Characterization of Small Renal Tumors With Magnetic Resonance Elastography
A Feasibility Study

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Small indeterminate renal tumors (SRTs), defined as solid enhancing renal lesions measuring up to 4 cm in diameter, pose a growing challenge to clinical practice.1–3 Renal cell carcinoma (RCC) accounts for most cases, but up to 20% of SRTs are benign.4 A recent estimate suggests that ~5600 benign renal tumors undergo surgical resection yearly in the United States.5 Image-guided biopsy is performed increasingly to confirm the diagnosis preoperatively.6 Despite providing excellent concordance with surgical histology, biopsy is invasive and nondiagnostic in up to 20% of cases.7 A reliable, noninvasive imaging strategy to distinguish benign from malignant SRT would be advantageous, mostly so in patients with multiple comorbidities, and potentially cost effective.

Anatomical and functional magnetic resonance imaging (MRI) parameters have shown potential individually to discriminate benign SRT from specific types of RCC,8–16 but their combined diagnostic accuracy has not been investigated in a prospective series to date. Oncocytoma and solid clear-cell RCC (ccRCC), respectively the most common benign and malignant indeterminate SRT, share structural and physiological traits (high water content, prominent stroma, and dense vascularity) that make their distinction by anatomical and functional MRI challenging in many cases.11,12 Yet their pathological gross appearance and microscopic structure clearly differ11,18; oncocytomas are typically homogenous lesions with frequent central scarring and absent necrosis; microscopically, they are composed of tight cellular nests surrounded by myxoid stroma. Clear-cell RCCs have a variegated appearance consisting of soft yellow material alternating with areas of hemorrhage, fibrosis, necrosis, and cystic degeneration; microscopically, they are composed of lipid- and glycoprotein-rich cells surrounded by an extensive capillary network. Oncocytomas have no recognized malignant transformation potential, and once diagnosed, conservative management is safe.19

Magnetic resonance elastography (MRE) is an emerging technique that evaluates soft tissue’s viscoelastic properties by measuring the shear waves produced by a vibrating mechanical transducer.20 It has been readily incorporated into clinical MRI protocols and has been used successfully in the assessment of hepatic fibrosis21,22 and for lesion characterization in the liver, central nervous system, and breast.23–26

We hypothesized that the viscoelastic shear properties of SRT measured by MRE would reflect the underlying tumor composition (eg, cellular density, extracellular collagen, hemorrhage, and necrosis) and architecture (eg, cellular and connective tissue distribution, vascular size, density, and permeability) and therefore differ between histopathological groups. In this study, we aimed to explore the feasibility and diagnostic potential of MRE, performed as part of a multiparametric MRI protocol, for characterizing indeterminate SRTs in patients scheduled for surgery.
MATERIALS AND METHODS

Participants
This prospective feasibility study was conducted between August 2015 and October 2016, following approval by the national research ethics committees; informed written consent was obtained from all subjects.

Twenty-one patients (15 men and 6 women) with a median age of 55 years (range, 25 to 72 years) and median body mass index of 27.0 (range, 19.0–29.4), were recruited from a tertiary-care urological clinic. Patients were potentially eligible if under consideration for surgical resection (partial or total nephrectomy) of an indeterminate solid renal mass measuring 5 cm or less in maximum diameter on cross-sectional imaging. Exclusion criteria were standard contraindications to contrast-enhanced MRI (eg, cardiac pacemaker, cochlear implant, significant renal impairment, ie, estimated glomerular filtration rate <50 mL/min or serum creatinine >180 μmol/L).

MRI Acquisition
Magnetic resonance imaging was performed on a 3.0 T system (Biograph mMR; Siemens Healthcare GmbH, Erlangen, Germany). The protocol included MRE, anatomical T1 and T2 weighted sequences, dynamic contrast-enhanced (DCE) MRI, and diffusion-weighted imaging. Patients lied supine (head first) in the scanner and fasted for 4 hours before imaging.

MRE Acquisition
Mechanical vibrations were generated at a frequency of 30 Hz and at 70% of the maximum power by a remote loudspeaker (Resoundant) and transmitted via compressed air to a disc-shaped passive transducer applied over the patient’s flank of interest (mid-axillary line, held in place by an elastic band). A frequency of 30 Hz was selected as a compromise between resolution and efficient wave penetration in the retroperitoneum. MRE was based upon a prototype 2-dimensional multislice interleaved gradient echo sequence synchronized with the transducer’s vibrations27; repetition time (TR), 11.11 milliseconds (3 shots with a vibration frequency of 30 Hz, corresponding to a period of 33.33 milliseconds); echo time (TE), 7.38 milliseconds; motion encoding gradient amplitude, 30 mT/m; generalized autocalibrating partial parallel acquisition parallel imaging acceleration factor, 2; field of view (FOV), 265 × 385 mm. Four acquisitions in consecutive expiratory breath holds of 3 minutes, resulting in a temporal resolution of 6.4 seconds. The dynamic acquisition was preceded by a T1 calibration sequence with the same parameters except a flip angle of 3°.

Diffusion-weighted imaging consisted of free-breathing single-shot echo-planar imaging in the axial plane with b values of 50, 500, and 800 mm²/s. Imaging parameters were as follows: TR, 6500 milliseconds; TE, 62 milliseconds; number of excitations, 5; parallel imaging acceleration factor, 2; FOV, 380 × 285 mm; pixel size, 3.7 × 3.0 × 4.0 mm. Anatomical and functional sequences were postprocessed and analyzed offline on a commercial platform (Modimodality Workplace, Siemens). All quantitative measurements were performed by a single radiologist (MRE observer 1), blinded to histopathology. Freehand ROIs were drawn on each slice displaying the lesion of interest; volumetric means were analyzed. T2 signal intensity (SI) ratio was calculated as the percentage ratio of tumor over renal cortex on the T2 HASTE sequence.8 Apparent diffusion coefficient (ADC) maps were generated by fitting a monoexponential function to all $b$ values.

Statistics
All statistical analyses were performed using IBM SPSS version 23.0 software. Continuous variables were regarded as nonnormally distributed and expressed as medians and interquartile range (IQR). Measurements were compared between the 2 main histological groups using the nonparametric Mann-Whitney U test. Mean interobserver MRE values were used in the analysis. $P < 0.05$ was considered indicative of significance.
| Case no. | Diameter, cm | $c$, m/s | $\alpha$, mm$^{-1}$ | $\text{iAUC}_{60}$, mmol/min$^{-1}$ | $K_{\text{trans}}$, min$^{-1}$ | $V_p$, mL/100 mL | $T_2$ SI Ratio, % | ADC, $10^{-6}$ × mm$^2$/s |
|----------|--------------|----------|----------------|-----------------------------|-----------------------------|----------------|-----------------|----------------|----------------|
| ONCO-1   | 4.2          | 0.83 ± 0.16 | 0.093 ± 0.033 | 72 ± 34                     | 0.31 ± 0.17                 | 0.99 ± 0.37   | 0.30 ± 0.14     | 93 ± 30     | 1949 ± 338     |
| ONCO-2   | 5.0          | 0.79 ± 0.16 | 0.082 ± 0.035 | 32 ± 16                     | 0.09 ± 0.05                 | 0.32 ± 0.16   | 0.28 ± 0.15     | 86 ± 27     | 1319 ± 260     |
| ONCO-3   | 5.0          | 0.77 ± 0.14 | 0.082 ± 0.048 | 80 ± 38                     | 0.41 ± 0.24                 | 1.15 ± 0.58   | 0.33 ± 0.17     | 89 ± 24     | 1348 ± 284     |
| ONCO-4   | 3.1          | 0.76 ± 0.11 | 0.087 ± 0.044 | 59 ± 22                     | 0.24 ± 0.10                 | 0.62 ± 0.23   | 0.39 ± 0.14     | 124 ± 40    | 1961 ± 315     |
| ONCO-5   | 4.5          | 0.71 ± 0.11 | 0.087 ± 0.042 | 51 ± 32                     | 0.20 ± 0.13                 | 0.66 ± 0.26   | 0.29 ± 0.16     | 93 ± 30     | 1363 ± 231     |
| **Median (IQR)** | **4.5 (4.2–5.0)** | **0.77 (0.76–0.79)** | **0.087 (0.082–0.087)** | **59 (51–72)** | **0.24 (0.20–0.31)** | **0.66 (0.62–0.99)** | **0.30 (0.29–0.33)** | **93 (89–93)** | **1363 (1348–1949)** |
| ccRCC-01 | 3.3          | 1.00 ± 0.28 | 0.060 ± 0.027 | 29 ± 20                     | 0.11 ± 0.09                 | 0.47 ± 0.30   | 0.24 ± 0.17     | 126 ± 40    | 1760 ± 326     |
| ccRCC-02 | 3.0          | 0.79 ± 0.12 | 0.072 ± 0.054 | 63 ± 29                     | 0.21 ± 0.10                 | 0.51 ± 0.15   | 0.40 ± 0.17     | 106 ± 23    | 1590 ± 184     |
| ccRCC-03 | 3.6          | 0.83 ± 0.16 | 0.070 ± 0.040 | 70 ± 43                     | 0.19 ± 0.20                 | 0.41 ± 0.36   | 0.33 ± 0.30     | 101 ± 34    | 1695 ± 365     |
| ccRCC-04 | 2.8          | 0.94 ± 0.19 | 0.066 ± 0.035 | 55 ± 34                     | 0.22 ± 0.17                 | 0.74 ± 0.46   | 0.29 ± 0.17     | 102 ± 31    | 1722 ± 320     |
| ccRCC-05 | 2.5          | 0.84 ± 0.23 | 0.083 ± 0.045 | 46 ± 32                     | 0.17 ± 0.13                 | 0.33 ± 0.23   | 0.45 ± 0.26     | 141 ± 44    | 2118 ± 394     |
| ccRCC-06 | 3.0          | 0.86 ± 0.18 | 0.085 ± 0.030 | 23 ± 22                     | 0.09 ± 0.09                 | 0.63 ± 1.42   | 0.18 ± 0.17     | 121 ± 37    | 1929 ± 303     |
| ccRCC-07 | 2.7          | —           | —               | 62 ± 44                     | 0.24 ± 0.18                 | 0.62 ± 0.38   | 0.33 ± 0.23     | 94 ± 32     | 1433 ± 255     |
| ccRCC-08 | 3.5          | 1.11 ± 0.30 | 0.052 ± 0.032 | 27 ± 21                     | 0.11 ± 0.09                 | 0.30 ± 0.24   | 0.38 ± 0.27     | 152 ± 47    | 2483 ± 424     |
| ccRCC-09 | 4.2          | 0.92 ± 0.24 | 0.046 ± 0.033 | 61 ± 31                     | 0.27 ± 0.16                 | 0.71 ± 0.28   | 0.37 ± 0.20     | 124 ± 45    | 1512 ± 460     |
| ccRCC-10 | 4.0          | 0.93 ± 0.19 | 0.032 ± 0.022 | 47 ± 43                     | 0.19 ± 0.18                 | 0.68 ± 0.56   | 0.26 ± 0.24     | 104 ± 35    | 1795 ± 295     |
| ccRCC-11 | 3.4          | 1.00 ± 0.23 | 0.075 ± 0.050 | 29 ± 21                     | 0.11 ± 0.09                 | 0.38 ± 0.38   | 0.30 ± 0.19     | 120 ± 54    | 1984 ± 348     |
| ccRCC-12 | 2.2          | 0.80 ± 0.14 | 0.056 ± 0.028 | 51 ± 19                     | 0.15 ± 0.07                 | 0.30 ± 0.15   | 0.49 ± 0.22     | 134 ± 39    | 1612 ± 155     |
| **Median (IQR)** | **3.2 (2.8–3.5)** | **0.92 (0.84–0.97)** | **0.066 (0.054–0.074)** | **48 (29–57)** | **0.18 (0.11–0.21)** | **0.49 (0.36–0.64)** | **0.33 (0.28–0.39)** | **120 (103–128)** | **1741 (1606–1943)** |
| Papillary Renal Cell Carcinoma | | | | | | | | | |
| papRCC-01 | 3.7          | 0.77 ± 0.10 | 0.062 ± 0.029 | 30 ± 20                     | 0.11 ± 0.10                 | 0.68 ± 0.40   | 0.17 ± 0.14     | 74 ± 17     | 839 ± 218      |
| papRCC-02 | 4.1          | —           | —               | 15 ± 19                     | 0.06 ± 0.04                 | 0.50 ± 0.55   | 0.16 ± 0.10     | 55 ± 35     | 959 ± 602      |
| Metanephric Adenoma | | | | | | | | | |
| MA-01    | 5.0          | 0.78 ± 0.15 | 0.079 ± 0.033 | 19 ± 12                     | 0.11 ± 0.07                 | 0.17 ± 0.20   | 0.37 ± 0.21     | 58 ± 14     | 1222 ± 339     |

Tumor diameters as measured at surgical histopathology. Mean values ± standard deviation. $P$ values for between-group comparisons were determined with the Mann-Whitney $U$ test.

MR indicates magnetic resonance; SI, signal intensity; ADC, apparent diffusion coefficient; IQR, interquartile range; —, missing value.
of a significant difference. Interobserver agreement was assessed using Bland-Altman statistics and intraclass correlation coefficients. Magnetic resonance elastography within-subject variability in healthy renal parenchyma was expressed in terms of mean differences and coefficients of variance (CVs). Missing data were omitted from the analysis.

RESULTS

One patient did not complete imaging because of claustrophobia, leaving 20 complete imaging datasets including MRE. Surgical histopathology became available for 19 patients and revealed 4 renal oncocytomas, 12 ccRCC (1, Fuhrman grade 3; 8, grade 2; 3, grade 1), 2 papillary RCC, and 1 metanephric adenoma. One further case of renal oncocytoma was diagnosed from image-guided biopsy and surgery was deferred. Tumor diameters ranged between 2.2 and 5.0 cm. All imaging sessions were completed in less than 60 minutes.

MRE of Tumors

Two tumor MRE datasets were excluded for insufficient quality, secondary to poor patient compliance with breath hold instructions and
consequent high data nonlinearity (>50%), leaving a cohort of 11 ccRCCs and 5 oncocytomas for statistical analysis.

Shear wave velocity $c$ was significantly lower in oncocytomas (median, 0.77 m/s; IQR, 0.76–0.79) than in ccRCCs (median, 0.92 m/s; IQR, 0.84–0.97) ($P = 0.007$). Shear wave attenuation $\alpha$ was significantly higher in oncocytomas (median, 0.087 mm$^{-1}$; IQR, 0.082–0.087) than in ccRCCs (median, 0.066 mm$^{-1}$; IQR, 0.054–0.074) ($P = 0.008$). Complete results, including case-by-case mean values and standard deviations, are reported in Table 1. Pictorial examples are shown in Figure 1. Oncocytomas displayed a relatively narrow range of values ($c$ range, 0.71–0.83 m/s; $\alpha$ range, 0.082–0.093 mm$^{-1}$), corresponding to data point clustering in a bidimensional scatter plot (Fig. 2). Clear cell RCC had wider ranges ($c$ range, 0.79–1.11 m/s; $\alpha$ range, 0.046–0.083 mm$^{-1}$), resulting in a broader data point scatter.

The only papillary RCC imaged with sufficient data quality showed relatively low $c$ (0.77 m/s, coinciding with the median value of oncocytomas) and low $\alpha$ (0.064 mm$^{-1}$, close to the median of ccRCC). Metanephric adenoma displayed relatively low $c$ (0.78 m/s) and intermediate $\alpha$ (0.079 mm$^{-1}$).

MRE Interobserver Agreement

Mean ROI size was 226 ± 109 pixels for observer 1 and 196 ± 102 pixels for observer 2.

Mean differences in tumors were 0.002 m/s [$c$] and −0.0005 mm$^{-1}$ [$\alpha$]. Bland-Altman limits of agreement were the mean differences as previously ±0.055 m/s [$c$] and ±0.0077 mm$^{-1}$ [$\alpha$], respectively (Fig. 3). Intraclass correlation coefficients (95% confidence intervals) were 0.982 (0.953–0.993) [$c$] and 0.984 (0.957–0.994) [$\alpha$], indicating excellent agreement.

MRE of Normal Kidney

A total of 31 MRE measurements of acceptable quality were performed in normal portions of the tumor-containing kidneys. Mean shear velocity $c$ in the renal parenchyma was 0.89 ± 0.10 m/s; mean shear attenuation $\alpha$ was 0.072 ± 0.012 mm$^{-1}$.

Two separate measurements in different portions of the same kidney were acquired in a subset of 10 patients. Mean within-subject differences were 0.10 ± 0.05 m/s for $c$ and 0.014 ± 0.010 mm$^{-1}$ for $\alpha$, corresponding to CV of 7.81% ± 4.61% and 14.24% ± 10.72%, respectively.

Anatomical and Functional MRI of Tumors

Tumor parametric values are reported in Table 1. Oncocytomas had significantly lower T2 SI ratio (median, 93%; IQR, 89%-93%) than ccRCC (median, 120%; IQR, 103%-128%) ($P = 0.020$). No statistically significant difference between the 2 histological groups was observed among functional MRI parameters. Oncocytomas appeared on average more vascular on DCE MRI, with higher iAUC$_{60}$ (median, 59 mmol; $P = 0.100$), $K_{trans}$ (median, 0.24 min$^{-1}$; $P = 0.126$), and $K_{ep}$ (median, 0.66 min$^{-1}$; $P = 0.193$) and lower $\alpha_{v}$ (median, 0.30 mL/100 ml; $P = 0.692$). Apparent diffusion coefficients varied considerably within both groups, being on average lower in oncocytomas (median, 1363 ± 10$^{-6}$ mm$^{2}$/s) ($P = 0.193$).

Both papillary RCCs displayed markedly restricted diffusion (ADC, 839 and 959 ± 10$^{-6}$ mm$^{2}$/s) and low T2 SI ratios (74% and 55%), in line with the existing literature.$^{2,3}$ The metanephric adenoma showed relatively low T2 SI ratio (58%) and contrast enhancement (iAUC$_{60}$, 19 mmol). Only partial data point clustering was obtained by plotting T2 SI ratio against ADC (Fig. 2B). No clustering was observed by plotting DCE magnetic resonance (MR) $K_{trans}$ against $\alpha_{v}$ (Fig. 2C).
Among qualitative anatomical tumor features, a T2 pseudocapsule was present in 2 of 5 oncocytomas and 10 of 12 ccRCCs; central T2 hyperintensity was observed in 3 oncocytomas and 1 ccRCC; and signal drop on opposed-phase chemical shift MRI in no oncocytoma and 7 ccRCCs.

**DISCUSSION**

Our study shows that MRE is feasible, as part of a multiparametric MR protocol, for the characterization of small indeterminate renal tumors and represents a promising technique for distinguishing benign oncocytoma from malignant clear cell carcinoma. The strongest imaging discriminators between oncocytoma and ccRCC in this initial prospective cohort of 20 patients were MRE shear velocity $c$ and shear attenuation $\alpha$.

Identifying renal oncocytoma among indeterminate SRT is problematic based on imaging alone, even using multiparametric MR, as highlighted by current literature. Among anatomical MRI parameters, T2 SI has been shown to be higher in ccRCC than in oncocytoma and chromophobe RCC, but the overlap is substantial. The T2 SI ratio was in fact the third best discriminator between oncocytoma and ccRCC in our study. The presence of a central area of T2 signal hyperintensity, compatible with necrosis or fibrosis, can be observed in both oncocytoma and RCC. Chemical shift MR, combined with delayed contrast enhanced imaging, has been found to have a high negative predictive value for oncocytoma (97%) by revealing the typical absence of fat and the presence of enhancing central fibrosis; these findings, however, have yet to be validated prospectively. A T2 hypointense pseudocapsule, commonly observed in SRT, is also nonspecific.

Diffusion and contrast enhancement characteristics can discriminate between types of RCC but are known to overlap between oncocytoma and ccRCC. Chemical shift MR, combined with delayed contrast enhanced imaging, has been found to have a high negative predictive value for oncocytoma (97%) by revealing the typical absence of fat and the presence of enhancing central fibrosis; these findings, however, have yet to be validated prospectively. A T2 hypointense pseudocapsule, commonly observed in SRT, is also nonspecific.

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FIGURE 4. Type 1, 4, and 1 cm papillary RCC in a 66-year-old man: axial MRI sections. Anatomical T2 HASTE (left), MRE gradient-echo magnitude image (middle), and MRE non-linearity parametric map (right). Intra-tumoral hemorrhage, confirmed at histology, corresponds to low signal intensity in A and B. MRE phase signal shows elevated nonlinearity within the tumor (~80%) compared to adjacent renal parenchyma (~35%). Figure 4 can be viewed online in color at www.investigativeradiology.com.
14.24% ± 10.72% for α. Similarly, Rouvière et al. found a mean shear wave velocity variation of 6% (range, 2%–16%) between 2 independent measurements in the kidney of young healthy adults at 45 Hz, also using a gradient echo sequence at 1.5 T. Although not directly comparable, a recent meta-analysis on MRE repeatability in the liver identified a measured change in hepatic stiffness of 22% or greater as a reliable true change (95% confidence).48

Despite our promising results, our study does have limitations: the small study cohort reflects its exploratory nature and does not allow us to draw definitive conclusions on the diagnostic accuracy of MRI parameters. Prospective recruitment of consecutive patients from a single tertiary clinic meant that only the most common SRT histologies were captured. The decision to include tumors 5 cm or less in diameter (contrasting with the conventional definition of small renal mass, ≤5 cm) was made to facilitate patient recruitment. Less common histologies such as chromophobe RCC, often morphologically indistinguishable from oncocytoma, and fat poor angiomyolipoma were not part of our prospective cohort.

In conclusion, MRE is feasible and practicable for the characterization of small indeterminate renal tumors as part of a multiparametric MR protocol. This feasibility study highlights the diagnostic potential of MRE for distinguishing renal oncocytoma from ccRCC, strengthening the case for confirmation of these results in a powered diagnostic accuracy study.

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