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The role of the diffusion-weighted MRI in the differential diagnostics of the clear cell renal cell carcinoma of different fuhrman grades

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Renal cell carcinoma (RCC) is the most common primary tumour of the kidney and is found in 3 % of all malignancies and in 90 % of cases of the renal malignant neoplasms. In recent years, magnetic resonance imaging (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 computed tomography.

Objective. The purpose of the study was to assess the information content of MRI using diffusion-weighted imaging (DWI) modality in the diagnosis of clear cell RCC (ccRCC) and determining the degree of its differentiation.

Materials and methods. The study involved 62 adult patients with pathologically verified ccRCC and 15 healthy volunteers. All patients underwent renal MRI which included DWI with subsequent apparent diffusion coefficient (ADC) measurement.

Results and discussion. We observed significant difference in mean ADC value of the normal renal parenchyma and ccRCC — $1.82 \pm 0.16 \cdot 10^{-3} \text{ mm}^2/\text{s}$ vs $2.15 \pm 0.12 \cdot 10^{-3} \text{ mm}^2/\text{s}$, respectively ($p < 0.05$). Additionally, statistically reliable difference in ADC values in patients with high and low ccRCC grades was obtained.

Conclusions. Application of DWI modality of MR imaging with ADC calculation allows to obtain valuable information that is vital for the diagnosis of ccRCC and differentiation of its degree of malignancy which can be used in order to enhance the biopsy results as well as a separate diagnostic tool.

Key words: renal cell carcinoma, clear cell carcinoma, magnetic resonance imaging, diffusion-weighted imaging, apparent diffusion coefficient.

Introduction. Renal cell carcinoma (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. Among various histological subtypes clear cell RCC (ccRCC) is the most common which appears in 70–80 % of pathological conclusions [1]. 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 (Table 1). 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 [2].

Recently, computed tomography (CT) is considered to be the «golden standard» in diagnostic 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 [3]. 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 [4]. 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. 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 [5].

The application of diffusion-weighted imaging (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*. 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. The apparent diffusion coefficient (ADC) is a quantitative parameter calculated from DWI images which is used

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Table 1

Fuhrman nuclear grading system (Fuhrman S.A. et al., 1982)

Grade	Nuclear size	Nuclear shape	Chromatin	Nucleoli
I	< 10 μm	Round	Dense	Inconspicuous
II	15 μm	Round	Finely granular	Small, not visible at 10 · magnification
III	20 μm	Round/oval	Coarsely granular	Prominent, visible at 10 · magnification
IV	> 20 μm	Pleomorphic, multilobated	Open, hyperchromatic	Macronucleoli

as a measure of diffusion in healthy and affected tissues [6].

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.

The purpose of the study was to assess the information content of MRI using DWI modality in the diagnosis of ccRCC and determining the degree of its differentiation.

Materials and methods

Retrospective study was conducted among 67 adult patients with ccRCC (35 men and 32 women) with 69 renal tumors aged 41–73 years old (mean age 58.6 ± 1.3 years). The control group consisted of 18 healthy volunteers with no renal disease according to clinical and radiological examinations (10 men and 8 women) aged from 23 to 46 years (mean age 25.3 ± 1.6 years). All patients with RCC and healthy volunteers were performed an MRI, which included DWI, followed by ADC measurement. Research was allowed by Ethics Committee and conducted on the basis of clinics of the Department of Urology and Department of Radiology and Radiation Medicine of Lviv National Medical University named after Danylo Halytsky and at the medical center «Euroclinic» during 2013–2014.

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 — 15 patients, II grade — 19 patients, III grade — 22 patients, IV grade — 11 patients. Anticancer therapy in patients prior to the MRI and surgical treatment was not performed.

MR imaging was performed with a 1.5 T body scanner (Signa HDxt, General Electric, USA) using an eight-channel phased-array body coil. MR Imaging Protocol for renal masses included such series:

- Coronal T2-weighted single-shot fast spin-echo (SSFSE), repetition time (TR) = 2625 ms, echo time (TE) = 90 ms, flip angle = 90°, field of view = 40 · 40 cm, matrix = 200 · 192, breath-hold, supplying valuable T2-weighted information;
- Axial 2D fast imaging employing steady-state acquisition with fat saturation (FIESTA FAT SAT), TR = 4.1 ms, TE = 1.8 ms, flip angle = 90°, field of view = 40 · 40 cm, matrix = 224 · 320, — ultrafast pulse sequence that provides high-resolution images with outstanding image contrast and high signal-to-noise ratio (SNR) relative to the SSFSE. Compared with other steady-state pulse sequences, the FIESTA sequence does not subject to excessive signal saturation or motion artifacts and offers an excellent image;
- Axial DWI with the following parameters: TR = 12 000 ms, TE = 90 ms, field of view = 40 · 40 cm; matrix = 200 · 192; NEX = 3; bandwidth = 250 kHz, diffusion direction = slice, slice thickness = 6.0 mm, interscan gap = 1.0 mm with b-value = 0.800 mm²/s, acquisition time = 17 s. DWI was conducted before contrast media administration, using single-shot echo-planar imaging sequence with parallel imaging technique and fat saturation during one breath-hold;
- Axial T1-weighted fast spoiled gradient-recalled echo dual-echo (FSPGR-DE), TR = 130 ms, TE = 2.1 ms and 4.3 ms, flip angle = 70°, field of view = 43 · 43 cm, matrix = 320 · 192, breath-hold;
- Axial T2-weighted fast-recovery fast spin-echo (FRFSE), TR = 8750 ms, TE = 78 ms and 132 ms, flip angle = 90°, field of view = 44 · 44 cm, matrix = 384 · 192;
- Sagittal T2-weighted SSFSE, TR = 1760 ms, TE = 87.4 s, flip angle = 90°, field of view = 37 · 37 cm, matrix = 384 · 256;
- Axial 3D fat-saturated T1-weighted spoiled gradient echo liver acquisition with volume acquisition

(LAVA), TR = 4.5 ms, TE = 2.2 ms, flip angle = 15°, field of view = 38 · 38 cm, matrix = 320 · 192, during, and following administration of gadopentate dimeglumine, in a dose of 0.1 mmol/kg of body weight as a bolus injection with 20 s between each breath-hold acquisition. This technique combines contrast-enhanced, multi-phase imaging of the abdomen with high resolution, large coverage and uniform fat suppression. In one breath hold, LAVA acquires a stack of overlapping thin slices with high in-plane resolution. The usual protocol repeats this acquisition three or more times. In this way, LAVA produces images of the arterial and venous phases that not only precisely depict anatomy and contrast uptake, but also contain vascular information, easily revealed by a maximum intensity projection post-processing.

The signal intensity of the tumors on DWI was classified as high, iso-, and low signal intensity when compared with contralateral parenchyma. Color ADC map was generated automatically at the workstation (Advantage Windows, GE Healthcare). The ADC was calculated with linear regression analysis of the function:

$$S = S_0 \cdot \exp(-b \cdot \text{ADC}),$$

where S is the signal intensity after application of the diffusion gradient and S₀ is the signal intensity on the DW image acquired at b = 0 sec/mm².

The region of interest (ROI) was placed within a portion of the solid area where the minimum ADC value on the ADC map was registered according to the color by visual inspection. An average of two to three measurements per lesion were performed, depending on the lesion size. Necrotic regions were identified with conventional MRI sequences and were avoided for ROI placement. For comparison, the ROI placed in the tumor was copied and then placed on the normal parenchyma of the contralateral kidney in the same site in relation to tumor, and in the corresponding upper or lower pole if the tumor was remarkably bulgy outside the contour of the kidney. The mean ADC value was recorded within ROI. In all cases maps of the exponential apparent diffusion coefficient (EADC) were used for more precise positioning of the RIO over the lesion. The EADC-maps were generated automatically at the workstation.

Functool software was used for ADC and EADC maps generation and measurements, SPSS 22.0 software was used for data processing. The ADC value was expressed as mean + standard deviation. Statistical significance was considered when P value was < 0.05.

Results and discussion

Tumors had predominantly irregular shape on MRI images with irregular and indistinct outlines. All tumors had a diameter exceeding 3 cm, with an average size of 5.8 ± 2.4 cm (range from 3.0 to 13.7 cm). 4 of 67 (6 %) patients had multifocal tumors, the remaining

63 (94 %) — monofocal. Patients with ccRCC in 60 (90 %) cases demonstrated homogeneous signal and the remaining 7 patients (10 %) 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.

In the result of the performed analysis it was found that the average ADC value of malignant tumors was significantly lower compared to normal renal parenchyma and was 1.82 ± 0.16 · 10⁻³ mm²/s vs 2.15 ± 0.12 · 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 ± 0.12 · 10⁻³ mm²/s, in patients with the II grade this value was 1.84 ± 0.14 × 10⁻³ mm²/s, in patients with the III grade the mean ADC value was 1.79 ± 0.12 · 10⁻³ mm²/s, and in patients with the IV grade of nuclear polymorphism the mean ADC value was 1.72 ± 0.11 · 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 2. 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.

Table 2
Mean ADC values of normal renal parenchyma and ccRCC

Pathologic type/stage (cases)	Mean ADC value (· 10 ⁻³ mm ² /s)
Normal renal parenchyma (n = 18)	2.15 ± 0.12*
ccRCC (n = 67)	1.82 ± 0.16*
Grade I (n = 15)	1.92 ± 0.12*
Grade II (n = 19)	1.84 ± 0.14*
Grade III (n = 22)	1.79 ± 0.12*
Grade IV (n = 11)	1.72 ± 0.11*

* p < 0.05.

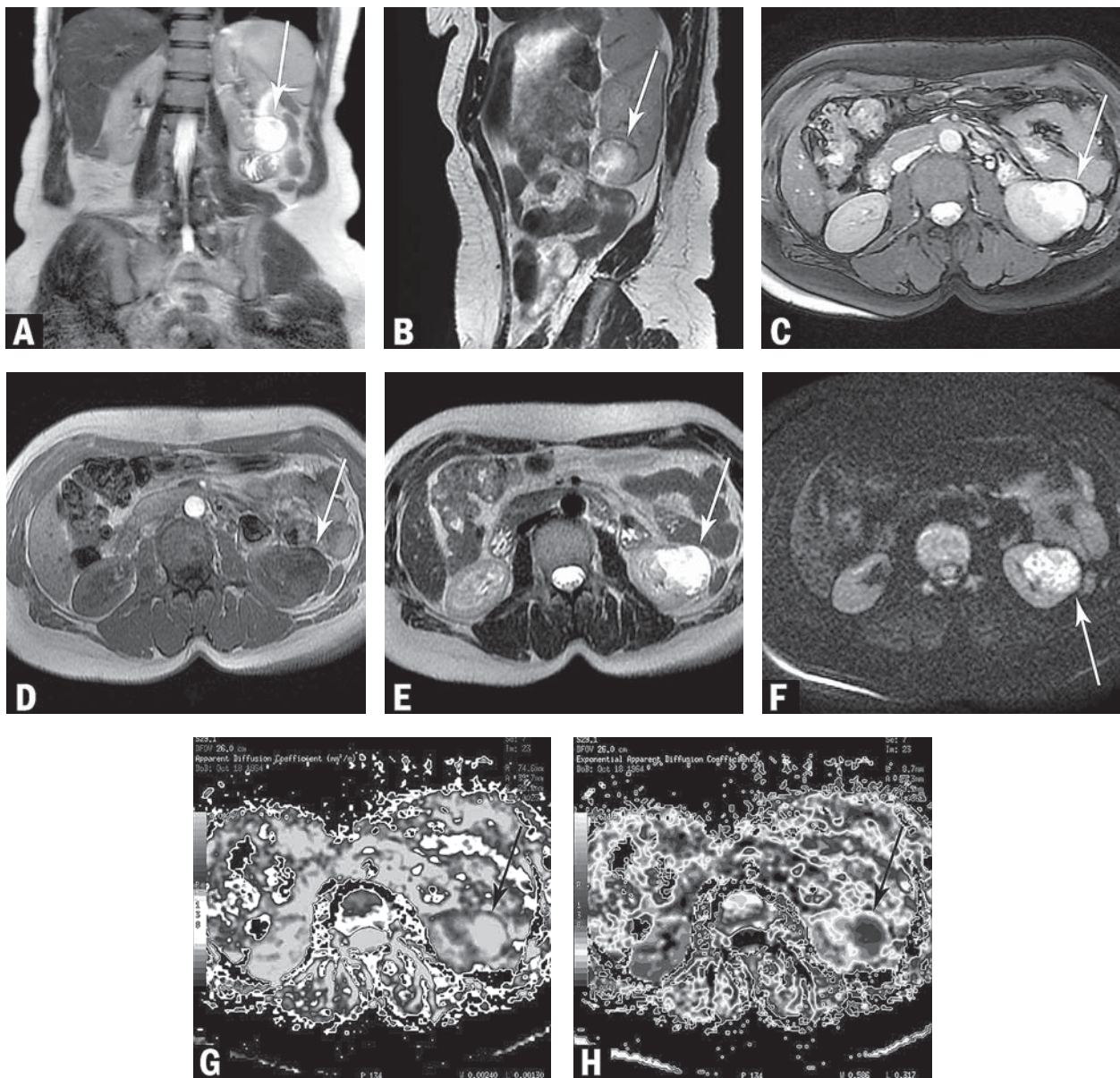


Figure 1. MRI of the patient with left ccRCC. MRI of the patient L., 40 y.o, pathomorphology conclusion: ccRCC of the left kidney, III grade of differentiation by Fuhrman. The tumor is labeled with arrows. *A*: on the coronal T2-weighted image in the SSFSE mode, tumor of the lower third of the left kidney with inhomogeneous hyperintense signal, with no signs of invasion of perirenal fat; *B*: sagittal T2-weighted image in FRFSE mode, inhomogeneous iso- and hyperintense signal over the tumor, no signs of perirenal invasion; *C*: axial 2D FIESTA FAT SAT, inhomogeneous hyperintense signal over the tumor, no signs of perirenal invasion; *D*: axial T1-weighted DEcho FSPGR, the region of tumor is inhomogeneous and hypointense; *E*: axial T2-weighted image in SSFSE mode, the tumor is noticeably inhomogeneous and hyperintense; *F*: diffusion-weighted image, b-value = $0.800 \text{ mm}^2/\text{s}$, the tumor site is hyperintense; *G*: ADC-map, part of the tumor is hypointense, ADC value in the region of interest over the tumor is $1.78 \cdot 10^{-3} \text{ mm}^2/\text{s}$ and over the area of unaffected contralateral kidney renal parenchyma — $2.13 \cdot 10^{-3} \text{ mm}^2/\text{s}$; *H*: EADC-map, the signal over the tumor and healthy kidney is better differentiated in comparison to ADC-map

On EADC maps better differentiation of the signal in comparison to ADC maps was admitted. It was helpful for the precise positioning of the ROI over the tumor lesion and for the assessing of the diffusion ability of the healthy kidney (Figure 1, H).

Conclusions

1. 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.

2. Mean ADC value of the normal renal parenchyma was significantly higher than in ccRCC tissues and was $2.15 \pm 0.12 \cdot 10^{-3} \text{ mm}^2/\text{s}$ and $1.82 \pm 0.16 \cdot 10^{-3} \text{ mm}^2/\text{s}$, respectively ($p < 0.05$). We observed a statistically significant difference in the 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.

3. Application of DWI modality of MR imaging with ADC calculation allows to obtain valuable information that is vital for the diagnosis of ccRCC and differentiation of its degree of malignancy which can be used in order to enhance the biopsy results as well as a separate diagnostic tool.

4. Further research is needed to establish the difference in the ADC values of the other histological subtypes of RCC and benign tumors of the kidney as well as assessing the role of the EADC measurement in this process.

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Ю.О. Мицик

Роль дифузійно-зважених зображень МРТ у диференціальній діагностиці світлоклітинного раку нирки різних ступенів диференціації за Fuhrman

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Нирково-клітинний рак (НКР) є найпоширенішою пухлиною нирки і спостерігається у 85–90 % випадків, що становить 1–3 % вісцеральних новоутворень. Ступінь злоякісності світлоклітинного НКР (скНКР) визначають за різними гістологічними класифікаціями, та найчастіше використовують градацію за Fuhrman, яка ґрунтується на чотирьох морфологічних критеріях. В останні роки магнітно-резонансна томографія (МРТ) все частіше привертає увагу клініцистів як метод вибору для діагностики й стадіювання НКР, оскільки має низку переваг над КТ.

Мета роботи — оцінка інформативності магнітно-резонансної томографії із використанням модальності дифузійно-зважених зображень (ДЗЗ) у діагностиці скНКР та визначенні ступеня його диференціації.

Матеріали та методи. У дослідженні взяли участь 67 хворих із патоморфологічно доведеним скНКР та 18 здорових волонтерів. Усім їм проводили МРТ з використанням ДЗЗ із подальшим визначенням вимірюваного коефіцієнта дифузії (ВКД).

Результати та обговорення. Встановлено, що середнє значення ВКД злоякісних новоутворень було значно нижчим, ніж у нормальної ниркової паренхіми, і становило $(1,82 \pm 0,16) \cdot 10^{-3} \text{ mm}^2/\text{s}$ порівняно з $(2,15 \pm 0,12) \cdot 10^{-3} \text{ mm}^2/\text{s}$ відповідно ($p < 0,05$). Також виявлено статистично вірогідну різницю в показниках ВКД у хворих із скНКР високого та низького ступеня диференціації.

Висновки. Результати обчислення вимірюваного коефіцієнта дифузії під час отримання дифузійно-зважених зображень магнітно-резонансної томографії надають важливу інформацію для диференціальної діагностики нирково-клітинного раку.

Ключові слова: нирково-клітинний рак, магнітно-резонансна томографія, дифузійно-зважені зображення, вимірюваний коефіцієнт дифузії.

Ю.О. Мыцик

Роль диффузионно-взвешенной визуализации МРТ в дифференциальной диагностике светлоклеточного рака почки разных степеней дифференциации по Fuhrman

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Почечно-клеточный рак (ПКР) является наиболее часто встречающейся опухолью почки и выявляется в 85–90 % случаях, что составляет 1–3 % от всех злокачественных висцеральных новообразований. На данный момент компьютерная томография и магнитно-резонансная томография (МРТ) являются основными методами исследования в диагностике, оценке и стадировании ПКР. Диффузионно-взвешенная визуализация (ДВВ) является модальностью МРТ, в которой используются сильные биполярные градиенты для усиления чувствительности к термически индуцированному броуновскому движению молекул водорода, что позволяет измерять молекулярную диффузию *in vivo*.

Цель работы — оценка клинической информативности МРТ с использованием модальности ДВВ в дифференциальной диагностике светлоклеточного рака почки разных степеней дифференциации.

Материалы и методы. Исследование проводилось у 67 взрослых пациентов с патоморфологически доказанным светлоклеточным подтипом НКР (скНКР) и у 18 здоровых волонтеров. Всем пациентам проводилась магнитно-резонансная томография с использованием ДВВ с последующим определением измеряемого коэффициента диффузии (ИКД).

Результаты и обсуждение. В результате проведенного анализа было установлено, что среднее значение ИКД злокачественных новообразований было значительно ниже, чем у нормальной почечной паренхимы и составляло $(1,82 \pm 0,16) \cdot 10^{-3}$ мм²/с против $(2,15 \pm 0,12) \cdot 10^{-3}$ мм²/с соответственно ($p < 0,05$). Также наблюдалась разница в показателях ИКД у больных со скПКР высокой и низкой степени дифференциации.

Выводы. Полученные данные говорят о том, что использование МРТ модальности ДВВ с исчислением ИКД позволяет получать ценную информацию, которая необходима для дифференциальной диагностики злокачественных и доброкачественных опухолей почек, что является крайне важным для выбора дальнейшей тактики лечения таких пациентов.

Ключевые слова: почечно-клеточный рак, магнитно-резонансная томография, диффузионно-взвешенная визуализация, измеряемый коэффициент диффузии.