Prediction of nuclear grade of clear cell renal cell carcinoma with MRI: intratumoral susceptibility signal intensity versus necrosis

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Aims and objectives

Renal cell carcinoma (RCC) is the most common type of primary renal malignancy in adults, responsible for approximately 85%-90% of cases (1). End-stage renal disease and dialysis patients have a higher incidence of RCC than the general population (2-4). Except recommended surgical operations, more novel treatments for RCC, such as active surveillance (5) and radiofrequency ablation (6), are optional. Preoperatively evaluating the biological behavior of RCC plays an important role in treatment decision making.

Fuhrman et al. (7) proposed a grading system for RCC based on the morphology of nuclei and nucleoli. This grading system has been widely used to predict the prognosis of patients with RCC and can help assess tumor aggressiveness (8, 9). Fine needle biopsy provides an opportunity to grade RCC by pathology, but the accuracy is low due to some disadvantages as sample errors and insufficient materials.

Magnetic resonance imaging (MRI) can non-invasively evaluate RCC preoperatively. Previous studies have reported encouraging results for grading RCC using various imaging approaches (10-13). In order to get an accurate result, contrast-enhanced MRI is an important method to rule out intratumoral hemorrhage or necrosis. Although anaphylactic reactions of contrast-enhanced MRI are rare, some contrast agents can increase the risk of nephrogenic systemic fibrosis (NSF) in patients with impaired renal function, especially in dialysis patients (14).

Until recently, most MR imaging reflects the difference of magnitude information. Phase images, which reflect local susceptibility changes between tissues, were ignored because the inhomogeneities of the background magnetic fields obscured useful phase information. A high-pass (HP) filter can remove the low-spatial frequency components of the background field and create susceptibility-weighted filtered-phase images (15). Susceptibility weighted imaging (SWI) is a gradient echo (GRE) method that combines magnitude and HP-filtered phase images. SWI can detect signal-intensity changes coming from both T2 and susceptibility differences between tissues. Because of its sensitivity to susceptibility effects, SWI can noninvasively visualize microvenous structures and blood products that are not visible by conventional MRI. Some previous studies on grading gliomas using SWI have demonstrated that the distribution and count of microvenous structure and hemorrhage correlated with tumor grade in the brain (16, 17). To our knowledge, SWI has not been used to grade clear cell RCCs (CRCC). This study is aimed to evaluate the feasibility of SWI in grading CRCCs and compare the ability of SWI and necrosis for grading CRCCs.

Methods and materials
Patients

A retrospective review was performed of patients with MR imaging for evaluation of renal masses. A total of 35 patients (20 men and 15 women; range, 29-77 years; median age, 57 years) were enrolled in this study. All patients enrolled in this study must have undergone MR imaging for evaluation of renal masses, radical nephrectomy and have pathological confirmation of CRCCs.

MR Imaging Protocol

All patients were examined on a 3T scanner using a commercialized 16-channel sensitivity encoding (SENSE) Torso coil. The protocol of MRI for all the patients included a T2-weighted coronal breath-hold ultrafast spin echo (UFSE) sequence (repetition time/echo time, 800/91 ms; slices thickness, 4 mm; matrix size, 117×256; flip angle, 160°; field of view, 380 mm × 380 mm; bandwidth, 781 Hz/pixel), a transversal T1-weighted high-resolution isotropic volume examination (THRIVE) gradient-echo (GRE) sequence (161/2.5 ms; slices thickness, 5 mm; matrix size, 180×320; flip angle, 70°; field of view, 285mm×380mm; bandwidth, 270Hz/pixel), a transversal T2-weighted UFSE sequence (700/96ms; slice thickness, 5 mm; matrix size, 168×320; flip angle, 150°; field of view, 285 mm × 380 mm; bandwidth, 488 Hz/pixel), and a transversal 2D breath-hold GRE (162/10.3 ms; slice thickness, 5 mm; matrix size, 187×384; flip angle, 20°; field of view, 285 mm × 380 mm; bandwidth, 620 Hz/pixel).

Postcontrast three-dimensional (3D) fat-suppressed T1-weighted THRIVE breath-hold examination was performed in transversal plane after administration of 0.1 mmol gadopentetate dimeglumine (Magnevist, Bayer Healthcare, Berlin, Germany) per kilogram of body weight at a rate of 2 mL/sec followed by 10 mL saline flush at the same rate.

The 2D SWI post-processing was done offline based on 2D GRE sequence using in-house software SPIN (Signal Processing In NMR, Wayne State University, Detroit, OH, USA) consisting of the following steps: 1) the uncorrected phase image obtained by the 2D GRE sequence was processed using a 32×32 homodyne high-pass filter, by which corresponding corrected phase image was produced; 2) a normalized phase mask was calculated directly from this corrected phase image and multiplied with the final magnitude image four times to produce the final SWI image.

Imaging Analysis

All images were analyzed by consensus of two radiologists (15 and 7 years of experience in abdominal MRI, respectively). In ambiguous cases, both reviewers reached a consensus in their decision.

Low signal intensities of microvenous structures and hemorrhage within tumors on SWI were defined as intratumoral susceptibility signal intensities (ITSS) (17). Intratumoral calcifications were excluded if the lesions showed hyperintensity in phase imaging
The morphology of the ITSS was classified into two categories: hemorrhage and microvessels. Hemorrhage was defined as dot-like or patchy (dots with conglomeration) foci > 0.5 cm in diameter and of low signal intensity on SWI (19). Microvessels were defined as fine linear or conglomerated linear hypointensity structures in transverse planes or cylindrical hypointensity foci which could be followed on contiguous images. The dominant structure of ITSS was judged with a 4-point confidence level scale (0= no ITSS in the tumor on SWI; 1= prominently microvascular structure; 2= hemorrhage and microvessels almost equally presented in the tumor on SWI; 3= prominently hemorrhage in the tumor on SWI).

Necrosis was defined as intratumoral areas which appeared hypointens on T1-weighted imaging (T1WI) and hyperintens on T2-weighted imaging (T2WI), and without enhancement after administrating contrast material. The presence or absence of necrosis was assessed (0=no necrosis; 1= the presence of necrosis).

**Histological Analysis**

Histopathology was obtained from all masses by radical nephrectomy. Fuhrman nuclear grade was assigned for all cases. On the basis of Fuhrman nuclear grade, all cases were merged into low- (Grade I+ II) and high-grade group (Grade III + IV) (20).

**Statistical Analyses**

Statistical analysis was performed using software (MedCalc, version 11.4. 2.0). Results were presented as mean±SD. Nonparametric Mann-Whitney test was used to compare the differences of dominant structure of ITSS on SWI and intratumoral necrosis between low- and high-grade tumors. The diagnostic values of ITSSs and necrosis in differentiating low- from high-grade group in CRCCs were compared by receiver operating characteristics (ROC). Diagnostic sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) corresponding to the cut-off value were calculated. A difference of $P< 0.05$ was considered significant.

**Results**

A total of 35 lesions in 35 patients were included in the statistical analysis. There were 12 grade I, 13 grade II, 8 grade III and 2 grade IV. Low-grade group contained 25 cases and high-grade group contained 10 cases.

ITSSs were seen in 31 of 35 patients. No ITSSs were seen in 4 of 35 patients with low-grade CRCCs. The dominant structures of ITSSs on SWI are listed in Table1. Mean scores of dominant structures of ITSSs for low- and high-grade CRCCs were 1.24±0.72 and 2.70±0.48, respectively. Mean scores of dominant structures of ITSSs on SWI were
significantly lower for low-grade CRCCs (Fig. 1) than that for the high-grade CRCCs (Fig. 2) \((P<0.01)\).

Intratumoral necrosis was seen in 25 patients. No significant necrosis was seen in 10 patients with low-grade CRCCs. There was a significant difference of the presence of intratumoral necrosis between low- and high-grade CRCCs \((P<0.05)\).

The areas under the ROC curve for the ITSSs and necrosis in differentiating low- from high-grade group were 0.94 and 0.70, respectively. The areas under the ROC curve of ITSSs in grading CRCCs was larger than that of necrosis \((P<0.05)\). When the ITSS score was larger than the cutoff of 2, which indicated that intratumoral hemorrhage was the prominently structure on SWI, CRCCs could be graded with a sensitivity of 70\%, specificity of 100\%, PPV of 100\% and NPV of 89.3\%. When intratumoral necrosis was seen, the sensitivity, specificity, PPV and NPV in grading CRCCs were 100\%, 40\%, 40\% and 100\%.

Images for this section:

<table>
<thead>
<tr>
<th>Table 1: The dominant morphology of ITSSs in CRCCs.</th>
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<tbody>
<tr>
<td>ITSSs (n)</td>
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<tr>
<td>Hemorrhage (dots with or without conglomeration)</td>
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<tr>
<td>Microvessels (fine linear structures with or without conglomeration)</td>
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<tr>
<td>Hemorrhage and microvessels almost equally presented in the tumor</td>
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CRCC, clear cell renal cell carcinoma; ITSS, intratumoral susceptibility signal intensities.

Table 1: Table 1.
Fig. 1: Fig. 1 A case with low-grade CRCC (Grade #). A left exophytic, midpole renal mass with ill-defined borders (arrow head) appears homogeneous hypointensity on T1WI (A) and hyperintensity on T2WI (B). After administrating contrast materials, the mass shows homogeneously avid enhancement (arrow head) (C). No significant necrosis is seen. On SWI (D), multiple linear ITSSs, which represent intratumoral microvessels, are seen (arrow head). No dot-like ITSS is present.
**Fig. 2:** A case with high-grade CRCC (Grade #). A round renal mass with patchy necrosis in the left kidney is observed. Intratumoral necrosis (arrow head) appears low signal intense on T1WI (A) and high signal intense on T2WI (B). On enhanced MRI (C), the parenchyma of the tumor is enhanced avidly. The area of necrosis is not enhanced (arrow head). On SWI (D), prominently intratumoral hemorrhage is seen. Intratumoral hemorrhage appears dot-like or patchy hypointensity (arrow head).
Conclusion

In conclusion, our study suggests that SWI is a useful technique to analyze the structural characteristics of CRCCs and grade CRCCs preoperatively based on dominant structures of ITSS.

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