Diffusion-weighted Imaging Using 3.0 T MRI as a Possible Biomarker of Renal Tumors

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Abstract. *Background/Aim: Diffusion-weighted imaging (DWI) allows for differentiation of benign from malignant tumors, histological tumor types and their grade. The aim of the study was to evaluate the capabilities of DWI using 3 Tesla Magnetic resonance inaging (3T MRI) in the preoperative assessment of renal tumors. Patients and Methods: This retrospective study included 143 tumors in 139 patients (130 malignant tumors and 13 benign tumors) that were examined using DWI with b values of 50, 400 and 800 s/mm^2. In all tumors, the lowest value of apparent diffusion coefficient (ADC) in the solid tissue was measured and correlated with the histological finding. Results: A significant difference between ADCs of malignant and benign tumors was found (p<0.001). Comparison of the most common malignant and benign tumors clear-cell renal carcinoma (CCRCC) grade I and oncocytoma resulted in a difference of borderline significance with a marked overlap (p=0.046). By assessing the histological types of malignant tumors, we detected a significant difference between CCRCC and all other histological types (p=0.048 for chromophobe (CH) RCC, p=0.002 for papillary (P) RCC and p=0.002 for urothelial carcinoma (UC)). Mutual differentiation of other types of carcinomas was not feasible (p=1.0 in all cases). The differences between low-grade (grade I+II) and high-grade (grade III+IV) CCRCC was significant (p<0.001). A significant difference was found even between CCRCC grade I and others (p=0.01 for grade II, p<0.001 for grade III+IV, respectively). Conclusion: DWI may contribute in distinguishing CCRCC from other histological types and to determin its grade. The method has certain potential for distinguishing benign from malignant tumors; however, differentiation of the most frequently represented types, CCRCC grade I and oncocytoma, remains difficult.*

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Worldwide, renal carcinomas represent approximately 3% of all malignancies (1). These tumors are most frequently encountered in developed countries of temperate climate, especially in Central and Eastern Europe. In the last twenty years, the detection rate of disease in the lower, asymptomatic stages has increased and improved the prognosis due to development of imaging techniques (2). However, despite improving imaging modalities, the differentiation between benign and malignant tumors in certain cases still remains a problem. According to published studies, benign tumors comprise up to one third of those resected (3, 4). An even bigger problem is the non-invasive differentiation between histological types of tumors and grade determination. Such information is important for the selection of appropriate therapeutic methods and prognosis estimation. For example, patients with clear-cell renal carcinoma (CCRCC) have a worse prognosis than patients with chromophobe (CHRCC) or papillary RCC (PRCC) (5, 6). In urothelial carcinoma (UC), different surgical treatments are used.

Modern imaging techniques allow for assessment of not only the morphological characteristics, such as size, contrast enhancement and relationship to surrounding structures, but also functional and molecular parameters. One of the parameters is the diffusion of water molecules, which can be

Table I. *MRI examination protocol*.

	T1 VIBE In-phase/ Opposed -phase	T1 FLASH 2D	T2 trueFISP	T2 HASTE	T2 TSE	EPI 2D Diffusion weighted	T1 FLASH 3D	T1 VIBE
Orientation	Axial	Coronal	Coronal	Coronal	Axial	Axial	Coronal	Coronal, axial
Time to repeat (ms)	4.35	162.0	3.52	1300	2200	6100	2.99	4.30
Time to echo (ms)	1.33, 2.45	3.69	1.54	91	100	61	1.06	1.89
Flip angle (degrees)	9	70	70	160	160	N/A	16	9.0
Paralell imaging acceleration factor	2	2	2	3	2	2	3	2
Pixel size (mm)	0.6×0.6	1.0×1.0	1.3×1.3	1.6×1.6	0.9×0.9	2.0×2.0	1.2×1.2	1.2×1.2
Slice thickness (mm)	3.0	5.0	5.0	5.0	5.0	5.0	1.1	3.0
Fat supression (mm)	No	Yes	No	Yes	Yes	Yes	Yes	Yes
b-value (s/mm^2)	N/A	N/A	N/A	N/A	N/A	50, 400, 800	N/A	N/A
Postcontrast circulation phase	N/A	N/A	N/A	N/A	N/A	N/A	Precontrast, arterial, arteriovenous, venous	Delayed, excretory
Acquisition time (min:s)	0:18	0:46	0:13	0:35	5:25	4:10	0:16	0:21

VIBE, Volumetric interpolated breath-hold examination; 2D, two dimensional; FLASH, fast low angle shot; trueFISP, true fast imaging with steady precession; HASTE, half-fourier acquisition single-shot turbo spin echo; TSE, turbo spin echo; EPI echo planar Imaging; 3D, three dimensional.

evaluated using diffusion-weighted magnetic resonance imaging (DW MRI). This method has previously been associated almost entirely with imaging of cerebral pathologies. Due to the use of stronger gradients and faster pulse sequences, DW MRI has recently been used more frequently in other organs, especially in oncological indications. Application of diffusion-weighted imaging to characterize the tissue is based on differences of diffusion of water molecules in benign and malignant lesions (Figure 1). The reason for this difference has not been yet fully explained. It is assumed that this difference is caused by tumor cellularity, extracellular space turtuosity, degree of tissue disorganization and, presumably, the cellular structure (7, 8). Diffusion-weighted imaging (DWI) can also be affected by perfusion (9, 10).

Images are obtained using diffusion-weighted sequences (the most common imaging is echo planar imaging (EPI)) with different b-values. The b-value expresses the impact of gradients on diffusion-weighted images. The higher the b-value is, the greater the diffusion weighting and, subsequently, the sensitivity of the movement of water are. To express the rate of diffusion of water molecules, an apparent diffusion coefficient (ADC) is used, which is expressed in unit mm^2/s (11). The ADC values are automatically calculated from diffusion-weighted images with at least two b-values and they are expressed either numerically or using the grayscale parametric maps.

The aim of the present study is to assess the possibility of diffusion-weighted imaging for the preoperative determination of dignity, histological type and grade of renal tumors using 3.0 Tesla (3T) MRI and comparison of the results with previously published studies.

Patients and Methods

From a group of 161 patients, who underwent MRI of kidneys for a suspected tumor between 2011-2014, we selected 139 patients with 143 tumors (61 females, 78 males, average age 65 years, range=37-86 years). Twenty-two patients with cysts (n=15), typical angiomyolipomas with fat content (n=5) and low quality DWI (n=2) were excluded. All tumors were resected and examined by a pathologist who is specialized in assessment of kidney tumors. In addition, for CCRCC the grade was specified according to Fuhrman (12).

All the examinations were carried-out with the 3.0 T MR scanner Siemens Magnetom Skyra (Siemens, Erlangen, Germany) using the matrix body coil with the standard protocol of our department for imaging of the renal carcinoma. Diffusion weighted images were obtained using echo planar sequences with b values of 50, 400 and 800 s/mm^2. From these three values, we automatically generated parametric maps of ADC, which were used to measure numeric values (Table I).

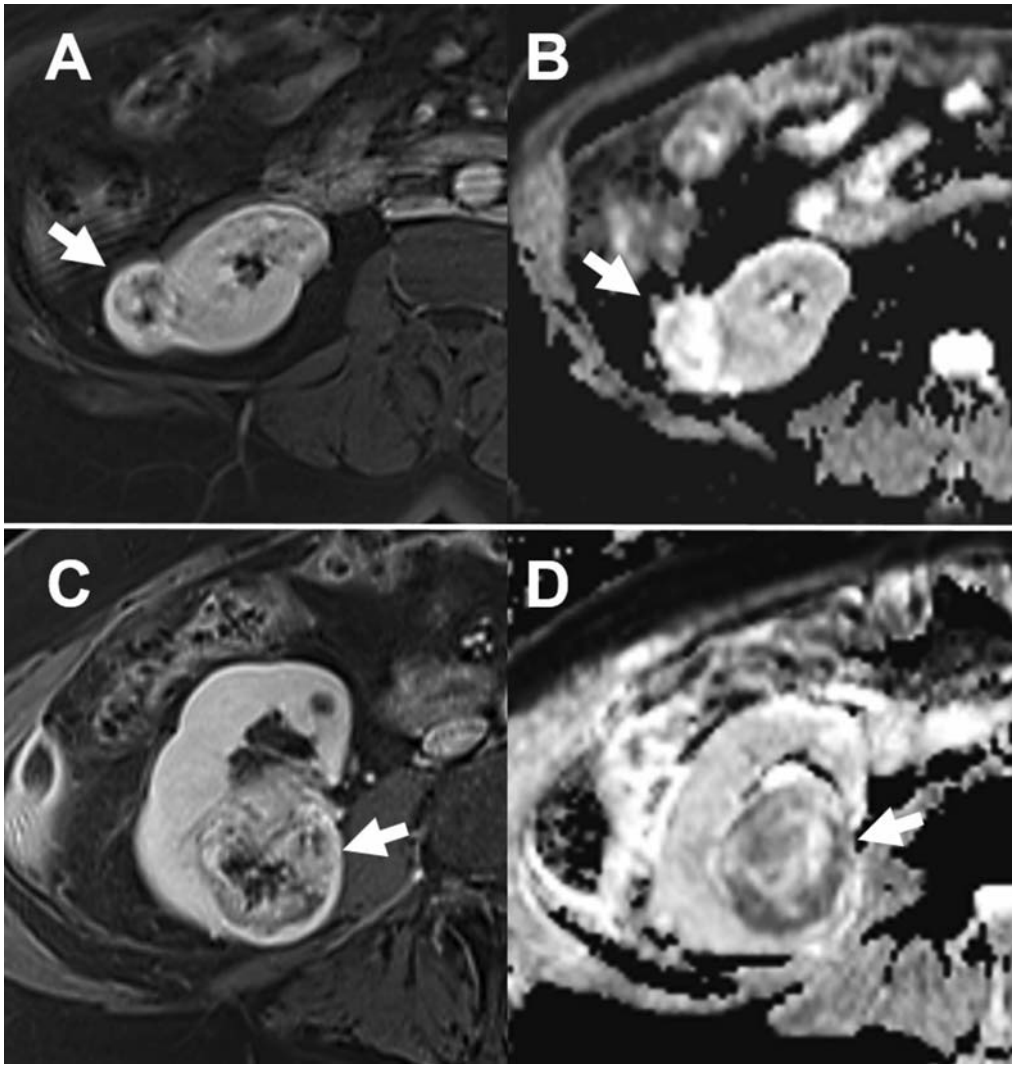

Figure 1. *Example of two patients with oncocytoma (A, B) and clear-cell RCC grade I (C, D). A similar appearance in postcontrast T1 weighted images (A, C) is observed. Apparent diffusion coeficient maps show high value for oncocytoma (1.868×10^{-3} mm^2/s) (C) and low value for clear-cel RCC (1.37×10^{-3} mm^2/s) (D).*

Image analysis was performed retrospectively by the two radiologists with 11 and 4 years of experience in the field of abdominal MRI without knowledge of the histological findings. For each tumor, three to five circular areas of interest with a diameter of at least 1 cm were selected based on the size of the tumor. The areas of interest had been selected to include only the solid tissue with contrast enhancement. Based on consensus, both radiologists selected areas of interest with the lowest value of the ADC that was included in the statistical analysis.

Statistical analysis was carried-out using the Statistica software (StatSoft, Tulsa, OK, USA). Due to the non-normal distribution of the ADC values, non-parametric methods were used. Assessment of the differences between the two groups of tumors (between malignant and benign tumors and between low-grade CCRCC and oncocytoma) was performed using the Mann-Whitney U test. For the assessment of the difference in the ADC among other carcinoma groups (individual histological types of tumors and the grade of CCRCC), we used the Kruskal-Wallis ANOVA test. The difference between the ADC of tumors and normal renal parenchyma was assessed using the Wilcoxon paired test. The Fischer exact test was used for testing of the impact tumor grade on the differentiation of various histological types. In all cases, the significance level of 5% was predetermined.

Results

In total, 130 malignant tumors were found. This number included 123 RCC and 7 intrarenal UC. The most frequent histological variant of RCC was CCRCC (n=102). CHRCC and PRCC were represented significantly less (n=8 and n=14, respectively). Furthermore, the CCRCCs were divided according to the grade. Grade I (n=48) was the most

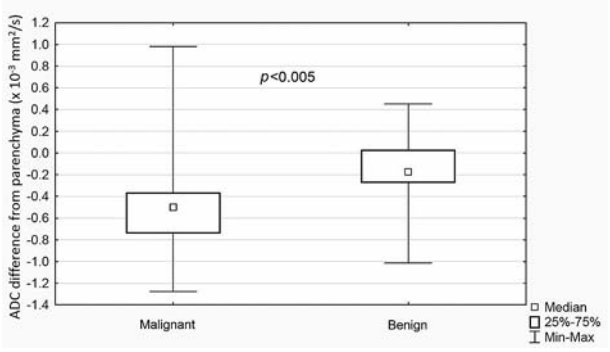

Figure 2. *Box and Whisker plot of ADC values difference of malignant and benign tumors from normal renal parenchyma shows significant difference between both groups of tumors. The difference between benign tumors and renal parenchyma is, contrary to malignant tumors, insignificant.*

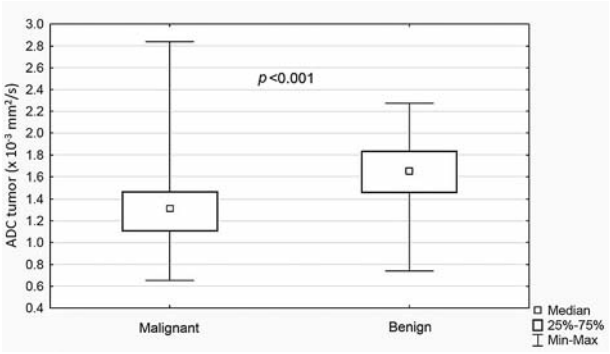

Figure 3. *Box and Whisker plot of ADC values in all malignant and benign tumors shows significant difference.*

frequently encountered grade; the number of carcinomas of grades II and III accounted for approximately half (n=25 and n=27, respectively). There was a very small number of grade IV carcinomas (n=2). Thirteen benign carcinomas included 11 oncocytomas and 2 mixed epithelial and stromal tumors. Measured ADC values are summarized in Table II.

Differentiation between benign and malignant tumors. Compared to the normal renal parenchyma in malignant and benign tumors, a tendency towards a lower ADC was found (median=1.825, interquartile range (IQR)=0.118×10^{-3} mm^2/s *vs*. median=1.305, IQR=0.365×10^{-3} mm^2/s and median= 1.671, IQR=0.415×10^{-3} mm^2/s, respectively). The difference was significant for malignant tumors (p<0.005). In the benign tumors, the difference between the ADC in tumors and renal parenchyma was insignificant (p=0.10) (Figure 2). The difference between the ADC values of all the malignant and benign tumors was significant (p<0.001) (Figure 3). Since CCRCC grade I, which was the most common type of malignant tumor in the group, had the highest ADC value of all malignant tumors (median=1.467, IQR=0.201×10^{-3} mm^2/s), we compared this group with the most common benign tumor-oncocytoma (median=1.652, IQR=0.362×10^{-3} mm^2/s). In this case, the difference was only on the border of statistical significance (p=0.046) with a marked overlap of ADC values (Figure 4).

Differentiation of histological types of tumors. We observed a tendency towards a decrease in the ADC from CCRCC (median=1.365, IQR=0.302×10^{-3} mm^2/s) over CHRCC (median=1.068, IQR=0.232×10^{-3} mm^2/s) and PRCC (median= 1.006, IQR=0.549×10^{-3} mm^2/s) to UC (median= 1.028, IQR=0.189×10^{-3} mm^2/s). The ADC in CCRCC was significantly higher than in any of the other groups. For CHRCC, the finding achieved the border of statistical significance (p=0.048), in PRCC (p=0.002) and UC (p=0.002) the finding was unambiguously significant. The mutual difference between CHRCC, PRCC and UC was not significant (p=1.0 in all cases) (Figure 5). In addition, it excluded that the differentiation of histological types of carcinomas was affected by the unequal representation of grade in each group (p=1.00).

Differentiation of grade. Statistical analysis of the grade of tumors was performed only in CCRCC. The results show that an increase in the grade of the tumor causes a tendency to reduce the value of the ADC. At first, the differences between tumors of high (grade I+II) and low grades (grade III+IV) were assessed (median=1.430 *vs*. 1.189×10^{-3} mm^2/s, p<0.001) (Figure 6). The result was statistically significant (p<0.001). A significant difference was found also between tumors of grade I and other grades (median=1.324, IQR=0.283×10^{-3} mm^2/s, p=0.01 for grade II and median= 1.189, IQR=0.290×10^{-3} mm^2/s, p<0.001 for grade III+IV, respectively). The grade II tumors did not differ significantly from grade III and IV tumors (p=0.057). In this group, there were only two grade IV tumors; therefore, this group was not assessed separately (Figure 7).

Discussion

According to the authors' best knowledge, this is the largest published set of renal carcinomas examined using DW MRI from a single center.

Due to the expected higher quality of diffusion-weighted images, we used the 3T system and calculated the ADC value from three b-values, with the highest b value at 800 s/mm^2 (8, 13). The considerable heterogeneity in structure can cause a problem in the assessment of diffusion in the renal tumors. A recommended technique for analysis of diffusion-weighted images has not been established; therefore, the approach of individual authors differs. In recent studies, the area of interest is focused on a solid portion of the lesion. Subsequently, the mean value (14-16) or the lowest ADC

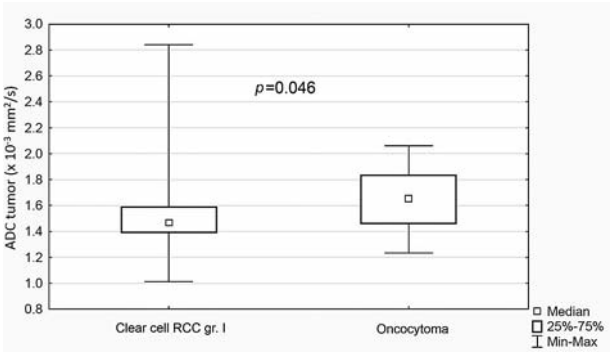

Figure 4. *Box and Whisker plot of ADC values in clear-cell RCC grade I and oncocytoma shows difference of borderline significance.*

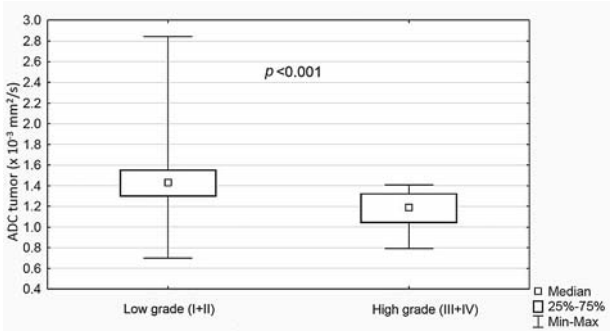

Figure 6. *Box nad Whisker plot of ADC values in low-grade (GI+GII) ahd high- grade (GIII+G IV) clear cell RCCs shows significant difference.*

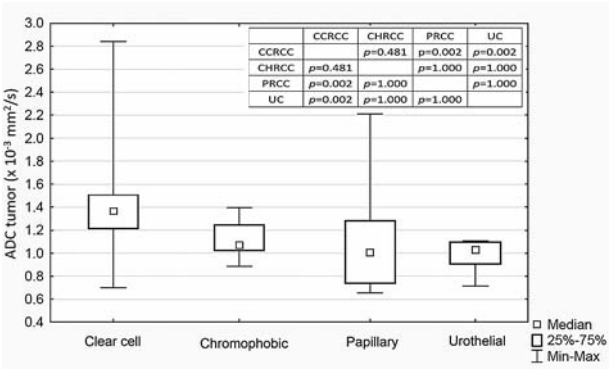

Figure 5. *Box and Whisker plot of ADC values in different types of malignant tumors. Difference between clear cell RCC and chromophobe RCC is of borderline significance, difference between clear cel RCC and other tumor is clearly significant.*

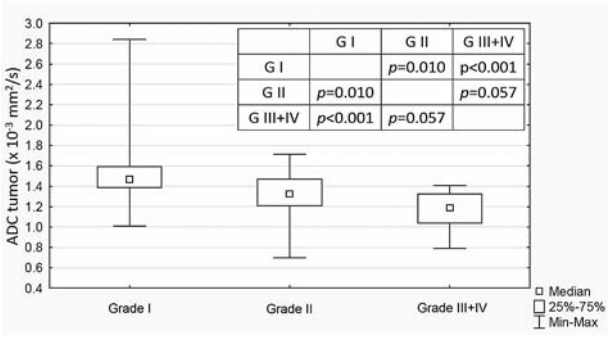

Figure 7. *Box and Whisker plot of ADC values distribution among clear cell RCC grade I, grade II and grade III+IV. Insignificant difference between grade II and grade III+IV; other differences are significant.*

value (9, 17-21) have been assessed by measuring multiple areas, with the number of considered areas depending on the size of the tumor. In one study, the authors focused on a histogram of the entire lesion to distinguish RCC and angiomyolipoma without visible fat content (22). Our technology of ADC assessment was based on selection of one area of interest with the lowest measured value, which in our opinion is appropriate for routine clinical assessment. We chose the region of interest for ADC measurement based on the consensus of two radiologists; therefore, analysis of interobserver agreement was not performed.

Comparison of ADC for each lesion with other studies is difficult due to differences in the equipment used and the design of diffusion-weighted sequences. This can be documented with the mean ADC in the renal parenchyma. In recent literature, these values vary between 1.64×10^{-3} and 2.35×10^{-3} mm^2/s (14, 15, 18-23). In our group of patients, we found a median of 1.825×10^{-3} mm^2/s with an IRQ of 0.118×10^{-3} mm^2/s. Similar differences can be observed even in pathological lesions (24).

Preoperative differentiation between benign and malignant tumors has been an ongoing problem. Some of the earlier publications have shown that DWI can be particularly useful in differentiating oncocytomas, which may look similar to carcinomas on other types of MR imaging (24). We proved a statistically significant difference in ADC values between all benign and malignant tumors ($p<0.001$). When we assessed the most frequently abundant malignant tumors with the highest ADC values (CCRCC G I) and the most frequently benign tumor (oncocytoma) in isolation, the result had borderline statistical significance ($p=0.046$) with marked overlap. This finding demonstrates the problematic utility of ADC for safe differentiation of these two entities, which is also mentioned in another study with 10 oncocytomas from one center (14). In other studies, which present significant differences, the oncocytomas were represented only in very small numbers; therefore, the results might be distorted (16, 19, 25-27). An interesting fact is that cellularity, which is significantly higher than in CHRCC, does not become a factor determining the diffusion of water molecules in oncocytoma (19). The group of benign lesions did not

Table II. *Apparent diffusion coefficients in renal parenchyma and different tumor types.*

Tumor type	Number of patients	ADC (median, IQR) ($\times 10^{-3}$ mm^2/s)
Renal parenchyma	139	1.825, 0.118
Malignant tumors	130	1.305, 0.365
Benign tumors	13	1.671, 0.415
Clear-cell RCC	102	1.365, 0.302
Chromophobe RCC	8	1.068, 0.232
Papillary RCC	14	1.006, 0.549
Urothelial carcinoma	7	1.028, 0.189
Oncocytoma	11	1.652, 0.362
Clear-cell RCC GI	48	1.467, 0.201
Clear-cell RCC GII	25	1.324, 0.283
Clear-cell RCC GIII	27	1.206, 0.221
Clear-cell RCC GIV	2	1.011, N/A
Clear-cell RCC GI+II	73	1.430, 0.262
Clear-cell RCC GIII+IV	29	1.189, 0.290

ADC, Apparent diffusion coefficient; IQR, interquartile range; RCC, renal cell carcinoma; G, grade.

include cysts and angiomyolipoma that could be specifically distinguished by the presence of liquid or fat by other sequences and the ADC is either significantly higher (cysts) or lower (angiomyolipoma) and could modify the results.

When differentiating the histological types of carcinoma, we found higher ADC values in CCRCC compared to all other malignant tumors, similar to most published studies (15, 18, 21, 22). In our group, the difference was statistically significant. Other histological types of tumors were not distinguishable based on measurements of ADC to distinguish. Slightly higher, but not significantly different, the values are still found in CHRCC. This result does not correlate with histological characteristics of presented tumors because CCRCC has a higher cellularity than PRCC and CHRCC. A likely explanation is the difference in perfusion, which also affects the diffusion-weighted images. CHRCC and PRCC are typically hypovascular compared to CCRCC (15, 22, 28). We did not even prove significant difference between UC and non-clear RCCs (p=1.00). This is most likely related to the higher cellularity of this tumor type. The surprising fact is represented in this year´s published study that presents a significantly higher ADC in CHRCC and PRCC than in CCRCC ($1.59\pm0.55\times10^{-3}$ mm^2/s *vs.* $6.72\pm1.85\times10^{-3}$ mm^2/s) (18). To our knowledge, this observation is unique.

In the observed group, a tendency to decrease the ADC was correlated with increasing tumor grade. Using the simplified differentiation of the low-grade and high-grade tumors, which is recommended to reduce the variability among observers assessing the histology (29), the difference was statistically very significant. A significant difference was even observed between grade I and grade II tumors (p=0.01). Grade II tumors did not show a significant difference compared to grade III+IV. The assessment of the grade according to Fuhrman is important, particularly in CCRCC, where it is based on the morphology of the cell nuclei and does not have a direct link with the cellularity of the tumor. Low-grade tumors have large cells with large amounts of glycogen, unlike the higher-grade tumors with less amount of glycogen and more organelles. It is possible that this difference affects intracellular diffusion, which may also contribute to the value of the ADC (9).

The presented study suffers four main limitations. The first one is its retrospective character. The second one is based on the unequal representation of different histological variants of carcinomas arising from their prevalence (30). A third limitation is represented with the absence of interobserver agreement, an important point that has to be aimed at due to the great heterogeneity of carcinoma structures and inconsistent methodology for future separate studies. The fourth limitation is represented by an independent ADC assessment, without other types of MR imaging that could contribute to better differentiation of the individual groups.

Conclusion

Assessment of diffusion of water molecules in renal tumors using ADC may help to distinguish CCRCC from other histological variants of renal carcinomas and to determine its grade. The method has also some potential for differentiating benign from malignant tumors, especially between the most common representatives, oncocytoma and CCRC grade I. It is not currently possible to reduce the number of unnecessary resections of these benign lesions based on ADC assessment. To use DWI in common practice, it is necessary to define a suitable and proper methodology for measuring ADC. Due to differences of measured values using different equipment and different designs of pulse sequences, we can determine limit values transferable within differently equipped institutions.

Acknowledgements

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