

Clinical-Kidney cancer  
Diagnostic performance of prospectively assigned clear cell Likelihood scores (ccLS) in small renal masses at multiparametric magnetic resonance imaging

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## Abstract

**Introduction:** Detection of small renal masses (SRM) is increasing with the use of cross-sectional imaging, although many incidental lesions have negligible metastatic potential. A method to identify this subtype would aid in risk stratification. A previously reported clear cell likelihood score (ccLS; 1-very unlikely, 2-unlikely, 3-equivocal, 4-likely, and 5-very likely), based on retrospective review of multiparametric magnetic resonance imaging (mpMRI), predicted the likelihood of encountering clear cell renal cell carcinoma (ccRCC) at surgery. Here, we assess the performance of ccLS prospectively assigned for prediction of ccRCC.

**Methods:** Patients with a known renal mass who underwent mpMRI at a single institution between June 2016 and April 2018 were prospectively assigned a ccLS as part of the clinical MRI report. These patients were retrospectively reviewed, and those with a cT1a lesion and available pathological tissue diagnosis (diagnostic biopsy or extirpative surgery) were selected for analysis.

**Results:** In total, 57 patients (mean age  $61.7 \pm 14.9$  years) with 63 cT1a renal masses were identified. Mean tumor size was  $2.7 \pm 0.7$  cm. Defining ccLS 4-5 lesions as positive demonstrated an overall accuracy of 84%, sensitivity of 89%, specificity of 79%, positive predictive value of 84%, and negative predictive value of 86%. A ccLS of 1-2 demonstrates an 86% accuracy and 100% sensitivity/positive predictive value of identifying non-ccRCC histology.

**Conclusions:** Utilizing prospectively assigned ccLS, we confirm that mpMRI can reasonably identify ccRCC histology in cT1a renal masses. Standardization of imaging protocols and reporting criteria such as the ccLS can be used to aid in the diagnosis and management of small renal masses. © 2019 Elsevier Inc. All rights reserved.

**Keywords:** Multiparametric Magnetic; Resonance Imaging; Renal Cell Carcinoma; Small Renal Mass; Renal Mass Biopsy; Partial Nephrectomy; Clear Cell Likelihood Score

**Abbreviation:** SRM, Small Renal Mass; ccLS, Clear Cell Likelihood Score; mpMRI, multiparametric Magnetic Resonance Imaging; RCC, Renal Cell Carcinoma; ccRCC, clear cell Renal Cell Carcinoma; RMB, Renal Mass Biopsy; pRCC, papillary Renal Cell Carcinoma; chrRCC, chromophobe Renal Cell Carcinoma; fpAML, fat-poor Angiomyolipoma; PACS, Picture Archiving and Communications System; PPV, Positive Predictive Value; NPV, Negative Predictive Value; Onco, Oncocytoma; Onco Neo, Oncocytic Neoplasm

## 1. Introduction

The incidence of small renal masses (SRM) is rising, [1,2] with up to 25% of cT1a masses being benign [3].

Thus, management of SRMs is a complex issue, as it is difficult to determine which lesions pose a significant oncological risk. Clear cell renal cell carcinoma (ccRCC), the most common RCC subtype, has the greatest potential for aggressive behavior among the most common subtypes [4]. Therefore, identification of clear cell histology can help in

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management decision making, including deciding between active surveillance and definitive intervention.

Renal mass biopsy (RMB) is an accurate method to establish a histological diagnosis for a SRM, however its use remains controversial [4,5]. Survey evidence indicates that it is underutilized [6], and is not without risk (1%–5% complication rate) [7]. Also, it has a reported nondiagnostic rate estimated to be up to 14% and is poor at determining tumor grade [8].

In contradistinction, multiparametric magnetic resonance imaging (mpMRI) is a noninvasive method to obtain both anatomical and histological information about a SRM [9–11]. Utilizing a combination of qualitative and quantitative measurements, determining RCC subtype on mpMRI is possible [12,13]. A clear cell likelihood score (ccLS) based on a Likert scale (1-very unlikely, 2-unlikely, 3-equivocal, 4-likely, and 5-very likely) for interpretation of mpMRI examinations has been reported as an approach to noninvasively detect ccRCC.

Canvasser et al. [14] demonstrated moderate to good inter-reader reliability of this paradigm ( $\kappa=0.53$ ). Utilizing the mean ccLS score assigned to each lesion by 7 radiologists, the system achieved 79% accuracy, 78% sensitivity, 80% specificity, and 80% positive and negative predictive values (NPVs) for the diagnosis of ccRCC. Similarly, Kay et al. [15] achieved diagnostic accuracies of 91%, 94%, 98%, and 94% for the diagnosis of papillary RCC (pRCC), chromophobe RCC (chrRCC), fat-poor angiomyolipoma, and oncocytoma, respectively, using a similar algorithm. However, these prior reports were based on retrospective analyses, demonstrating proof-of-concept. This study represents the clinical implementation of the ccLS system into the interpretation of the mpMRI. The goal of the present report is to validate the diagnostic performance of ccLS scores in cT1a masses assigned prospectively in clinical practice.

## 2. Methods

### 2.1. Patients

This was a single-center Health Insurance Portability and Accountability Act-compliant, Institutional Review Board-approved, retrospective review of prospectively generated data; requirement for informed consent was waived. Inclusion criteria were: (1) patients who underwent a mpMRI to evaluate a cT1a renal mass and received a ccLS from June 2016 until April 2018; (2) had histological confirmation of the renal mass by renal biopsy and/or surgical resection; Exclusion criteria: (1) unable to complete mpMRI examination; (2) nondiagnostic renal biopsy of the mass or no surgical pathology available. Patients with suboptimal mpMRI (e.g., motion artifact, noncontrast exams) were included in the analysis as they constitute an intent to treat cohort. Patient demographics and clinical findings (including age, gender, tumor size, and final pathology results) were also extracted from chart review. Tumors with

ambiguous pathology reports were categorized as the pathology with the more malignant potential. Each SRM was considered independently and only included if that specific lesion had a ccLS and histopathology. Histological analysis was performed by genitourinary pathologists according to the World Health Organization classification of renal neoplasms [16]. All nephrectomy and core biopsy samples were sampled, processed, and reviewed using routine standardized histology and immunohistochemistry protocols [17]. Renal tumors that did not fit the classic morphologies of well-recognized entities, especially on biopsies, were routinely confirmed by immunohistochemical biomarkers. All cases without classic morphologies were reviewed in a consensus conference led by the director of service with over 15 years' experience and attended by all the GU pathologists.

### 2.2. Image acquisition and analysis

All clinical mpMRI exams were performed at a single institution on 1.5T or 3T whole-body scanners using our standard clinical imaging protocol without and with contrast [15]. Briefly, it includes coronal and axial fat-saturated T2-weighted single-shot fast spin echo images; axial chemical shift T1-weighted images, diffusion weighted images with  $b$  values of 0, 50, 400, 800; and multiplanar fat suppressed, dynamic contrast enhanced T1-weighted imaging, including a corticomedullary, early and late nephrographic, and excretory phases. Apparent diffusion coefficient maps were generated at the MR scanner using all  $b$  values and a monoexponential decay model.

The MRI interpretation was performed by one of 14 experienced academic radiologists covering the clinical service. Each study was reviewed on a Picture Archiving and Communications System (PACS) workstation (iSite, Philips Healthcare, Best, Netherlands). As part of the clinical, structured report, a ccLS [14,15,18] was prospectively assigned for each renal tumor identified. If multiple, a separate score was assigned to each. The basis for this algorithm can be seen in Fig. 1. Features associated with ccRCC increased T2W signal intensity, heterogeneous T2W texture, intravoxel fat, and intense and heterogenous CM enhancement [18]. Interpretative radiologists calculated the CM enhancement and arterial-delayed enhancement ratio ad libitum during the clinical interpretation [19,20].

### 2.3. Statistical analysis

SPSS version 25 (International Business Machines Corporation, Armonk, NY) was used to perform the data analysis. To determine the classification function of the ccLS a contingency table was made. Analysis consisted both of ccLS score of 4 or 5 defined as a positive for ccRCC histology as well as ccLS of 1-2 defined as positive for non-ccRCC histology. The histopathological subtype as determined on biopsy or extirpative surgery was considered the gold standard. Accuracy,

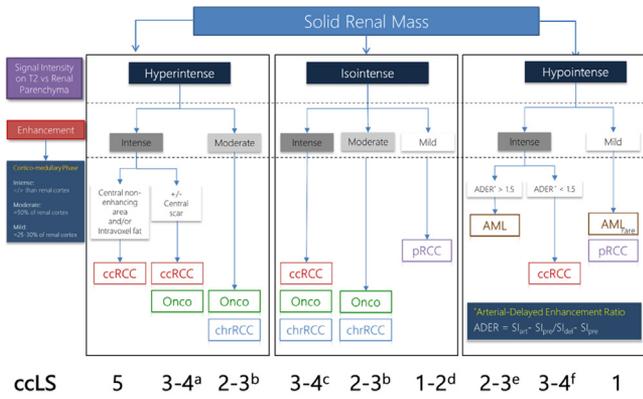


Fig. 1. Multiparametric algorithm for small renal masses. Suggested clear cell likelihood scores (ccLS) for each column are provided at the bottom of the figure (1-very unlikely, 2-unlikely, 3-equivocal, 4-likely, and 5-very likely). <sup>a</sup>ccLS3 if segmental enhancement inversion (SEI) present; <sup>b</sup>ccLS2 if segmental enhancement inversion (SEI) present; <sup>c</sup>ccLS4 if microscopic fat present; <sup>d</sup>ccLS2 if enhancement between 25% and 50%; <sup>e</sup>ccLS2 if homogeneous or marked restriction on DWI; <sup>f</sup>ccLS3 if homogeneous or marked restriction on DWI. ccLS4 if heterogenous. (Adapted with permission from Kay FU and Pedrosa I. Radiol Clin N Am 2017). ADER = arterial-delayed enhancement ratio; AML = fat poor angiomyolipoma; ccRCC = clear cell renal cell carcinoma; chrRCC = chromophobe renal cell carcinoma; onco = oncocytoma; pRCC = papillary renal cell carcinoma.

sensitivity, specificity, NPV, and positive predictive value (PPV) were calculated from the contingency table. Differences in means of continuous variables were analyzed using the student’s *t* test. All *P* values were 2-sided and statistical significance was defined as *P* < 0.05.

**3. Results**

A total of 256 lesions in 218 patients were given ccLS scores (Fig. 2). Of the 256 lesions, 128 (50%) had a confirmatory tissue based histopathological diagnosis. Of these, 63 masses in 57 patients were clinical T1a lesions and therefore met the inclusion criteria. Mean patient age was 61.7 years. Mean tumor size was 2.7 cm. Patient demographics and tumor characteristics of the final cohort are described in Table 1. Of the tumors in the cohort, 41/63

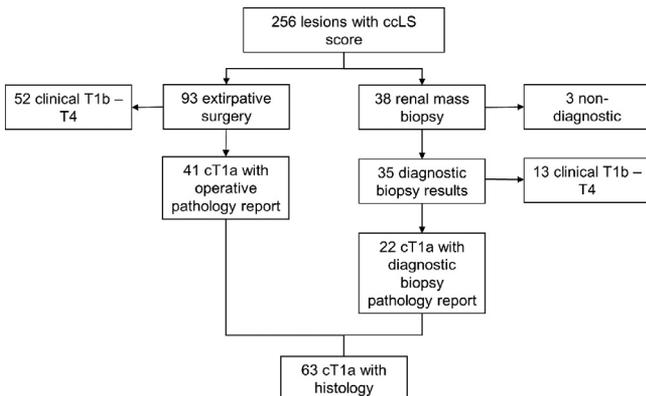


Fig. 2. Lesion exclusion flowchart. ccLS = clear cell likelihood score.

Table 1 Demographic/pathological information of cohort.

Demographical/pathological information	Value
No. of pts/no. of tumors	57/63
Mean age ± SD (y)	61.7 ± 14.9
% Male/female	67%/33%
Mean BMI ± SD (kg/m <sup>2</sup> )	29.3 ± 6.6
Mean tumor size ± SD (cm)	2.7 ± 0.7
No pathology source (%)	
Extirpative surgery	41 (65%)
Renal mass biopsy	22 (35%)
No histology (%)	
Clear cell RCC	35 (55%)
Papillary RCC	14 (22%)
Chromophobe RCC	3 (5%)
Oncocytic neoplasm	3 (5%)
Oncocytoma	5 (8%)
Benign	3 (5%)
No final path (%)	
pT1a	35 (56%)
pT1b	2 (3%)
pT3a	2 (3%)
N/A	24 (38%)

(65%) underwent extirpative surgery, and the pathology report was used to determine definitive histology. For the remaining 22/63 (35%), the tumor was not excised, therefore a RMB yielded the pathological diagnosis for this analysis. Fig. 2 demonstrates the lesions included in the study. Thirty-five of 63 lesions (55%) were found to be ccRCC. Fig. 3 demonstrates histological breakdown by ccLS score. Defining ccLS 4-5 lesions as positive demonstrated an overall accuracy of 84%, sensitivity of 79%, specificity of 86%, PPV of 84%, and NPV of 85% for ccRCC. Of the 37 ccLS 4 and 5 lesions, 6 were false positives (16% false discovery rate, 1 pRCC, 1 oncocytic neoplasm, 1 chrRCC, 2 oncocytoma, 1 benign interstitial fibrosis). As 34 of 37 lesions scored as 4 or 5 were determined to be a malignancy, the PPV of detecting any form of renal malignancy was 92%.

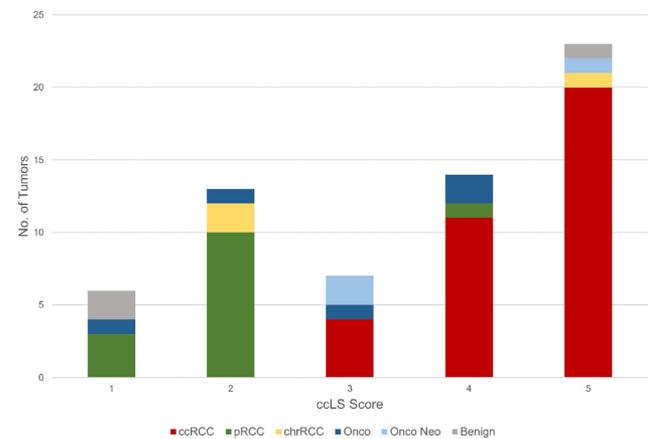


Fig. 3. Histology distribution of cohort by ccLS. ccRCC = clear cell renal cell carcinoma; chrRCC = chromophobe renal cell carcinoma; Onco = Oncocytoma; Onco Neo = oncocytic neoplasm; pRCC = papillary renal cell carcinoma.

Table 2  
Diagnostic accuracy of the ccLS scoring system.

	ccLS 4-5 detecting ccRCC	ccLS 1-2 detecting non-ccRCC
No. of lesions (%)	37/63 (59%)	19/63 (30%)
Accuracy	84%	86%
Sensitivity	89%	68%
Specificity	79%	100%
PPV	84%	100%
NPV	86%	80%

Twenty-six lesions were classified as ccLS 1-3. Of those 4 were ccRCC yielding a false negative result (15% false omission rate, 85% NPV). All false negative lesions were scored a ccLS of 3. The false negative lesions were an average diameter of 2.1 cm  $\pm$  0.4 compared to 2.6 cm for the entire cohort ( $P=0.14$ ).

There were no lesions found to be ccRCC that scored a ccLS 1 or 2. This inversely gave ccLS 1-2 an accuracy of 86%, sensitivity of 68%, specificity and PPV of 100%, and a NPV of 80% for all non-ccRCC histologies. Seven lesions were classified as equivocal (ccLS of 3). Of these 7 lesions, 3 were ccRCC and 4 were non-ccRCC histology (2 oncocyctic neoplasms, 1 oncocytoma). Table 2 summarizes the diagnostic accuracy of the ccLS scale. Two tumors were upstaged on size (measured to be 3.7 cm and 3.3 radiographically but measured  $>4$  cm in pathology) and 2cm were upstaged to pT3a. There was no correlation between ccLS and Fuhrman grade of the lesion, however, 37/48 (77%) of tumors were grade 2.

#### 4. Discussion

Multiparametric MRI should be considered in the pre-treatment evaluation of SRM as an alternative to RMB that can provide histological insight and aid in planning intervention. The ccLS system was implemented at our institution in June 2016, and a score has been assigned prospectively for renal masses evaluated with mpMRI since. In the development of ccLS, MRIs were reviewed retrospectively by several radiologists and the system yielded a 78% sensitivity and 80% specificity (for ccLS 4-5 as positive). Inter-reader variability of the previous study was demonstrated to be moderate to good with a mean weighted  $\kappa$  of 0.53 (range 0.38–0.64) [14]. However, multiple reviewers for each study are both impractical and not representative of true "real world" practice. Thus, it is necessary to confirm similar accuracy when implemented into standard clinical interpretation. This report of prospectively generated data corroborates that the diagnostic performance of the ccLS was similar, if not slightly superior, to prior reports (89% sensitivity and 79% specificity). Furthermore, when evaluating a ccLS score of 1 or 2, the scoring system perfectly predicted that lesions would not contain ccRCC.

This study demonstrated a 16% false positive rate (84% PPV) for SRM graded as ccLS 4-5. Of the 6 false positives, 4 were oncocyctic in nature (1 oncocyctic neoplasm, 1 chrRCC, 2 oncocytoma). Distinguishing between oncocytoma/chrRCC from ccRCC on MRI (as well as on RMB) is a well-documented challenge. Oncocytoma is more likely if a central scar is present, whereas ccRCC is more likely if necrosis is present, however this may be difficult to distinguish [15]. Other studies have noted difficulty in finding distinction between ccRCC and oncocytoma (19% sensitivity) [10]. It is important to point out that despite the 6 false positives in this study, only 3 lesions were benign. This yields a PPV of a ccLS 4-5 for any malignant tumor of 92%, and conversely ccLS 1-2 lesions having a 100% specificity and PPV for non-ccRCC pathology.

The diagnostic accuracy of the ccLS characterization system could support an algorithm in which all patients with ccLS 4-5 are encouraged to undergo curative intervention and all with ccLS 1-2 could consider active surveillance, especially if lesions are less than 3 cm. Equivocal lesions with a ccLS 3 would undergo a RMB depending on the clinical scenario and patient wishes. This paradigm has not been implemented in our institution, and RMB is performed at the providers discretion. If, however, this paradigm was applied in our cohort, only 6 of 57 patients (11%; 1 patient had 2 ccLS 3 renal masses) in this cohort would a RMB be indicated. In this equivocal group, 4/6 patients (67%) would have been found to have ccRCC. For these patients, RMB would clearly be of clinical value. Of the 18 patients placed on active surveillance for ccLS 1-2 lesions, none of them (0%) would have ccRCC. Most (12/18, 67%) patients with a ccLS of 1-2 were found to have type 1 pRCC. While this is a malignancy, it is indolent and can often be observed. Furthermore, while the possibility of characterizing a more aggressive tumor (e.g., papillary type II) as ccLS 1-2 exists, 1 could monitor the potential growth of such small aggressive tumors under active surveillance, which is a safe, established standard of care. Intervention would be offered for 37 tumors (ccLS 4-5) in 33 patients. Of these, 27 patients (82%) would have ccRCC and in only 3 (9%) would a benign lesion have been treated. Importantly, in this paradigm the number of patients undergoing surgery with benign disease could be reduced substantially. Indeed, 4/57 (7%) patients with benign disease underwent surgical resection in our series. This includes the 3 with a false positive as well as an additional patient with a ccLS 1 lesion electively resected revealing angiomyolipoma. This estimate compares favorably to a published meta-analysis of surgical series citing a prevalence of benign histology of up to 20% of SRM [21].

The limitations of RMB have been well documented. He et al. report a sensitivity of 95% and a specificity of 100% for detecting malignancy, however this analysis excluded nondiagnostic biopsies. Also, evaluation of specificity (true-negative) is obfuscated by the fact that negative biopsies did not lead to extirpative surgery and therefore had no

confirming pathology [22]. Moreover, diagnostic performance of RMB is commonly inflated because patients in whom a biopsy is considered unsafe are not included in the final cohort. Patel et al. performed a meta-analysis demonstrating a 4.0% false-positive and 3.1% false-negative rate for malignancy, however concordance between biopsy and final pathology was poor (52%–76%) [8]. Another study reported a higher (96%) concordance of histopathology, though many biopsies omitted carcinoma subtype [23]. RMB also risks complication; on the order of 1% to 5%. Hematoma (~5%), significant pain (~1%–2%), pneumothorax (~0.5%), and hemorrhage (~0.4%) are the most common and clinically significant complications [24,25]. Clavien III or greater complications [26]. were reported to be 0.5% to 1% [8,23]. Many proponents of RMB note that the overall risk of complication is low, especially when compared against other procedural interventions. However, these risks must be weighed against the fact that SRM are inherently low risk. Likewise, hematoma or hemorrhage due to RMB will often complicate or delay subsequent treatment of the tumor. Lastly, reported accuracy of RMB may be subject to selection bias towards tumors that are in a favorable location for biopsy. Hilar or anterior tumors may particularly benefit from a MRI-based histological classification as RMB could lead to an inferior diagnostic rate and/or greater complication rate [27].

This study has several strengths. All ccLS data were collected prospectively on every patient that underwent mpMRI and was found to have a renal tumor. The mpMRI studies were interpreted by a relatively large number of radiologists in real conditions utilizing a standard protocol and structured reporting to minimize variances. Also, having experienced uropathologists allows for confidence in the histological reports.

This study, however, has some limitations. Though mpMRI examinations were interpreted by fellowship-trained radiologists with experience using the algorithm, given the somewhat subjective nature of assigning the ccLS score, diagnostic accuracy could vary based on radiologist's experience. Not every patient with a SRM at our institution underwent a mpMRI. Therefore, a selection bias for patients in which there was a difficult clinical decision-making process is possible and could alter the performance of ccLS. Patient management decisions were at the discretion of the treating physician. Without randomization of management (surveillance, RMB, and surgery), there is inherent selection bias in which patients had histopathology available. In the analysis of any diagnostic test, the standard of reference is critical. In this study, the standard of reference was histology, obtained both by RMB (35%) and surgery. RMB is prone to diagnostic errors although these are predominantly driven by its poor NPV [8]. However, there were no lesions with benign or nondiagnostic pathologic diagnosis on RMB in our study. In contrast, a definitive diagnosis on RMB has

a PPV of 99.8% for RCC [8]. Therefore, RMB results for histological type were felt to be accurate. Approximately half of all our patients (126/256) with a ccLS score had no pathologic confirmation. While the final number of renal masses ( $n = 63$ ) is a relatively small cohort, it is the largest series to date evaluating the diagnostic performance of prospectively assigned ccLS [10,12,14].

## 5. Conclusions

Utilizing prospective data, we confirm previously reported data that mpMRI can reasonably identify ccRCC histology in cT1a renal masses. A RMB should be considered for ccLS 3 tumors if active treatment is considered and can likely be omitted for ccLS 4–5. Standardization of imaging protocols and reporting criteria such as ccLS can be used to aid in the diagnosis and management of SRM and may reduce the number of patients who undergo routine biopsy.

## Authors' Contribution

B Johnson: Data collection, data analysis, and manuscript writing/editing.

S Kim: Data collection.

R Steinberg: Manuscript writing/editing, data analysis.

A Diaz de Leon: Development and updating of Fig. 1, manuscript review/editing.

I Pedrosa: Protocol/project development, manuscript writing/editing, and data analysis.

JA Cadeddu: Protocol/project development, manuscript writing/editing, and data analysis.

## Informed consent

Informed consent was waived by the Institutional Review Board based given the retrospective nature of this review.

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