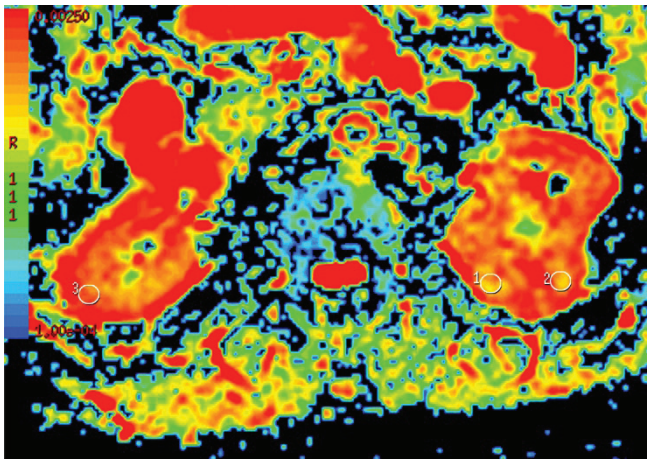

F

Fig. 2.
MRI of the patient, 74 y.o., pathologically proven ccRCC of the left kidney, 67×78×57 mm, III grade of differentiation by Fuhrman. A: T2-weighted SSFSE. B: axial T2-weighted FIESTA with fat saturation. C: axial T2-weighted SSFSE. D: axial double-echo FSPGR. E: axial DWI. F: ADC-map, ROI1 (tumor) – 1.76×10^{-3} mm^2/s, ROI2 (tumor) – 1.77×10^{-3} mm^2/s6 ROI3 (normal parenchyma) – 2.15×10^{-3} mm^2/s

Conclusions

The data obtained in the survey show a significant restriction of diffusion of hydrogen molecules in tissues of ccRCC compared to the healthy renal parenchyma due to the greater density of tumor. We observed a statistically significant difference in a mean ADC values of ccRCC tumors with different degrees of nuclear atypia by Fuhrman: tumors with a low grade of differentiation demonstrated higher mean ADC value compared to highly differentiated tumors. Calculation of ADC of DWI is useful for the diagnosis of ccRCC of different grades of differentiation.

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