Measuring Perfusion and Permeability in Renal Cell Carcinoma With Dynamic Contrast-Enhanced MRI: A Pilot Study

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Purpose: To retrospectively assess an improved quantitative methodology with separate assessment of perfusion and permeability for characterization of primary renal cell carcinoma (RCC) and monitoring antiangiogenic treatment.

Materials and Methods: Fifteen RCC patients before surgery, 6 RCC patients before and after neoadjuvant antiangiogenic therapy, and 15 patients without renal disease underwent dynamic contrast-enhanced (DCE)-MRI of the kidney with integrated retrospective respiratory triggering and an individual arterial input function. Tracer kinetic analysis was performed with a two-compartment-filtration-model for the kidney data and a two-compartment-exchange-model for the tumor data, providing four independent parameters: the perfusion-parameters plasma flow (FP) and plasma volume (VP), and the permeability-parameters extraction flow (FE) and extravascular-extracellular volume (VE).

Results: In tumors FP and FE were significantly lower than in normal kidneys. Tracer kinetic analysis displayed hemodynamic alteration caused by vessel infiltration or necrosis. Papillary RCC could be differentiated from clear-cell variants by a distinct perfusion pattern. In antiangiogenically treated RCC V_E was not significantly decreased, while the perfusion parameters VP and FP were significantly diminished.

Conclusion: DCE-MRI with integrated motion compensation enables evaluation of primary RCC and detects distinct perfusion patterns. Quantification with a two-compartment-exchange-model produces a separate perfusion- and permeability characterization and may become a diagnostic tool to monitor antiangiogenic treatment.

Key Words: RCC; DCE-MRI; neoadjuvant antiangiogenic therapy; perfusion; two-compartment-model; tumor

RENAL CELL CARCINOMA (RCC) is the most common malignant tumor of the kidney (1). As response rates to radiation and nonantiangiogenic chemotherapy are low (2), surgical excision including radical and partial nephrectomy is the treatment of choice. Immunomodulatory therapies, for example with interleukin-2 (3), have also shown effect on RCC. Currently evolving therapies include stem-cell transplantation (4), tumor vaccines (5), and antiangiogenic therapy (6). As RCCs show vascular richness, antiangiogenic therapy targeting vascular endothelial growth factor (VEGF) and its tyrosine kinases seems particularly promising. Multi-kinase-inhibitors (MKI) like Sunitinib have been recently approved by the Food and Drug Administration for neoadjuvant treatment of advanced RCC (7). With the advent of these novel therapeutic antiangiogenic agents appropriate monitoring options are warranted. Currently, antiangiogenic therapy evaluation in clinical routine is based only on morphological imaging information (8), but changes in tumor size may lag behind functional changes. The vascular richness and commonly large size of RCC make them easy imaging targets for functional evaluation. Several dynamic contrast-enhanced (DCE) computed tomographic (CT) studies have already been conducted to assess the vascularization of various tumors (9,10). However, DCE-CT suggests an additional exposure of 10 mSv per acquired minute (10), so that assessment of the slowly changing extravascular concentrations...
to measure permeability (in tumors) or filtration (in kidney tissue) is problematic. MRI of the kidney has been established as a pivotal imaging modality for the diagnosis of renal tumors (11,12). T1-weighted DCE-MRI allows the assessment of the temporal enhancement pattern and provides physiological information on the tumor vasculature, tumor blood flow and microvessel permeability which may precede tumor shrinkage (13). DCE-MRI enables visualization of tumor responses to antiangiogenic drugs using semiquantitative approaches and different compartment models (14–16). In Ewing’s sarcoma, evaluation with DCE-MRI after neoadjuvant chemotherapy showed a high wash-in rate in viable remnant tumors (14). In pleural mesothelioma, responders showed a significantly lower tracer redistribution compared with non-responders after treatment with gemcitabine (15). Treatment with anti-VEGF antibodies resulted in rapidly decreased tumor vessel permeability and vascular volume in a murine colorectal cancer model (16). The potential of DCE-MRI has also been explored for assessment of RCC vascularity (11,13) and as a predictive pharmacodynamic biomarker for antiangiogenic therapy in metastatic RCC (17,18).

Tissue hemodynamic characteristics can be accessed from DCE-MRI data using either semiquantitative or quantitative parameters (19). Semiquantitative parameters depend on the contrast injection, hardware settings, sequence choice, and systemic changes in the circulation, and have an unclear physiologic interpretation. A quantitative analysis is independent on these factors, but the only quantitative method previously proposed in RCC uses a Tofts model for tracer kinetic analysis (17,18). This produces a parameter $K^{\text{trans}}$, which has an unspecific physiologic interpretation and is sensitive to changes in both perfusion and permeability (20). For data measured at high temporal resolution, the problem can be resolved by the use of a two-compartment-exchange model (21). This produces separate measures of perfusion and permeability, thus in principle allowing for a separation of both effects. A similar approach is proposed in studies focusing on other tumor types (21,22), and is motivated by the fact that tumors tend to be highly vascularized, so that the tracer concentration in the capillary bed cannot be assumed negligible. None of these studies have been performed in tumors as high flow as RCC. A related approach, the two-compartment filtration model, has been applied successfully in several renal perfusion studies (19,23). Other groups have assessed RCC with a simplified DCE-MRI approach with higher spatial resolution and lower temporal resolution, providing a semiquantitative enhancement threshold, allowing separation of clear cell and papillary RCC (11). A second limitation of all previous studies on DCE-MRI in RCC is that they focus exclusively on the metastases in regions that are not subjected to breathing motion (17,18).

The aim of this retrospective study was to propose and evaluate a methodology that allows quantifying perfusion and permeability in RCC, and that can be applied to primary as well as metastatic tumors. We perform a first assessment of the potential of DCE-MRI for the presurgical characterization of the primary tumor in RCC, and for monitoring of the effect of first line antiangiogenic therapy.

**MATERIALS AND METHODS**

**Patients**

A total of 21 consecutive patients (August 2007–September 2008) with renal tumors before surgery or neoadjuvant antiangiogenic first line therapy were included in the study. Local ethics committee approval was waived for this retrospective study as DCE-MRI was applied within routine MRI examinations. Informed consent was obtained from all patients. Indication for the MR-examination was characterization of the primary tumor, depiction of local infiltration and blood supply. No additional contrast application was required for this study. All patients previously underwent routine CT examination of the thorax and the abdomen as primary staging modality. Common criteria for exclusion from MRI (e.g., pacemaker, contrast allergies, glomerular filtration rate < 30 mL/min) were applied.

Of the 21 patients, 6 underwent neoadjuvant therapy and were examined morphologically before therapy onset. 4/6 with DCE-MRI, the other 2 did not undergo DCE-MRI because the initial examination was focused on the liver. The patients had not undergone previous chemotherapy. All tumors were surgically excised, so that histological correlation was available for all tumors. Neoadjuvant therapy was performed with a regimen including the Multi-Kinase-Inhibitor Sunitinib (Sutent®, Pfizer, New York, NY) as first line therapy (50 mg/day) for 4 weeks, followed by 2-week washout period. The follow-up examinations were performed in the first week after completion of the 4-week therapy cycle, which was completed by all six patients. Time to death after finishing the therapy cycle was monitored until July 2009.

As a point of reference for the quantitative parameters, 15 patients (48 ± 15 years) without history of renal disease and normal serum creatinine (e.g., living organ donation) were also included in this study. These patients also signed informed consent.

**Imaging**

All examinations were performed on a 1.5 Tesla (T) 32-channel whole-body MR-scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). A dedicated six-element body array matrix coil and six elements of the integrated spine coil were used for signal acquisition. Morphologic images were acquired including axial fast-imaging with a steadystate free precession sequence to allow proper slice positioning (True-FISP; TR 3.77 ms/TE 1.52 ms/FA 60°). This was followed by coronal half-Fourier single-shot turbo-spin-echo (HASTE; TR 1000 ms/TE 81 ms/FA 180°), coronal and transverse volume-interpolated breath-hold examination (VIBE; TR 4.31 ms/TE
1.52 ms/ FA 15°) and axial fat-saturated T2-TSE sequences (TR 3200/TE 100/FA 180°).

DCE-MRI was performed with a Saturation-Recovery Turbo-FLASH sequence (TR 277 ms; TE 0.95 ms, TI 148 ms; flip angle 12°, slice thickness 8 mm, slice gap 4 mm, matrix 192 × 134; field of view 440 mm × 366 mm, phase encoding direction right → left). To minimize inflow effects, a magnetization preparation with a pulse train of three short π/2 pulses with constant amplitude and phase cycling in a phase angle of π/2 is applied. Four slices were acquired within 1 s for a measurement time of up to 4 min, with an in-plane resolution of 3.3 mm × 2.3 mm. Positioning of the slices was supervised by a radiologist. The sequence was started simultaneously with an intravenous injection of 7 mL Gd-DTPA (Magnevist, Bayer Schering Pharma, Berlin, Germany) at 4 mL/s and a 30-mL saline flush at the same flow rate using an MR-compatible automated injector (Spectris Solaris, MedRad, Indiana, PA, USA) (19). DCE-MRI data were acquired during free breathing. Three slices were placed along the long axis of the kidney in an oblique coronal plane covering the entire kidney and the major solid portions of the renal tumor. One transverse slice was positioned at the level of the renal arteries for the measurement of the arterial input function (AIF).

After DCE-MRI, the rest of a full body weight adapted dose (0.2 mL/kg) was administered and a postcontrast VIBE was acquired for local staging and vascular anatomy.

Data analysis
The morphologic sequences were analyzed by two blinded radiologists with 3 and 11 years of experience in abdominal MRI in consensus. Analysis of morphological features included tumor diameter, signal intensity, signs of necrosis, hemorrhage, and liquefaction as well as vascular tumor infiltration. Particular tumors, features with hemodynamic relevance, such as necrosis, vascular invasion were recorded. We recorded T1 and T2-properties of the tumors. Increased T1-signal was regarded as deposition of methemoglobin. Decreased T1- and T2- signal was regarded as hemosiderin.

Hemorrhage and/or necrosis were assessed using a 5-point scale: − = 0%; + = 1–25%; ++ = 25–50%; +++ = 50–75%; ++++ = 75–100%.

Postprocessing was performed offline by one of the radiologists using the in-house built software FMI 0.3 written in IDL 6.4 (ITT Visual Informations Solutions, Boulder, CO). On the transverse slice a four-pixel region of interest (ROI) was drawn manually in the lumen of the aorta to measure the individual arterial input function (AIF) (Fig. 1a). Because the aorta does not move during breathing, the AIF was not triggered, thus exploiting the full temporal resolution in the rapidly changing signal of the arterial blood (Fig. 1b).

A retrospective respiratory triggering approach was used to remove the motion due to breathing. For this purpose, a rectangular ROI was manually defined at the interface between tissue and air on the axial slice (23) (Fig. 1a). The signal intensity time curve of the triggering ROI was filtered with a low-pass filter with a frequency cutoff of 0.05 Hz. Dynamic images with signal intensity above the filtered curve were ignored in subsequent calculations (Fig. 1c). The triggering ROI was not placed in coronal slices, as contrast enhancement of liver and spleen alter the signal intensity curve, while signal intensity on axial slices is only dependent on motion.

To assist in tissue ROI definition, relative signal enhancement curves were first fitted on the pixel level to the two-compartment filtration model (19). For patients without renal disease, a whole cortex ROI was segmented semi-automatically by first selecting those pixels with 15 ml/100 ml (19), then manually excluding extrarenal pixels. The model fit was then repeated on ROI level. A ROI encompassing the major solid portion of the tumor was defined manually on the parametric maps, and compared with the morphological maps. Relative signal enhancement curves in the tumors were fitted to the two-compartment exchange model (21) (Fig. 1d) and those in the cortex to the two-compartment filtration model (24). Both models produce four independent parameters: the plasma flow $F_p$, the plasma volume $V_p$, the extraction flow $F_E$ and the mean transit time $T_E$ of the extravascular extracellular space. In the tumors, the product $F_pT_E$ equals the volume of the interstitium ($V_i$). Due to the effects of reabsorption, the product $F_E/T_E$ has no clear physiological interpretation in the kidney (19). The extraction fraction ($E$) expresses the extraction flow relative to the total inflow: $E = F_E/F_p$.

Statistical Analysis
Significant differences between normal kidneys, pre-treated and treated tumors were assessed with the Mann-Whitney U-test using SPSS 15.0 (SPSS Inc., Chicago, IL).

Intraindividual correlation of the tumors before and after neoadjuvant treatment was performed with the Wilcoxon-signed-rank test. Two kidneys of the same patient and measurements before and after antiangiogenic therapy were statistically dependent, so that the number of individuals was used for statistical analysis. Statistical significance was defined at a $P$ value < 0.05.

RESULTS
All studies were completed successfully. Minor wrap-around artifacts in the kidney region occurred in two patients, but all relevant structures could be readily identified.

Morphology and Histology
Detailed results of the morphological analysis and histological diagnosis of the patients without antiangiogenic therapy are listed in Table 1. The kidneys of
patients without history of renal disease and the kidneys contralateral to the tumor bearing kidneys showed no morphologic abnormalities apart from sporadic simple renal cysts. Of the 21 examined tumors, 14 were histologically diagnosed as clear cell carcinomas. Two tumors exhibited a papillary phenotype and five tumors a sarcomatoid-clear cell subtype.

Table 1

| Patient | Histology                  | pT | Tumor size (cm) | Particularities       | Necrosis/hemorrhage |
|---------|----------------------------|----|-----------------|-----------------------|---------------------|
| 1       | Clear cell                 | 2  | 5.8             |                       | –                   |
| 2       | Sarcomatoid clear cell     | 3b | 6               | IVC infiltration      | +                   |
| 3       | Clear cell                 | 1a | 2.5             |                       | –                   |
| 4       | Papillary                  | 3a | 5.7             |                       | –                   |
| 5       | Clear cell                 | 2  | 4.6             |                       | ++                  |
| 6       | Clear cell                 | 2  | 5.2             |                       | ++                  |
| 7       | Sarcomatoid clear cell     | 3b | 13.5            |                       | ++++                |
| 8       | Clear cell                 | 1b | 7               |                       | +                   |
| 9       | Clear cell                 | 2  | 10.1            | IVC infiltration      | +                   |
| 10      | Clear cell                 | 3b | 3.1             |                       | –                   |
| 11      | Clear cell                 | 1a | 4.6             | exophytic             | –                   |
| 12      | Clear cell                 | 1a | 3.6             |                       | +                   |
| 13      | Clear cell                 | 3b | 10.2            |                       | ++                  |
| 14      | Clear cell                 | 1a | 2.5             |                       | –                   |
| 15      | Papillary                  | 1a | 9.3             |                       | ++++                |

*Grading of necrosis/ hemorrhage: – = 0%; + = 1-25%; ++ = 25-50%; +++ = 50-75%; ++++ = 75-100% IVC = inferior vena cava.
Nineteen tumors presented as a solid mass, whereas two tumors showed signs of massive necrosis with viable parts only in the periphery of the tumor. Two of the solid tumors showed vascular infiltration of the renal veins and the inferior vena cava, no vessel infiltration was seen in the necrotic tumors.

Of 21 tumors, 6 were also morphologically examined after antiangiogenic treatment (4 also with DCE-MRI) (Table 2). Three of the treated tumors were clear cell carcinoma, three were sarcomatoid-clear cell. Five of six tumors showed T1- and T2- signal alteration indicating necrosis and hemorrhage. 5/6 showed diameter reduction, but not significant according to RECIST-criteria. Four patients died due to disease-related events during the monitoring interval with a mean time to death of 7 months after finishing therapy. One of the patients was clinically considered as nonresponder. The patient died 1 month after the follow-up examination due to rapid progressive metastatic disease. Tumor enhancement after antiangiogenic therapy was decreased compared with normal kidneys.

**Perfusion and Permeability**

The results of the perfusion analysis are summarized in Figure 2 and Table 3. Figures 3–7 illustrate the individual results for some typical cases.

Normal kidneys (Fig. 3) exhibited SI curves with a steep upslope, high signal changes and an early peak during the first pass of the contrast agent. The excretory phase is characterized by an uptake corresponding to glomerular filtration, followed by a washout by loss of tracer to the medulla. The structure of the observed curves and the quantitative values were comparable to data obtained with the same method in a volunteer cohort (19) (Table 3).

Untreated solid clear cell tumors without vessel infiltration (Fig. 4) showed SI curves with a steep upslope and high signal changes in the first pass that were not significantly different from normal renal parenchyma. On the other hand, the tumors showed a more rapid washout. The plasma volume \( V_P \) of these tumors was not significantly different from normal kidneys, but \( F_P \) and \( V_E \) were significantly lower (Table 3). A subset of six tumors showed very small \( V_E \) values, suggesting a one-compartment architecture.

Two of the solid tumors (Fig. 5) showed a clear uptake of tracer, but no vascular peak, suggesting hypoperfusion. This is confirmed by the quantitative values (Table 3): \( F_E \) and \( V_E \) are in the upper range of the group of untreated solid tumors, but \( F_P \) relatively low, so that \( E \) was relatively high. These tumors showed infiltration of the inferior vena cava and the renal vein. Interestingly, the vascularity \( V_E \) was comparable to the other noninfiltrating tumors.

The solid papillary RCC presented with an atypical signal pattern. The signal-time curves showed an absence of the vascular peak suggesting hypoperfusion, similar to the vessel infiltrating tumors. The tumor showed a slow uptake of tracer with no obvious sign of tracer washout within the time window of the acquisition. Quantitative modeling produced a large extravascular compartment \( V_E \) (41.6 mL/100 mL) and small values for the perfusion parameters \( V_P \) (8.6 mL/100 mL) and \( F_P \) (15 mL/100 mL/min).

The solid portion of the two untreated mostly necrotic and liquefied tumors (papillary and clear cell) also showed distinct signal dynamics: no clear vascular peak, low signal enhancement and an essentially constant plateau with no washout. In these tumors, \( F_P \) and \( V_P \) were small, \( V_E \) was in the lower range of the group of untreated tumors, but \( F_E \) was relatively high (Table 1).

Figure 6 shows the results of one of the four antiangiogenically treated tumors measured both before and after therapy. Before therapy, the tumor has a signal intensity curve with similar characteristics as other nonvessel infiltrating tumors (Figs. 4b, 6a). After therapy, the curve shows a loss of the vascular peak and an overall reduction in signal changes (Fig. 6b) suggesting hypoperfusion. In five of six treated tumors (including the two patients without baseline DCE-MRI, because initial examination was focused on the liver), the quantitative parameters characterizing the plasma compartment \( V_P \) and \( F_P \) were significantly reduced compared with solid untreated tumors, but \( V_E \) and \( F_E \) were comparable (Table 3). However, in three of four tumor patients examined before and after neoadjuvant therapy a decrease of \( V_E \) and \( F_E \) could be detected \( V_E \) decreased (11.0 → 7.0 mL/100 mL; \( F_E \) 6.8 → 3.9 mL/100 mL/min). After therapy a significantly higher \( E \) \((P < 0.05) \) could be detected.

One antiangiogenically treated tumor (Fig. 7) did not show significant morphological changes or diameter reduction. Clinically, this patient was classified as nonresponder and died shortly after the second examination, because of rapid progressive metastatic disease. The signal dynamics remained unchanged with an early arterial peak and a consecutive washout. In this tumor a considerable decrease in \( F_E \) (217.8 →

### Table 2

| Patient | Histology         | pT | Size before therapy | Size after therapy | Necrosis/hemorrhage before therapy | Necrosis/hemorrhage after therapy | Time to death |
|---------|-------------------|----|--------------------|--------------------|-----------------------------------|-----------------------------------|---------------|
| 16      | Clear Cell        | 3b | 11                 | 11.6               | +                                 | ++                               | 14 months     |
| 17      | Sarcomatoid Clear Cell | 3b | 6.8                 | 5.8                 | –                                 | +                                 | 1 month       |
| 18      | Sarcomatoid Clear Cell | 2  | 8.2                 | 6.7                 | +                                 | ++                               | Survived      |
| 19      | Clear Cell        | 3a | 13                 | 12.2               | +                                 | ++                               | 8 months      |
| 20      | Clear Cell        | 2  | 8.4                 | 7.7                 | –                                 | ++                               | Survived      |
| 21      | Sarcomatoid Clear Cell | 3a | 10.5                | 10.0               | +                                 | ++                               | 5 months      |

*Grading of necrosis/ hemorrhage: – = 0%; + = 1-25%; ++ = 25-50%; +++ = 50-75%; ++++ = 75-100%.*
50.8 mL/100 mL/min) and $F_E$ (26.3 → 11.2 mL/100 mL/min) could be detected, but no substantial alteration of the other quantitative parameters.

**DISCUSSION**

**Methodology**

The basic methodology presented in this study was first proposed by Sourbron et al (19) for the assessment of kidney perfusion and filtration. The results presented in this study indicate that it is feasible for the evaluation of the primary tumor in RCC as well, provided the two-compartment filtration model designed for the renal cortex is replaced by the two-compartment exchange model appropriate for tumors (21).

A major problem in the characterization of tumors and the evaluation of therapy effects is that...
differences may occur in perfusion, permeability, or both. Flaherty et al (18) and Hahn et al (17) evaluate Sorafenib therapy in RCC-metastases by the use a Tofts model (20) for tracer kinetic analysis, which produces a parameter $K_{\text{trans}}$ with an ambiguous physical interpretation. In a flow-limited regimen, it should be interpreted as plasma flow $F_p$, in a permeability-limited regimen as extraction flow $F_E$. In reality an intermediary regimen may be more common, where $K_{\text{trans}}$ represents an unknown compromise between both effects. The two-compartment exchange model produces a separate value for $F_p$ and $F_E$, thus aiming to remove any possible ambiguity in the interpretation and providing a more complete tumor characterization (21,24). The large variability in both parameters suggests that permeability- and perfusion limited regimens both occur in RCC (Table 2), in which case $K_{\text{trans}}$ is unspecific. This may be particularly relevant for understanding and evaluating the effects of antiangiogenic therapy, which specifically targets the vasculature. The data presented in this study indicate that the main effect of antiangiogenic therapy is a severe reduction in the vascularity and perfusion of the tumors (measured by the parameters $V_P$ and $F_P$). This suggests that the observed reduction of $K_{\text{trans}}$ after therapy (18) essentially reflects a reduction in perfusion. On the other hand, our results indicate that untreated tumors are highly perfused, so that they may be in a permeability-limited regimen where baseline $K_{\text{trans}}$ values reflect permeability. This suggests that therapy induces a transition from a permeability-limited to a flow-limited regimen, which adds additional ambiguity in the interpretation of $K_{\text{trans}}$ in clinical praxis and may reduce its sensitivity to therapy effects. The price to pay for the separate quantification of perfusion and permeability with the four-

### Table 3

Mean Values of Quantitative Perfusion Analysis

|                      | $V_P$ ml/100ml | $F_P$ ml/100ml/min | $V_E$ ml/100ml | $F_E$ ml/100ml/min | $E$  |
|----------------------|---------------|--------------------|---------------|-------------------|-----|
| Normal kidneys (n = 15) | 15.3 ± 3.8   | 171.5 ± 58.2      | *            | 21.3 ± 7.5       | 12.4 ± 2.1 |
| Solid tumors untreated (n = 15) | 15.5 ± 8.1   | 82.0 ± 59.6       | 8.5 ± 10.8   | 2.9 ± 2.7        | 5.4 ± 20.0 |
| Vessel infiltrating tumors (n = 2) | 11.7 ± 5.0  | 6.0 ± 1.2         | 11.0 ± 0.3  | 4.1 ± 0.1        | 39.0 ± 16.3 |
| Necrotic tumors untreated (n = 2) | 0.2 ± 0.1    | 0.8 ± 0.2         | 2.7 ± 0.5   | 3.7 ± 2.2        | **      |
| Treated tumors (n = 6) | 4.0 ± 4.0     | 14.1 ± 6.7        | 9.7 ± 6.1   | 3.6 ± 1.5        | 27.9 ± 14.3 |

* $V_E$ not provided using the 2-compartment filtration model.
** Calculation of $E$ not sufficiently possible.

![Figure 3. Renal perfusion characteristics of a healthy patient (age 38 y). a: Coronal HASTE (TR 1000 ms/TE 81 ms/FA 180°) shows a normal kidney anatomy. The exemplary color-coded maps visualize the quantitative parameters $F_P$ and $F_E$. b: The normal kidneys exhibited a typical perfusion curve. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]]
Figure 4. Perfusion characteristics of a solitary clear cell RCC. a: Coronal HASTE: small renal mass with partial necrosis at the lower pole of the right kidney (arrow). Due to a different tilt angle, the left kidney is not completely covered. The plasma volume $V_P$ of these tumors was not significantly different from normal kidneys, but $F_P$ and $F_E$ were significantly lower. b: Solid clear cell RCC showed a typical perfusion curve with a steep upslope, distinct peak, and recirculation phase. There was only a small tracer accumulation suggesting a small extravascular compartment. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 5. Perfusion characteristics of a clear cell RCC infiltrating the renal vein and inferior vena cava. a: Coronal HASTE: renal mass with diffuse infiltration of the right kidney (arrow) and renal vein and inferior vena cava (empty arrow). Compared with RCC without compromise of the vascular structures the plasma compartment $V_P$ was small. The extravascular compartment remained small, however $F_E$ was rather high compared with $F_P$, so that $E$ was increased compared with solitary RCC. b: The perfusion curve shows loss of the early vascular peak and decreased perfusion. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
parameter exchange model, is the need for a high
temporal resolution, and the corresponding con-
straints on coverage and/or spatial resolution.

A possible error in interpretation arises when the
data are accurately described with a one-compartment
model. Three different physiological situations
are consistent with such an observation: either one of
the volumes $V_p$ or $V_E$ is negligible, or the permeability
$F_E$ is so high that concentration differences between
intra- and extravascular spaces are negligible (the
fast-exchange limit). In each of those three situations,
the system behaves like a single compartment. When
a two-compartment model is applied to such data,
each of the three possible solutions may be found,
depending on the choice of initial values, so that the
solution does not necessarily reflect the actual state
of the tissue. The data show some evidence that this
situation arises in some of the tumors. Within the
group of untreated solid tumors without vascular
infiltration, two subgroups could clearly be identified
based on their extravascular volume: “two-compartment tumors” with a large $V_E$ (14.1 ± 10.6) and “one-
compartment tumors” with small $V_E$ (0.2 ± 1.5). No
particular morphological or histological differences
could be determined between these tumors. Also the
two necrotic tumors fit this category. Because it is
unlikely that tumors have a negligible interstitial vol-
ume, the possibility arises that the tracer in the group
of one-compartment tumors is actually in the fast
exchange regimen, in which case the proposed inter-
pretation of the parameters is false. The methodology
in future studies might have to be refined by an
approach where data are analyzed both with a two-
compartment exchange model and a Tofts model,
combined with an automatic selection criterion (such
as the F-test) to decide which of both models is most
appropriate.

A problem specific to the evaluation of primary RCC
tumors is the effect of breathing motion in the data.
In this study, data acquisition was performed during
free breathing, but a retrospective triggering approach
was applied to remove the effect of breathing motion.
Compared with breathhold approaches, this allows for arbitrary long measurement times to accurately assess the excretion phase (23). Moreover, because the motion is removed on the postprocessing level, the analysis is not limited to areas where motion artifacts are small. To our knowledge, this is the first study to apply a motion compensation approach allowing for assessment of the primary tumor, whereas a previous studies on quantitative DCE-MRI in RCC (17,18) did not use motion compensation, so that the primary tumor could not be evaluated and the data analysis was effectively limited to metastases in locations with limited breathing motion (bone, superficial lymph nodes, abdominal masses). Finally, motion correction allows for a pixel-by-pixel analysis of the data, producing quantitative parametric maps that have proven useful to assess the heterogeneity of tumor hemodynamics, and support a semi-automatic definition of tumor ROIs. Compared with manual drawing of ROIs on the dynamic series (18), this may have the added advantage of reduced intra-observer differences and improved reproducibility. In addition, the arterial input ROI-size has been standardized to four pixels in this study, which is expected to remove a major part of the user-dependence observed in a previous study by Attenberger et al (23). As the full temporal resolution of the AIF is exploited, the peak arterial gadolinium concentration is well modeled. The individual AIF also compensates for individual weight differences.

The current protocol does not contain a precontrast T1-measurement to allow for an accurate quantification of tracer concentration. As a result, concentrations were approximated by relative signal enhancement, which leads to systematic errors when the signal is not in the linear regime, or when T1-values are variable, such as in heterogenous, necrotic tumors. A practical method to measure T1 in the kidney has been proposed recently (25). Future studies may therefore incorporate a more exact calculation of concentration, thus further improving the specificity of the technique. A second limitation of the current measurement setup is the limited coverage of large tumors with only three slices in a two-dimensional acquisition. Future studies may benefit from the use of a three-dimensional acquisition, allowing for full coverage of the kidneys. A separate issue in MRI signal analysis is the assumption of fast-water exchange (26). This may no longer be valid in tumors where high concentration differences exist between the separate compartments. When future studies confirm that these effects are significant, the signal model may have to be refined by allowing for limited water exchange.

Characterization

Compared with other tumors assessed with a two-compartment model, such as prostate- (22) or breast-cancer (21), RCC shows distinct hypervascularity, which is reflected by the typical early arterial peak, rapid washout and the very much higher values of the parameters modeling the vascular component (VP and Fp). This retrospectively provides a motivation for our assumption that the conventional one-compartment Tofts model should be refined for these data by adding an additional vascular compartment.

The perfusion parameters showed strong inter-individual variance in the group of untreated tumors. It is known that there is a wide range of variation in the degree of tumor vascularization in different RCC, for example, between papillary and clear cell variants, showing a greater overall enhancement and internal heterogeneity of clear cell RCC on CT and MR imaging (11,12). Surprisingly, in this study the number of
RCC with at least partial sarcomatoid differentiation (5/19) was much higher as known from the literature (27), although no preselection of patients was performed. A potential explanation is that most of the tumors referred for DCE-MRI were metastasized or locally advanced, which increases the probability for a sarcomatoid component.

The single solid papillary RCC included in this study showed distinctly different perfusion characteristics, reflecting the relative hypovascularity of papillary RCC relative to that of clear cell RCC. A recent study by Sun et al (11) was able to separate clear cell from papillary RCC by defining an enhancement ratio threshold; however, assessment of perfusion or permeability was not performed in this simplified, semi-quantitative DCE-MRI approach. Compared with clear cell RCC, the interstitial compartment was large, whereas the plasma compartment and the blood flow were relatively small.

The quantitative perfusion parameters also mirrored pathophysiological alteration of tumor hemodynamics. Two RCC showed compression of the renal artery and infiltration of the inferior vena cava, resulting in delayed venous drainage and thus prolonged retention of the contrast material. This is consistent with the values of the perfusion parameters, which resulted in a relatively low $F_P$ compared with $F_E$, indicating a high rate of tracer exchange between the plasma and the extravascular compartment. In untreated necrotic tumors, the plasma compartment was very small compared with the extravascular volume, which is consistent with the fact that necrotic regions mainly take up contrast agent through diffusion from neighboring regions.

Six antiangiogenically treated tumors were included in this study. In all tumors, intraindividual correlation of morphology before and after therapy was performed, showing decrease in tumor size in all but two cases. Antiangiogenic drugs are designed to affect the tumor vasculature, with the objective of reducing tumor blood supply. The main expected effect of successful therapy, a reduction of vascularity, is consistent with the observed reduction of the plasma compartment. Compared with the group of untreated tumors, the mean permeability $F_E$ remained relatively stable compared with the perfusion $F_P$. However an intra-individual comparison in the four patients examined with DCE-MRI before and after therapy detected a decrease in $F_E$ (and thus tumor permeability) of approximately 42%. One patient presented clinically as a nonresponder to therapy and died shortly after the first cycle. In this patient, we detected a substantial decrease in $F_P$ and $F_E$; however the values were comparable to untreated tumors and considerably higher than in the other treated tumors, so that DCE-MRI might potentially separate responders from nonresponders to angiogenic therapy. Similar effects were demonstrated DCE-CT perfusion studies, showing that antiangiogenic treatment leads to reduction of tumor blood flow and tumor blood volume (28,29). However, acquisition time of those studies was approximately 2 min, so that calculation of the permeability may be unreliable, as a minimum acquisition time of approximately 4 min may be required to quantify tracer uptake (30).

The small number of patients included in this study, and absence of long-term follow-up studies, clearly do not allow for definite conclusions regarding the potential of the technique for tumor characterization or evaluation of therapy effects. Nevertheless, the observations produce several working hypotheses to be verified in a larger study cohort including various histological types of RCC. An open question for future studies is the specific use of perfusion and permeability parameters for the evaluation of therapy. Because data were only acquired at one point in time after therapy, we cannot evaluate whether perfusion or permeability changes precede morphological changes, and which of both is most useful as an early marker for therapy response.

In conclusion, DCE-MRI with a general two-compartment exchange model compared with the well-known but unspecific parameter $K_{trans}$ allows assessment of renal tumor vascularity, perfusion, permeability, and size of the extravascular space. These parameters reflect pathophysiological alteration and thus may provide further insight in tumor biology. Data show a reduction in perfusion parameters in the antiangiogenically treated patients, suggesting that the methodology is feasible for the monitoring of such therapy. Further clinical evaluation with a larger patient group and a larger number of different histological phenotypes should be performed to appraise the diagnostic value of DCE-MRI, for example, to identify nonresponders to antiangiogenic therapy and identify patients suited for such a therapy.

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