Characterization of Renal Masses in MR Reporting: Pathologic Correlation as Part of a Performance Quality Review at an Academic Center.

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Scholarly Report Title: Characterization of renal masses in MR reporting: Pathologic correlation as part of a performance quality review at an academic center.

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Abstract:

Purpose:

The aim of this study was to evaluate the accuracy of MR diagnosis of renal masses in clinical practice during a 7-year period through retrospective review of MRI reports with pathologic correlation as gold standard.

Materials and Methods:

A retrospective review was performed of MRI reports in patients who underwent contrast-enhanced renal mass protocol MR examinations prior to biopsy/surgical resection from January 2008 to May 2015. 217 renal masses were included in the study group. The leading diagnosis, differential diagnoses, and imaging descriptors from clinical MR reports were compared with pathologic diagnosis for each lesion.

Results:

Pathologic diagnoses included clear-cell renal cell carcinoma (ccRCC)(n=88), papillary RCC (pRCC)(n=17), chromophobe RCC (chrRCC)(n=36), AML (n=18), oncocytoma (n=35), urothelial carcinoma (n=5), atypical RCC (n=10), atypical oncocytic neoplasm (n=6) and benign/other lesions (n=2). The sensitivity/specificity of the primary MRI differential diagnosis for malignancy was 95.1%/23.6%. The sensitivity/specificity of a primary MRI diagnosis of ccRCC was 92.3%/60.3%, for pRCC 75.0%/89.3%, and for AML 44.4/98.3%. The most common MR misdiagnoses included chrRCC misdiagnosed as pRCC/ccRCC and oncocytoma misdiagnosed as ccRCC.

Conclusion:

MR is highly sensitive for the diagnosis of malignancy. Diagnostic performance is lower for challenging differential diagnoses, including ccRCC versus oncocytoma, and for the diagnosis of oncocytic neoplasms.

Student's role:

This was a collaborative project involving Dr. Maryellen Sun and Dr. Leo Tsai from the Department of Radiology, Dr. Eric Yee from the Department of Pathology and myself.
The conception of the study design came from Dr. Sun and Dr. Tsai. Dr. Yee identified the initial cohort of patients with renal mass during the study period using text search in the Pathology Department database. By going through the pathology and radiology reports, I screened the patients for those meeting the study inclusion criteria and recorded the following information: pathologic diagnosis, leading MR diagnosis, differential diagnoses, whether the leading diagnosis or all differential diagnoses were malignant, description of signal intensity on T1 and T2 weighted images (hyper-/iso-/hypo-intense/heterogeneously intense in comparison with renal cortex), presence or absence of enhancement, description of enhancement pattern (hyper-/iso-/hypo-enhancing or heterogeneously enhancing), presence or absence of the following features—segmental enhancement inversion, intravoxel fat, bulk fat, diffusion restriction, cystic features, concurrent adrenal masses, hemorrhage and MR evidence of local spread of tumor.
In terms of pathologic analysis, Dr. Yee classified atypical lesions and reanalyzed pathologic specimens of angiomyolipomas to designate these lesions further as fat poor AML or non-fat poor AML.
With help and guidance from Dr. Tsai, I perform the statistical analysis as reported in the manuscript.
I drafted the manuscript, barring the section on MRI technique that was written by Dr. Tsai, which underwent extensive revision by both Dr. Sun and Dr. Tsai.

Abbreviation:

ccRCC: clear-cell renal cell carcinoma

pRCC: papillary renal cell carcinoma

chrRCC: chromophobe renal cell carcinoma

AML: angiomyolipoma

MRI: magnetic resonance imaging

SI: signal intensity

WI: weighted image

DWI: diffusion weighted imaging

GRE: gradient recall echo

HOCT: hybrid oncocytoma and chromophobe tumor

PPV: positive predictive value

NPV: negative predictive value

Submitted manuscript:

Title:

Characterization of renal masses in MR reporting: Pathologic correlation as part of a performance quality review at an academic center.

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Abstract:

Rationale and Objectives:
Data is lacking regarding the performance of MRI in clinical practice for diagnosis of renal mass subtype. The aim of this study was to evaluate the accuracy of MR diagnosis of renal masses in clinical practice during a 7-year period through retrospective review of MRI reports with pathologic correlation as gold standard.

Materials and Methods:
A retrospective review was performed of MRI reports in patients who underwent contrast-enhanced renal mass protocol MR examinations prior to biopsy/surgical resection from January 2008 to May 2015. 217 renal masses were included in the study group. The leading diagnosis, differential diagnoses, and imaging descriptors from clinical MR reports were compared with pathologic diagnosis for each lesion.

Results:
Pathologic diagnoses included clear-cell renal cell carcinoma (ccRCC)(n=88), papillary RCC (pRCC)(n=17), chromophobe RCC (chrRCC)(n=36), AML (n=18), oncocytoma (n=35), urothelial carcinoma (n=5), atypical RCC (n=10), atypical oncocytic neoplasm (n=6) and benign/other lesions (n=2). The sensitivity/specificity of the primary MRI differential diagnosis for malignancy was 95.1%/23.6%. The sensitivity/specificity of a primary MRI diagnosis of ccRCC was 92.3%/60.3%, for pRCC 75.0%/89.3%, and for AML 44.4/98.3%. The most common MR misdiagnoses included chrRCC misdiagnosed as pRCC/ccRCC and oncocytoma misdiagnosed as ccRCC. Clear cell RCC and oncocytomas had similar T2 and enhancement characteristics, but intravoxel fat was present in 42% of ccRCCs and in no oncocytomas.

Conclusion:
MR is highly sensitive for the diagnosis of malignancy. Diagnostic performance is lower for challenging differential diagnoses, including ccRCC versus oncocytoma, and for the diagnosis of oncocytic neoplasms.

Keywords: Renal Cell Carcinoma, Magnetic Resonance Imaging, characterization, Sensitivity and specificity

Introduction

With the advancement and increased utilization of cross-sectional imaging, the incidence and prevalence of renal masses has been rising due to increased detection in asymptomatic

patients. [1] More than 50% of renal cell carcinomas are detected at imaging performed for other indications. [2]

The increasing incidence of renal masses presents a management dilemma, since some incidentally detected small (<4cm) renal masses are benign or have low malignant potential,[3] and consequently may not warrant surgical intervention. Furthermore, renal cell carcinoma is comprised of multiple distinct subtypes with varying histopathology, molecular pathogenetic and prognostic features. The three most common subtypes of renal cell carcinoma include ccRCC (65-70% of RCC and associated with worst prognosis of the major RCC subtypes), pRCC (10-15% of RCC, with lower risk of visceral metastases for stage matched cohorts), and chrRCC (6-11%, with less likelihood of metastasis and better prognosis in the setting of metastatic disease than either of the most common subtypes).[4,5,6] Further subtypes of renal cell carcinoma exist with varying histopathology and clinical features. Due to such heterogeneity, management strategies for both metastatic and localized disease can vary widely, and thus preoperative histopathologic diagnosis of renal masses is important for effective clinical and surgical decision-making.

Needle biopsy is a minimally-invasive method for preoperative renal tumor diagnosis but is subject to sampling error and can be nondiagnostic in 2.5-22% of cases [7,8,9]. Also, some lesions, such as angiomyolipomas, are difficult to identify in biopsies due to nuclear atypia and pleomorphisms.[10] Finally, biopsy is an invasive procedure with accompanying risks. Magnetic resonance imaging (MRI) presents advantages for potential noninvasive diagnosis of renal masses due to its noninvasive nature and reduction of sampling effect through assessment of the features of the entire lesion. In recent years, various MR features of common subtypes of renal masses have been described, including signal intensity (SI) on T1 and T2 weighted image (WI), presence or absence of intravoxel fat, enhancement, presence or absence of restricted diffusion at diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC) value, as well as morphologic features. These findings can contribute to the ability of MR to allow characterization of renal masses noninvasively. While many investigations center upon specific features of renal mass subtype diagnosis, the aggregate performance of MRI in clinical practice for the

preoperative diagnosis of unknown renal masses is not well established. The aim of this study is to assess the accuracy of clinical interpretations of multiparametric MRI from an academic referral center, for preoperative diagnosis of renal masses which ultimately underwent biopsy or resection, using histopathology as reference standard.

Methods

Patient Selection

This retrospective, HIPAA-compliant study performed at a single site was approved by the institutional research board and the need for informed consent was waived. The study group included patients who underwent MRI for evaluation of a renal mass with subsequent pathologic diagnosis between January 2008 and May 2015. Patients were identified through search of pathology database. Patients with known pathologic diagnosis of the renal mass at the time of MRI, and patients in whom a renal mass was an incidental finding on an MR examination performed for other purposes utilizing an MR protocol not optimized for renal mass diagnosis, were excluded.

MRI Technique

MRI examinations were performed at 1.5 T (Symphony or Espree, Siemens Medical Solutions, Iselin, NJ, or Signa Excite TwinSpeed, GE Medical Systems, Waukesha, WI) or at 3.0 T (Signa Excite 3.0T, GE Medical Systems, Waukesha, WI). Two protocols were included in the study, both including focused evaluation of the kidneys with or without additional coverage of the ureters, bladder and pelvis. The minimum set of sequences for a complete evaluation of the kidneys are summarized in Appendix A. Between 2008 and 2015, additional sequences were added to MR protocols for renal imaging. Diffusion-weighted imaging was incorporated in 2012 in both renal mass and urogram protocols on all imagers, and an axial T2-weighted fast spin echo sequence was added in 2012 for only the renal mass protocol, with imaging parameters included in Appendix A.

Intravenous contrast agent consisted of either gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ), gadobutrol (Gadavist; Bayer AG, Leverkusen, Germany), or gadoteridol (ProHance, Bracco Diagnostics, Monroe Township, NJ). Gadobutrol replaced gadopentetate dimeglumine as the default contrast agent in 2013. Gadoteridol was used for patients with renal insufficiency, using an estimated glomerular filtration rate (eGFR) cutoff of 30 mL/min/1.73m^2(or 35 mL/min/1.73m^2 on POC). The contrast bolus was timed to the corticomedullary phase using a 2 cc test bolus administered during a timing run prior to the post-contrast series. The nephrographic phase was initiated 20 seconds after the corticomedullary phase. A third venous phase, 20 seconds after the nephrographic phase, was added to both the renal mass and urogram protocols on all imagers beginning in 2009. Contrast was administered as a 0.1 mmol/kg bolus at a rate of 2 mL/sec and flushed with 20 mL of saline solution at the same rate.

MRI Interpretation and Morphological Analysis

A retrospective review of clinical MR reports was performed. Reinterpretation of MR examinations was not performed for study purposes. The MR reports and interpretation evaluated in the study were generated as part of clinical practice by a group of 9 abdominal radiologists with fellowship training in abdominal imaging and MRI. Years of post fellowship experience in abdominal imaging/MRI for the radiologists whose reports were included in the study ranged from a minimum of 1 year to a maximum of 38 years during the study period. Retrospective review of clinical MRI reports was performed by a single individual in order to ensure consistency in the interpretation of the reports. Each clinical MR report was evaluated by a single investigator (HX, MS-IV) and the following data recorded: Description of signal intensity on T1 and T2 weighted images (hyper-/iso-/hypo-intense/heterogeneously intense in comparison with renal cortex), presence or absence of enhancement, description of enhancement pattern (hyper-/iso-/hypo-enhancing or heterogeneously enhancing), presence or absence of the following features: segmental enhancement inversion, intravoxel fat, bulk fat, diffusion restriction, cystic features, concurrent adrenal masses, hemorrhage and MR evidence of local spread of tumor. At the study institution, intravoxel fat is reported when a loss of signal intensity at

opposed phase images is observed in comparison with in phase images at dual echo T1W gradient recall echo (GRE) imaging, with confirmation at 3.0 T requiring use of acceleration with auto-calibrating reconstruction for cartesian sampling (ARC). Bulk fat is diagnosed when boundary, or India ink artifact, is observed at opposed phase T1W GRE images and/or when chemically selective or other fat suppression methods produce loss of signal in a portion of the lesion. Hemorrhage is diagnosed for areas of high signal intensity at T1WI without enhancement, with or without evidence of hemosiderin as seen at in phase and opposed phase gradient echo imaging.

MR diagnosis and differential diagnosis:

Diagnoses and differential diagnostic considerations were recorded from MR reports. The primary differential diagnostic consideration was designated as follows: syntax in the report indicating a favored diagnosis (e.g. phrases such as "is felt most likely", "is favored", "is consistent with, with other entities felt less likely") was used to establish a primary differential diagnosis, if applicable. If such syntax clearly indicating the preferred diagnosis was not used, the diagnostic consideration occurring first in the Impression was recorded as the primary diagnostic consideration. Secondary and subsequent differential diagnostic considerations were numbered according to order of occurrence in the report, unless syntax existed in the report to indicate least likely diagnostic consideration (e.g. "is felt unlikely", "is unlikely", "is doubtful").

MR diagnosis of malignancy or benignity:

MR reports in which any differential diagnosis included malignancy were designated as "MR malignant" and MR reports in which no malignant differential diagnosis was provided, or in which any malignant diagnosis was mentioned with syntax indicating unlikeliness ("is unlikely", "is doubtful") were designated "MR benign."

Pathologic Analysis:

Pathologic diagnoses were obtained from clinical pathology reports. Lesions were placed into 9 pathologic diagnosis categories as follows: ccRCC, pRCC, chrRCC, oncocytoma, AML, atypical RCC (including unclassified RCC, other renal cell carcinoma subtypes including

Xp11 translocation RCC, and/or mixed histopathology tumors including hybrid oncocytoma and chromophobe tumor (HOCT)), atypical oncocytic neoplasm (including oncocytic neoplasm with atypia, unclassified oncocytic neoplasm, and oncocytic neoplasm with papillary features); urothelial carcinoma, and benign/other lesions (including mesenchymal tumor and renal medullary fibroma). Additional reanalysis of pathology specimens was performed for angiomyolipomas by a single pathologist (EY, 2 years experience) to designate these lesions further as fat poor AML or non-fat poor AML; lesions with <25% fat according to histopathology were considered as fat poor AML.[11] For purposes of assessment of malignancy or benignity, the following groups were considered as malignant: ccRCC, pRCC, chrRCC, atypical RCC, atypical oncocytic neoplasm, urothelial carcinoma; and the following groups were considered as benign: oncocytoma, AML, and benign/other. Atypical oncocytic neoplasms were grouped with malignant lesions due to uncertainty of their malignant potential.

Statistical Analysis

The overall MR diagnosis of malignancy or benignity was compared with pathologic diagnosis of malignancy or benignity.

For MR reports in which a differential diagnosis was provided, the primary MR differential diagnosis was compared with the pathologic diagnosis.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for MR diagnoses of malignancy or benignity and for each differential diagnostic consideration. The association between tissue diagnosis groups and differential diagnosis/lesion characteristics were tested using chi-square and Fisher exact test. A Pearson's chi-squared test was used to evaluate the correlation between patterns of MR signal intensity and individual tumor subtypes. All *p*-values were two-sided, with *p*-value <0.05 considered as statistically significant. The statistical analysis was performed using JMP Pro (SAS Institute). The diagnostic performance was measured in terms of sensitivity and specificity based on the top differential as well as all differential diagnoses listed in the MRI report.

The number of cases in which signal intensity at T1WI and T2WI and enhancement was reported, were recorded. Calculations of T1 and T2 SI and enhancement were performed as proportions of only cases in which these were reported. Other findings were calculated as a proportion of all lesions.

Results

Patients and Histopathologic Diagnoses:

There were 217 renal lesions in 210 patients (130 males, 80 females, mean age 60 years (range, 18-87 years)) that met inclusion criteria during the 7-year study period. The 217 lesions included 88 (41%) clear cell RCC; 36 (17%) chromophobe RCC; 35 (16%) oncocytoma; 17 (8%) papillary RCC; 18 (8%) AML (including 13 fat poor AML, 2 typical, or non-fat poor AML, and 3 AML which could not be further characterized due to unavailability of sufficient residual tissue to permit accurate diagnosis), 10 (5%) atypical RCC (including 3 HOCT, 1 lesion consistent with chromophobe RCC and oncocytoma, 1 papillary RCC or unclassified RCC with papillary features, 1 unclassified RCC, 1 RCC with papillary and oncocytic features, 1 Xp11 translocation RCC, 1 tubulocystic carcinoma, and 1 unclassified RCC with predominantly papillary growth and focal clear cell features), 6 (3%) atypical oncocytic neoplasm (2 oncocytic neoplasm with atypia, 2 unclassified oncocytic neoplasm, 1 oncocytic neoplasm with papillary features and 1 oncocytoma with tubulo-papillary growth), 2 (1%) benign or indeterminate lesions (including 1 medullary fibroma and 1 mesenchymal tumor), and 5 (2%) urothelial carcinoma. Pathological specimens were obtained by biopsy for 26 (12%) lesions, by partial nephrectomy for 121 (56%) lesions and by total nephrectomy for 70 (32%) lesions. The methods of specimen acquisition by histopathology are shown in Appendix B.

Size of renal masses was reported for 214/217 lesions in the cohort. The mean maximum reported diameter was 4.5 cm (range, 0.7-14.1cm).

Diagnostic Performance of MR for malignancy vs. benignity--malignancy as first differential diagnosis:

MR indicated a malignant entity as the most likely differential diagnosis in 196 lesions and likely benign diagnosis in 21 lesions. 154/196 (78.6%) of lesions with malignancy provided as first differential diagnosis on the MRI report were proven to be malignant on pathology. 8/21 lesions that were reported as likely benign at MR proved to represent malignancy, including chrRCC (n=7) and pRCC (n=1). The sensitivity and specificity of an MR report of malignancy as first differential diagnosis consideration were 95.1% and 23.6%, respectively. The PPV of MR primary differential diagnosis of malignancy was 78.6% and NPV, 61.9%.

Diagnostic Performance of MR for malignancy vs. benignity--malignancy as any differential diagnosis:
MR indicated one or more malignant diagnoses in the differential diagnosis list ("MR Malignant") in 210 lesions, and included only benign differential diagnostic considerations ("MR benign") for 7 lesions. 160/210 (76.2%) of MR-malignant reports were proven to be malignant on pathology. The sensitivity and specificity of an MR diagnosis of malignancy as any differential consideration were 98.8% and 9.1%, respectively. 2/7 lesions reported as likely benign at MR ("MR-benign") ultimately proved to represent malignancy, including chrRCC (n=1) and pRCC (n=1). The MR performance for predicting malignancy vs. benignity is summarized on Table 1. The MR performance with respect to specific histopathology is detailed in Appendix C.

Performance of MR differential diagnosis for histopathologic subtype:
A specific differential diagnosis indicating likely tumor histopathology was provided in MR reports in 194/217 (89.4%) cases. In 23/217 (10.6%) cases, MR reports specified "likely renal cell carcinoma" without providing a more specific histopathologic differential diagnosis.

In 3/217 reports, lesions were reported as "renal mass" without further specification of a presumptive histopathologic diagnosis. These included ccRCC (n=2) and chrRCC (n=1). In each of these cases, a diagnosis of likely malignancy had been established at prior imaging,

though the histopathologic diagnosis was not known, and MR was performed for purposes of treatment planning.

Table 2 displays the primary differential diagnosis listed in the MRI report with respect to pathologic diagnosis.

Sensitivity and specificity for each of the RCC subtype differential diagnoses when provided as the favored differential diagnosis, were as follows: ccRCC, 92%/60%; pRCC, 75%/89%; chrRCC, 10%/94%; oncocytoma, 10%/96%; AML, 44%/98%; atypical RCC, 11%/98%; urothelial carcinoma, 100%/99%. For the calculation of sensitivity and specificity, cystic RCCs were grouped with ccRCC.

Lesions proving to represent chromophobe carcinomas were most commonly diagnosed prospectively as papillary RCCs at MRI: of 36 chromophobe RCCs, 12 were reported as papillary RCCs and 6 as ccRCCs. Lesions ultimately found to represent oncocytomas were most commonly reported prospectively as likely ccRCCs at MRI: of 35 oncocytomas, 25 were reported as ccRCC. The urothelial carcinomas included in this study were those found in the renal pelvis.

MR diagnostic failures:
There were 78 cases in which the pathologic diagnosis was not represented in the MR differential diagnosis. These included: 28 oncocytomas, 23 chrRCCs, 7 atypical RCCs, 6 atypical oncocytomas, 5 AMLs, 4 ccRCCs, 3 pRCCs, and 2 benign/other lesions.

MRI Characteristics

All pathologic diagnoses and details of their MRI characteristics are listed in Appendix D.

T2WI:

A description of the renal mass signal intensity characteristics on T2WI was provided in the MR reports in 167/217 cases. SI features at T2WI are displayed in Table 3 according to pathologic diagnosis.

There was a statistically significant correlation between SI at T2WI and pathologic diagnosis ($p < 0.0001$), and between predominant SI in T2 heterogeneous lesions and pathologic diagnosis ($p = 0.0062$). Hypointensity on T2WI was the most commonly reported pattern for AML, pRCC, and chrRCC (72%, 57%, and 41%, respectively), statistically significant only for AML (AML: $p < 0.001$, pRCC: $p = 0.14$, and chrRCC: $p = 0.08$). Clear cell RCC, oncocytoma and atypical RCC were most likely to be characterized as heterogeneous or hyperintense at T2WI (ccRCC: 55% and 39%; oncocytoma, 56% and 28%; atypical RCC, 63% and 25%, respectively), statistically significant for ccRCC and oncocytoma (ccRCC: $p < 0.0001$, oncocytoma: $p < 0.0001$, and atypical RCC: $p = 0.20$).

Precontrast T1WI:

There was no statistically significant association between pathology and lesion SI at precontrast T1WI ($p = 0.51$). Hemorrhagic components, as shown on T1WI, also did not have any statistically significant association with pathology.

Enhancement:

Enhancement characteristics were reported for 197/217 lesions. Enhancement characteristics and pathologic diagnoses are provided in Table 4.

A statistically significant correlation was noted between reported pattern of enhancement and pathology ($p < 0.0001$). Lesions found to be most frequently hypoenhancing included AML (60 %, $p = 0.32$), pRCC (50 %, $p = 0.090$) and urothelial carcinoma (60 %, $p = 0.65$), these were not statistically significant likely due to small sample size. The most frequently hyperenhancing tumor subtype was ccRCC (39%, $p < 0.0001$). Heterogeneous enhancement was most commonly seen in oncocytoma (38 %, $p = 0.0075$), atypical oncocytic neoplasm (80%, $p = 0.18$), ccRCC (43%, $p < 0.0001$) and atypical RCC (89%, $p = 0.020$). Chromophobe carcinomas showed a wide range of described enhancement

patterns, with heterogeneous enhancement (34%), unspecified enhancement (29%) and hyperenhancement (20%) representing the most commonly reported patterns.
There was statistically significant correlation between reported washout in the delayed nephrographic phase and pathologic diagnosis ($p = 0.036$), but not within each tumor subtype. Washout was reported in 39% of AML, 19% of chromophobe carcinomas; 10% of atypical RCC, 8% of clear cell RCC, and 6% of oncocytomas. There were 6 reports of segmental enhancement inversion occurring in 4/36 (11%) chromophobe RCC and 2/35 (6%) of oncocytomas. Segmental enhancement inversion was not reported for any lesions with other diagnoses. The sensitivity, specificity, PPV and NPV of segmental enhancement inversion for diagnosis of oncocytoma was 11%, 99%, 67% and 15%, and for chromophobe carcinoma was 6%, 98%, 33%, and 16%, respectively.

DWI:
DWI was introduced to renal imaging protocols during the study period and performed in 146/217 examinations. Renal tumor signal intensity characteristics at DWI were reported in only 27/217 lesions. DWI characteristics were most commonly reported when restricted diffusion was present, with only 3/27 reports mentioning the absence of restricted diffusion. There was no statistically significant association between reported lesion characteristics at DWI, and pathology ($p = 0.49$). Restricted diffusion was reported to be present in ccRCC (n=8, 9%), chrRCC (n=6, 17%), pRCC (n=2, 12%), oncocytoma (n=2, 6%), atypical RCC (n=2, 20%), AML (n=1, 6%), urothelial carcinoma (n=2, 40%), and benign/other lesion (n=1, 50%). There were no reports of restricted diffusion for atypical oncocytic neoplasm.

Intravoxel fat:
There was a statistically significant association between the presence of intravoxel fat and pathologic diagnosis ($p < 0.0001$). Definite or equivocal intravoxel fat was reported in ccRCC (n=37, 42%, $p < 0.0001$), chromophobe RCC (n=3, 8%, $p = 0.0076$), papillary RCC (n=1, 6%, $p = 0.018$), AML (n=6, 33%, $p = 0.012$), atypical RCC (n=1, 10%, $p = 0.010$), and atypical oncocytic neoplasm (n=2, 33%, $p = 0.56$). The PPV of intravoxel fat for ccRCC was

76% when considering all lesions in this cohort. The presence of intravoxel fat was not reported for any oncocytoma, papillary RCC, urothelial carcinoma or benign/other lesions.

Bulk fat:
The association between bulk fat and pathology was not statistically significant (p = 0.66). Equivocal or definitively present bulk fat was reported in AML (n=1, 6%), chromophobe RCC (n=1, 3%), and ccRCC (n=1, 1%).

Morphologic features:
Presence or absence of tumor invasion of adjacent structures was reported for 94/217 lesions (p =0.0076), more commonly associated with ccRCC (n=24, 27%), urothelial carcinoma (n=2, 40%), and atypical RCC (n=3, 30%), though there was no statistical significance seen for individual subtypes, likely from small sample size. There were 1 (17%) atypical oncocytic neoplasm, 3 (8%) chromophobe RCC, 1 (6%) AML, 2 (6%) oncocytoma and 1 (6%) papillary RCC that were described to be invasive.

Other features:
No significant association was observed between pathology and presence of adrenal mass, or presence/characteristics of cystic component.

Discussion

MRI is a useful tool for characterization of renal masses. Accurate diagnosis via MRI can triage likely benign lesions to biopsy instead of surgery or even obviate biopsy or active surveillance entirely and minimize the associated cost and risk for patients. New treatment strategies, such as cryoablation and radiofrequency ablation and molecular targeted therapy may also be utilized after accurate MR diagnosis of renal masses.[12]

In this study, we evaluated the diagnostic accuracy of MRI in differentiating between benignity versus malignancy, or by histopathology. By identifying areas of deficiencies and further elucidating the MR characteristics of different renal masses, we offer strategies to

improve diagnostic accuracy, especially with respect to distinguishing oncocytoma and fat poor AML from ccRCC, and fat poor AML and chrRCC from pRCC.

Diagnostic Performance

The overall sensitivity of MR diagnosis of malignancy (either for all differential diagnosis or first differential diagnosis) is high (98.8% and 95.1%, respectively); however, the specificity is low (9.1% by all differential diagnosis, 23.6% by first differential diagnosis). As a comparison, Kwon *et al.* reported the sensitivity and specificity of MRI for the diagnosis of RCC in indeterminate renal mass on CT scans to be 91.8% and 68.1%, including lesions that were diagnosed by clinical finding of stability ≥ 18 months instead of by pathology. [13] We attribute our low specificity for malignancy and high false positive rate of 90.9% to the exclusion of masses that were never biopsied or excised due to confident MR diagnosis of benignity. Selection bias thus favors lesions with any atypical or potentially malignant features on MRI. The predominance of fat poor AMLs in the group of AMLs in our cohort is a representative example of this effect. The high false positive rate can be attributed to the high prevalence of RCCs. Due to the poor prognosis of RCC, it was often included in the differential even when it was not the primary differential diagnosis, as shown by the higher specificity when only first differential diagnosis was included. In contrast, a relatively low pre-test probability for benign lesions likely decreased their inclusion in the differential diagnosis in MRI reports.[14,15]

MR-reported malignancies based on the first differential diagnosis demonstrated only a 4.9 % false negative rate, which could be attributed to selection bias. Of the 8 malignant lesions that were diagnosed as benign on the first differential, 7 were chrRCC and 1 was a pRCC. When all differential diagnoses were considered, only 2 malignant lesions (1 chrRCC and 1 pRCC) were diagnosed as benign on MR. This is similar to the Kwon *et al* study, which included lesions without pathologic diagnosis, where 6 out of 120 total lesions diagnosed as benign on MRI proved to represent RCC on final diagnosis.[13]

The factors that contributed to the high sensitivity and low specificity for the diagnosis of malignancies in general likely explain the 92.3% sensitivity and 60.3% specificity for the

diagnosis of ccRCC. For the examination of diagnostic accuracy, cystic RCCs were grouped with ccRCCs, as cystic RCCs are commonly ccRCC on pathology. In our cohort, 6 of 8 radiologically diagnosed cystic RCCs were ccRCCs on pathology; the remaining 2 were atypical RCCs. 10 of 88 ccRCCs were diagnosed as "RCC" without specification of subtype on MRI. Clinically, these were likely managed as ccRCCs, which would have placed the sensitivity for the diagnosis of ccRCC at approximately 93.3% if including nonspecified RCCs as ccRCC. The 75.0% sensitivity and 89.3% specificity for papillary RCC were satisfactory. The sensitivity and specificity for chromophobe RCC were 9.7% and 94.5%, respectively. The low sensitivity was largely due to the misdiagnosis of chromophobe RCC as pRCC or ccRCC. The low sensitivity and high specificity for benign lesions, as seen in Table 1, could be attributed to the same factors responsible for the high false positive rate in the detection of malignancy, namely the exclusion of lesions without pathology and the atypical features in the benign lesions.

MRI Characteristics for challenging diagnoses

Diagnosing oncocytoma vs. ccRCC:

The differentiation of oncocytoma and ccRCC has been a diagnostic challenge as oncocytoma has variable and often nonspecific appearance. [16] Both types of lesions had very similar T2 appearance and enhancement. 51.4% of oncocytomas and 53.4% of ccRCCs were hyperintense or heterogeneously hyperintense on T2 weighted images. 45.7% of oncocytomas and 48.9% of ccRCCs were hyperenhancing or heterogeneously hyperenhancing. The presence of intravoxel fat can be very helpful in differentiating the two entities, as none of the 35 oncocytomas were reported to have intravoxel fat. However, the PPV of intravoxel fat for ccRCC was 75.6% when considering all renal masses. This is concordant with others' observations. [17] -In addition to intravoxel fat, complete delayed enhancement of central scar in oncocytomas is another feature that is helpful in this diagnosis.[17,18] Of the 6 oncocytomas with reported multiphasic enhancement pattern, 2 had delayed phase enhancement and 2 had segmental enhancement inversion, findings which were not reported on any of the 8 ccRCCs for which multiphasic enhancement pattern was

described. Washout in the delayed phase was the most common descriptive feature reported when the enhancement pattern of ccRCCs was described (6/8 cases).

Diagnosing AML vs. ccRCC

The differentiation of AML (especially fat poor AML) and ccRCC on MRI has also been a challenge.[16] In our cohort, due to inclusion criteria of confirmatory histopathological diagnosis, most (13/18) AMLs were fat poor AMLs or had atypical features that led to biopsy/resection. Therefore, our findings relate primarily to MR findings of fat poor AML, as opposed to conventional lipid rich AML.

That intravoxel fat occurs in both fat poor AMLs and ccRCCs is known from prior studies[19,20,21] , with resultant poor diagnostic accuracy of intravoxel fat in differentiating fat poor AML from ccRCC.[11] In our cohort, 5 of 18 AMLs were explicitly reported as having intravoxel fat. Enhancement characteristic of these two lesion subtypes is expected to be similar, and demonstrated by our data. 7% of AMLs and 5% of ccRCCs were hypoenhancing, the remaining with varying degrees of enhancement.

Several studies have shown that because of the low proton density of smooth muscle components, fat poor AMLs are hypointense on T2 weighted images whereas ccRCCs are iso- to hyper- intense at T2 weighted imaging.[22,23,11,24,25] Our data was concordant with these previous findings, with 83.3% of AMLs, but only 4.5% of ccRCCs, being hypointense or heterogeneously hypointense on T2 weighted images, making T2 hypointensity a key distinguishing feature between the two types of lesions. Lack of necrosis has been shown to support a diagnosis of AML.[11] Nonenhancing areas/cystic change was seen in 22 of the ccRCC but in none of the AMLs in our data, though not statistically significant due to small sample size. This is in concordance with others' findings, as cysts in AMLs are extremely rare.[26]

Diagnosing AML vs. pRCC

Fat poor AML and papillary RCC share the characteristic of hypointensity on T2 weighted imaging, although other features such as small size and lack of necrosis as well as differential enhancement patterns may assist in differentiation.[11,27,28] According to previous literature, the enhancement of fat poor AML varies with the amount of vascular

tissue in the lesion.[16] Papillary RCCs are known to be hypoenhancing.[27] We found 17% of AMLs were hypoenhancing or heterogeneously hypoenhancing; while 56% of papillary RCCs were hypoenhancing or heterogeneously hypoenhancing. In our cohort, 1 AML was misdiagnosed as papillary RCC and no pRCC were diagnosed as AML.

Diagnosing chrRCC vs. pRCC:

The imaging features of chromophobe carcinoma and papillary RCC may overlap..[27,16,29,30] 16.6% of chromophobe RCCs were reported as ccRCCs while 33.3% were reported as papillary RCC.[16] The misdiagnoses of chromophobe RCCs for papillary RCCs is likely due to their similar appearance as T2-hypointense lesions. Difference in enhancement may help distinguish the two lesions— 19 % of chrRCCs were hypoenhancing or heterogeneously hypoenhancing, and 56 % of papillary RCCs were hypoenhancing or heterogeneously hypoenhancing. Segmental enhancement inversion is specific for chromophobe RCCs when compared with papillary RCCs. Chromophobe RCCs may also have central scar, similar to that of oncocytomas; however, oncocytomas were generally T2 hyperintense.[12,18]

Diagnosing urothelial carcinomas:

Urothelial carcinomas were diagnosed with the greatest accuracy of 100% sensitivity and 99% specificity. This was likely due to their unique location in the renal pelvis and their T1 and T2 characteristics. Previously described as isointense on T1 WI, hypo- or isointense on T2 WI and hypoenhancing, most urothelial carcinomas in our study were iso- to hypointense on T1 WI, isointense on T2 WI and mostly (60%) hypoenhancing.[16,31] 40% were reported as simply enhancing without specification of intensity.

Other notable MRI characteristics

Characteristics on T1 WI:

The utility of T1 features in the diagnosis of renal masses has been uncertain—one study demonstrated the association between T1 hyperintensity and fat poor AML, while another did not.[24,25] Olive *et al* reported that it was not useful in differentiating the subtypes of

RCC.[29] In our study, the association between T1 features and pathological diagnosis was not statistically significant ($p = 0.56$).

DWI:

A recent study by Mirka *et al* suggested that DWI can help differentiate ccRCCs from other subtypes of RCCs and help determine grade.[32] We found no statistically significant association between diffusion restriction and pathology ($p = 0.49$), however, we note that our study was likely underpowered for the examination of DWI, because DWI was performed in 146 MRIs, and our analysis is confined to the only 27/217 reports which explicitly stated diffusion characteristics.

Limitations

As this was a retrospective study and the images were read as part of clinical practice, not all MR features were reported for every lesion. Variations in MRI scanners and protocols, such as the introduction of DWI midway in the study period, were unavoidable.

Finally, as discussed above, the exclusion of renal masses that were not biopsied or resected resulted in selection bias for malignant lesions or benign lesions with atypical features. The frequencies of oncocytoma and chromophobe RCC in our cohort were higher than reported in other series, possibly because they were biopsied/resected more often due to low diagnostic sensitivity on MRI.[4]

This study reflects the general practice at an academic medical center over a number of years, and thus the interpretations that form the basis of this study, by necessity, do not uniformly reflect the advances in diagnosis of renal masses with MRI that accrued during the study period. This method of study design was intentional as it is felt that awareness of the actual aggregate performance of MRI for diagnosis of renal masses in clinical use, is of interest both to radiologists and referring clinicians. However, our findings likely underestimate the potentially achievable accuracy of MRI using current knowledge.

In summary, MR is highly sensitive for diagnosis of malignancy. For several mimickers of RCC and less common subtypes (oncocytoma, AML, atypical RCC, chrRCC), MR diagnosis was highly specific, though MR sensitivity for diagnosis was poor. Radiologists interpreting MR should be aware of particularly problematic differential diagnoses. However, our data confirms that several previously published observations carry into clinical practice and can be helpful in differentiating mimicking lesions. Specifically, in differentiating lesions in which T2 and enhancement features favor oncocytoma versus ccRCC, lack of intravoxel fat should increase level of suspicion for oncocytoma, while low signal intensity on T2WI can help differentiate fat poor AML from ccRCC.

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Tables:

Table 1. MR performance for predicting malignancy vs. benignity.

MR diagnosis	Malignant pathologic diagnosis	Benign pathologic diagnosis
MR malignant (any differential)	160	50
MR benign (any differential)	2	5
MR malignant (first differential)	154	42
MR benign (first differential)	8	13

Malignant pathologic diagnoses include ccRCC, pRCC, chrRCC, atypical RCC, atypical oncocytic neoplasm, urothelial carcinoma, and atypical oncocytic neoplasms. Benign pathologic diagnoses include oncocytoma, AML, and other benign.

Table 2. Primary differential diagnosis listed in the MRI report with respect to pathologic diagnosis.

Primary differential diagnosis at MRI	Pathologic diagnosis								
	ccRCC	pRCC	chrRCC	AML	Oncocytoma	Urothelial carcinoma	Atypical oncocytic neoplasm	Atypical RCC	Other benign
ccRCC	66	2	6	4	25	0	4	2	1
pRCC	3	12	12	1	1	0	1	1	0
chrRCC	1	1	3	3	1	0	0	3	0
AML	0	0	2	8	1	0	0	0	0
oncocytoma	0	0	5	1	3	0	0	0	0
Urothelial carcinoma	0	0	1	0	0	5	0	0	0
Abscess	0	1	0	0	0	0	0	0	0
Cystic RCC	6	0	0	0	0	0	0	2	0
lymphoma	0	0	1	0	0	0	0	0	0

Gray boxes indicate concordant MR and pathologic diagnoses.

Table 3: Renal mass SI features at T2WI, as provided in clinical MR reports, according to pathologic diagnosis.

T2 SI	ccRCC	pRCC	chrRCC	AML	Oncocytoma	Urothelial carcinoma	Atypical oncocytic neoplasm	Atypical RCC	Other benign
Hyperintense	26 (39%)	2 (14%)	3 (14%)	1 (6%)	9 (28%)	0 (0%)	1 (33%)	2 (25%)	1 (50%)
Isointense	2 (3%)	0 (0%)	2 (9%)	1 (6%)	1 (3%)	2 (100%)	1 (33%)	0 (0%)	0 (0%)
Hypointense	2 (3%)	8 (57%)	9 (41%)	13 (72%)	4 (13%)	0 (0%)	1 (33%)	1 (13%)	0 (0%)
Heterogeneous	36 (55%)	4 (29%)	8 (36%)	3 (17%)	18 (56%)	0 (0%)	0 (0%)	5 (63%)	1 (50%)
Predominant SI in heterogeneous lesions									

Hyperintense	21	2	2	0	9	0	0	1	0
Isointense	3	0	2	0	2	0	0	1	0
Hypointense	2	2	4	2	3	0	0	3	1

The predominant SI was described in some, but not all, T2 heterogeneous lesions.

Table 4: Renal tumor enhancement characteristics, as provided in clinical MR reports, according to pathologic diagnosis.

Enhancement	ccRCC	pRCC	chrRCC	AML	Oncocytoma	Urothelial carcinoma	Atypical oncocytic neoplasm	Atypical RCC	Other benign
Hyperinhancing	30 (39%)	1 (6%)	7 (20%)	3 (20%)	10 (29%)	0 (0%)	1 (20%)	1 (11%)	1 (50%)
Isoenhancing	1 (1%)	0 (0%)	1 (3%)	2 (13%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypoenhancing	4 (5%)	8 (50%)	5 (14%)	1 (7%)	2 (6%)	3 (60%)	0 (0%)	0 (0%)	0 (0%)
Heterogeneous	33 (43%)	3 (19%)	12 (34%)	3 20%)	13 (38%)	0 (0%)	4 (80%)	8 (89%)	0 (0%)
Degree of enhancement not specified	8 (11%)	4 (25%)	10 (29%)	6 (40%)	7 (21%)	2 (40%)	0 (0%)	0 (0%)	1 (50%)
Predominant SI in heterogeneous lesions									
Hyperinhancing	13	0	3	1	6	0	0	0	0
Isoenhancing	0	0	0	0	1	0	0	1	0
Hypoenhancing	2	1	2	2	1	0	0	1	0
Degree of enhancement not specified	11	2	6	0	2	0	3	5	0

The predominant enhancement characteristic was described in some, but not all, heterogeneously enhancing lesions.

Appendices:

Appendix A. List of the minimal set of MR sequences used for diagnostic evaluation of renal masses with typical parameters.

Sequences occurring in all MR examinations	Repetition time (ms)	Echo time (ms)	Flip angle (degrees)	Slice thickness (mm)	Matrix Size	Field of view (cm)
T2 Coronal fast spin echo	800–1000	60-70	90	4-5	256 x 192 (1.5 T) 288 x 192 (3.0 T)	38-42
T1 Axial dual-echo in and opposed phases, spoiled GRE	170-180	2.2–2.8/4.4-5.3 (1.5 T) 1.1–1.3/2.2-2.6 (3.0 T)	80	6-7	256 x 128–192 (1.5 T) 320 x 160 (3.0 T)	36–40
Sagittal oblique (oriented across each kidney) 3D GRE with fat saturation,	4-5	1-2	10 (1.5 T) 12 (3.0 T)	3–3.2	256 x 192 (1.5 T) 256 x 160 (3.0 T)	34–38
Coronal 3D GRE with fat saturation, pre- and post-contrast (2–3 phases)	4-5	1-2	10-11	3	256 x 192 (1.5 T) 256 x 160 (3.0 T)	38–42
Axial 3D GRE with fat saturation, post-contrast (only on renal mass protocol)	4-5	1-2	11–15	2.5–3.2	256 x 192	36–40
Sequences occurring in a subset of MR examinations						
Axial EPI DWI (b values 50, 800)	4100-4200	50-70	90	5-8	128 x 128 (1.5T) 128 x 84 (3T)	36-40
T2 Axial with fat saturation	1000-1500	60-70	90	5	256 x 160 (1.5 T) 288 x 160 (3.0 T)	36-40

The axial 3D GRE post-contrast sequence is available only on the renal mass protocol; the other sequences are covered in both the renal mass and urogram protocols. Any differences in parameters between 1.5 T to 3.0 T are indicated.

DWI: diffusion weighted imaging
EPI: echo planar imaging
GRE: gradient recal echo

Appendix B. Methods of acquisition of pathologic specimens by histopathology.

Pathologic diagnosis	Biopsy	Partial nephrectomy	Total nephrectomy
ccRCC	10	42	36
pRCC	0	12	5
chrRCC	3	21	12
AML	3	14	1
Oncocytoma	5	22	8
Urothelial carcinoma	2	0	3
Atypical oncocytic neoplasm	2	2	2
Atypical RCC	0	7	3
Other benign	1	1	0

Appendix C. MR performance for predicting malignancy vs. benignity with respect to histopathology.

MR diagnosis	ccRCC	pRCC	chrRCC	AML	Oncocytoma	Urothelial carcinoma	Atypical oncocytic neoplasm	Atypical RCC	Other benign
MR malignant (any differential)	88	16	35	13	35	5	6	10	2
MR benign (all differential)	0	1	1	5	0	0	0	0	0
MR malignant (first differential)	88	16	29	9	31	5	6	10	2
MR benign (first differential)	0	1	7	9	4	0	0	0	0

Appendix D. Pathologic diagnoses and MRI characteristics including

	ccRCC	pRCC	chrRCC	AML	Oncocytoma	Urothelial carcinoma	Atypical oncocytic neoplasm	Atypical RCC	Other benign	p-value
T1 SI (precontrast)										0.5639
Hyperinhancing	7 (21%)	3 (27%)	5 (24%)	1 (14%)	3 (16%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	
Isoenhancing	8 (24%)	0 (0%)	6 (29%)	2 (29%)	5 (26%)	1 (50%)	0 (0%)	2 (67%)	0 (0%)	
Hypoenhancing	6 (18%)	2 (18%)	3 (14%)	3 (43%)	3 (16%)	1 (50%)	0 (0%)	1 (33%)	0 (0%)	
Heterogeneous	12 (36%)	6 (55%)	7 (33%)	1 (14%)	8 (42%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	
Diffusion*										0.4940
Slight equivocal restriction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	
No restriction	2 (3%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Restriction	8 (11%)	2 (17%)	6 (43%)	1 (20%)	2 (9%)	1 (20%)	0 (0%)	2 (22%)	1 (100%)	
Hemorrhagic component										0.2051
No	0 (0%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Yes	13 (15%)	6 (35%)	12 (33%)	2 (11%)	3 (9%)	0 (0%)	2 (33%)	0 (0%)	0 (0%)	
Intravoxel fat										<0.0001*
Yes	34 (39%)	0 (0%)	3 (8%)	5 (28%)	0 (0%)	0 (0%)	2 (33%)	1 (10%)	0 (0%)	
No	14 (16%)	4 (24%)	14 (39%)	7 (39%)	13 (37%)	1 (20%)	1 (17%)	5 (50%)	2 (100%)	
Equivocal	3 (3%)	1 (6%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Bulk fat										0.6603
Yes	1 (1%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
No	8 (1%)	3 (18%)	9 (25%)	4 (22%)	4 (11%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	
Equivocal	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Presence of invasion										0.0076*
No	17 (19%)	3 (18%)	15 (42%)	7 (39%)	8 (23%)	0 (0%)	3 (50%)	3 (30%)	1 (50%)	
Yes	24 (27%)	1 (6%)	3 (8%)	1 (6%)	2 (6%)	2 (40%)	1 (17%)	3 (30%)	0 (0%)	
Adrenal mass										0.1836
Metastasis	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Adenoma/ hyperplasia	1 (1%)	1 (6%)	3 (8%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Unspecified	1 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Washout										0.0361*
Washout on delayed phase	6 (18%)	0 (0%)	3 (8%)	5 (28%)	2 (6%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	
Some/minimal washout	1 (1%)	0 (0%)	4 (11%)	2 (11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
No washout	1 (1%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (50%)	

Segmental inversion	0 (0%)	0 (0%)	4 (11%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Cystic component										0.8059
Cyst with internal enhancing septae/nodule	15 (17%)	2 (12%)	5 (14%)	0 (0%)	1 (3%)	0 (0%)	1 (17%)	4 (40%)	0 (0%)	
Cyst with internal non-enhancing septae/nodule	3 (3%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Cystic lesion (or partially cystic) with no internal septae/nodule	4 (5%)	0 (0%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

* The percentage of lesions with diffusion restriction is calculated based on the total number of lesions for which DWI sequence was performed, not the total number of lesions for which DWI characteristics was described in the MRI report.