Differentiation of clear from non-clear cell renal cell carcinoma using CT washout formula

Ryan P. Kopp, MD,[1,2] Lejla Aganovic, MD,[3,4] Kerrin L. Palazzi, MD,[1]
Fiona H. Cassidy, MD,[3,4] Kyoko Sakamoto, MD,[1,2] Ithaar H. Derweesh MD,[1,2]

[1]Division of Urology/Department of Surgery, University of California San Diego School of Medicine, La Jolla, California, USA
[2]Surgical Service, San Diego Veterans Administration Medical Center, La Jolla, California, USA
[3]Department of Radiology, University of California San Diego School of Medicine, La Jolla, California, USA
[4]Radiology Service, San Diego Veterans Administration Medical Center, La Jolla, California, USA

KOPP RP, AGANOVIC L, PALAZZI KL, CASSIDY FH, SAKAMOTO K, DERWEESH IH. Differentiation of clear from non-clear cell renal cell carcinoma using CT washout formula. *Can J Urol* 2013;20(3):6790-6797.

Introduction: *To further elucidate potential patterns of contrast enhancement for renal neoplasm subtypes, we investigated utility of contrast washout formula to differentiate renal tumor histology after multiphase computerized tomography (CT).*

Materials and methods: *Single center retrospective cohort study of 163 patients with multiphase CT for renal masses obtained October 2007 to July 2012. Pathology confirmed clear cell (CC-RCC; n = 92), papillary (Pa-RCC; n = 43), chromophobe (Ch-RCC; n = 6), oncocytoma (OC; n = 11), or angiomyolipoma (AML; n = 11) histology. Two radiologists in consensus and blinded to histology recorded tumor size, morphology, and attenuation measurements in Hounsfield Units (HU). Data were analyzed between subgroups based on histology. Enhancement washout of the tumor was calculated by the formula (Mass nephrographic HU-Mass delayed HU)/(Mass nephrographic HU-Mass non-contrast HU) and used to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).*

Results: *Tumor size was largest among CC-RCC ($p < 0.001$). Homogeneous composition was more common among Pa-RCC and Ch-RCC ($p < 0.001$). Median washout for Ch-RCC (0.27) was significantly different from that of OC (0.54, $p = 0.05$). Overall 25 (15.3%) of tumors had washout < 0. Tumors with washout value < 0 were Pa-RCC 24/43 (56%), and Ch-RCC 1/6 (14%). Washout value < 0 had a specificity of 99.2% for Pa-RCC and 100% for non-CC-RCC. Washout value ≥ 0 had a sensitivity and NPV of 100% for CC-RCC, OC, and AML. Washout value ≥ 0 had a specificity of 35.2% and a PPV of 66.7% for CC-RCC.*

Conclusions: *Enhancement washout value < 0 is highly specific for Pa-RCC and non-CC-RCC. Washout value ≥ 0 is highly sensitive for CC-RCC, OC, and AML while there was a significant difference in median washout between OC and Ch-RCC. Further prospective investigation is requisite to confirm these findings.*

Key Words: carcinoma, renal cell, computerized tomography, diagnosis, enhancement, histology, Hounsfield unit

Introduction

An increasing number of individuals are diagnosed with renal cell carcinoma (RCC) each year, with more cancers diagnosed at earlier stages,[1] presumably secondary to increased utilization of cross sectional imaging. Computerized tomography (CT) is currently a standard method for identification and clinical staging of renal masses, but may also demonstrate advantage for surgical planning, surveillance of small renal masses, and assessment of response to ablative and systemic therapy.[2-4] A substantial number of patients with localized masses identified on CT who undergo extirpative surgery have an inaccurate or incomplete preoperative estimation of pathological risk--historically extirpative surgery has been the key method of diagnosis and therapy for RCC, however many small renal masses have limited pathological risk—roughly 10%-20% of patients who undergo extirpative surgery may have benign lesions, and another 60% are indolent variants of RCC, and chance of benign histology increases with decreasing size of the mass.[5,6]

Accepted for publication April 2013

Address correspondence to Dr. Ithaar H. Derweesh, Division of Urology, Moores UCSD Cancer Center, 3855 Health Sciences Drive, Mail Code: 0987, La Jolla, CA 92093-0987, USA

The significant prevalence of benign lesions and preponderance of indolent RCC on surgical pathology of small renal masses has lead to further investigation towards improvement of diagnostic methods and pre-treatment risk assessment. Utility of renal mass biopsy for initial diagnosis remains controversial; despite improvements in technique in recent years,[7] up to 20% of percutaneous biopsies remain non-diagnostic in modern series, with imperfect assessment for presence of malignancy and tumor subtype.[3,8,9] Noninvasive methods that increase the diagnostic ability to differentiate types of renal masses will be increasingly important as knowledge regarding disease progression and response to therapy continues to develop. This has led to investigation through a heterogeneous selection of imaging modalities to differentiate renal tumor histologies.[10-12] Recent studies suggest ability to differentiate between benign and malignant lesions using enhancement patterns on contrast CT, however these reports are of small cohorts with conflicting results,[13,14] and to date there is no validated consensus on how to differentiate tumor histology with imaging. We sought to identify if application of contrast washout formula on contrast enhanced CT may aid in the differentiation of renal tumor histology.

Materials and methods

Study population

Institutional review board approved retrospective cohort study includes individuals at San Diego Veterans Affairs Medical Center who underwent multiphase CT for cortical solid renal masses from October 2007 to July 2012 (n = 163). The scans were obtained as part of a work up for renal tumors suspicious for malignancy ('renal mass protocol' CT scan) prior to planned extirpative surgery (radical nephrectomy, partial nephrectomy). Neoplasms not diagnosed by renal mass protocol CT [magnetic resonance imaging or CT urogram protocol] were excluded (n = 34). Cystic, urothelial, inflammatory/infectious and hematologic malignant lesions were excluded were excluded from analysis, and patients with non-lipid poor angiomyolipoma (AML) and those without confirmed tumor histology were also excluded from the analysis (n = 53). Standard pathological examination of the corresponding renal masses confirmed clear cell (CC-RCC; n = 92), papillary (Pa-RCC; n = 43), chromophobe (Ch-RCC; n = 6), oncocytoma (OC; n = 11), or angiomyolipoma (AML; n = 11) histology.[15] Radiologists were blinded to the tumor histology while interpreting the imaging until after analysis of the data.

CT imaging evaluation

CT exams were performed with 4- (Aquilion 4, Toshiba Medical Systems, Otawara, Japan) or 64- detector row helical scanners (GE Medical Systems, Milwaukee, WI, USA). CT images were acquired with the following parameters: 120 kVp, 200 mA-600 mA depending on the size of the patient. The pitch varied from 0.75 to 1.5. In 64 slice scanner section thickness measured 0.625 mm reconstructed at 5 mm and at 4 slice scanner 5 mm section thickness was obtained. Patients were scanned using a renal mass protocol that included 3 or 4 phases. The 4 phase protocol (n = 83 patients; 48 CC-RCC; 28 Pa-RCC; 0 Ch-RCC; 8-OC; 7-AML) consisted of a non-contrast phase through the kidneys, a corticomedullary phase (35 second-delay) through the kidneys, a nephrographic phase (80 second delay) from the diaphragm to the symphysis pubis and a 180 second delay through the kidneys. The 3 phase CT scan (n = 72 patients; 44 CC-RCC; 15 Pa-RCC; 6 Ch-RCC; 3-OC; 4-AML) omitted the corticomedullary phase, which was not used in the washout analysis. All patients received 140 cc of nonionic intravenous contrast material (Iohexol 350, Omnipaque; GE Healthcare, Milwaukee, WI, USA) at a rate of 4 mL/sec. Images were reviewed on a picture archiving and communication system workstation.

Data and image analysis

Clinical data included demographics, history of smoking, hypertension, and preoperative serum creatinine. Two radiologists, blinded to pathological outcome, interpreted the images and when there was discordance in image interpretation, the final decision was reached by consensus. Interpreted parameters included numerical values for tumor size (cm), attenuation measurements in Hounsfield Units (HU), and categorical measurements of heterogeneous or homogeneous composition, collecting system entry, presence of necrosis, and cystic components. Region of interest was placed over the area with the highest attenuation on corticomedullary and/or nephrographic phase for attenuation measurements. Matching regions of interest were placed in the same location on the non-contrast and delayed phases. The region of interest covered the maximal measurable area that demonstrated highest enhancement. If the mass enhanced homogeneously, the region of interest covered one half to two thirds of the mass. Cystic, calcified, or necrotic areas were not included in the region of interest.

Statistical analysis and measures of performance

Data were analyzed between histologic subgroups using comparative statistics. Clinicopathological characteristics were compared using univariable

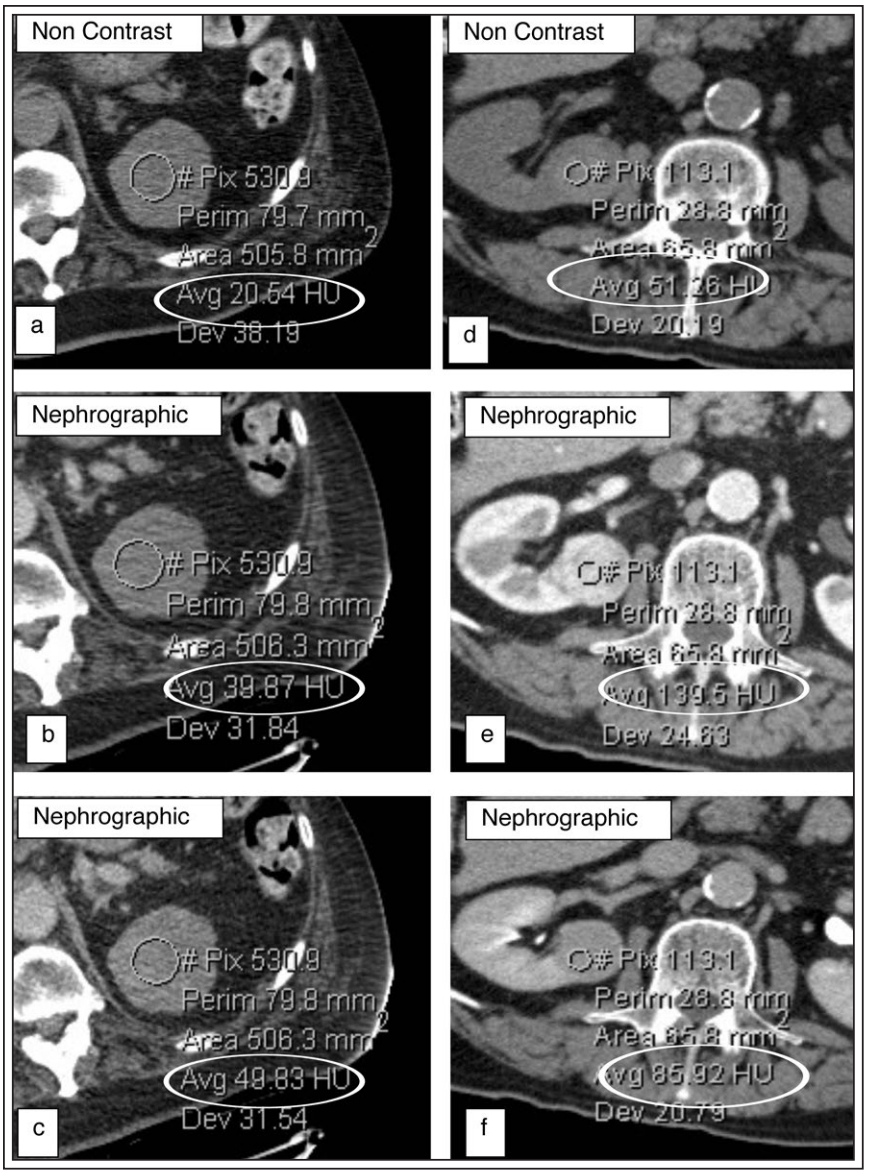

Figure 1. [HU in the ellipsoid in each image]. **a)** 69-year-old male with left papillary renal cell carcinoma. Non-contrast CT demonstrates mass to measure 20 HU; **b)** after contrast administration, the mass progressively enhances from 39 HU on nephrographic scan, and then **c)** to 49 HU on 3 minute delayed image. The enhancement washout of this mass equals (Mass Nephrographic HU-Mass Delayed HU)/(Mass Nephrographic HU-Mass Non-contrast HU) = 39-49/39-20= -0.5; **d)** 63-year-old male with right clear cell renal cell carcinoma. Non-contrast CT demonstrates right renal mass to measure 51 HU; **e)** the mass achieves maximal enhancement at nephrographic CT scan measuring 139 HU, with significant washout by 3 minute delayed image when it measures 85 HU; **f)** the enhancement washout of this mass equals 139-85/139-51= 0.6

analysis with Chi-square for categorical variables, ANOVA/independent t-test (Bonferroni correction) for normally distributed continuous measures and Kruskal-Wallis/mann-whitney u-test for non-normally distributed continuous variables. Absolute enhancement washout value was calculated by the formula (Mass nephrographic HU-Mass delayed HU)/(Mass nephrographic HU-Mass non-contrast HU) and is reported as a raw value.[16] The corticomedullary phase is omitted from the washout formula. Examples of washout calculation are demonstrated in Figure 1. Washout value was used to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for predicting tumor subtypes. After preliminary review of the data a threshold value of 0 was initially designated for categorical analysis comparing washout < 0 versus ≥ 0 to maximize simplicity of potential use in clinical practice. A second threshold of 0.16 was designated for categorical analysis comparing washout ≥ 0.16 versus washout < 0.16 to maximize measures of test performance according to the distribution of washout values for all tumor types. Additional analysis included measurements of relative enhancement of tumor to cortex primarily in the corticomedullary phase, but also the other phases, to determine if these measurements could differentiate between oncocytoma and RCC.[13,14] Statistical analysis was performed with SPSS version 17.0 (Chicago, IL, USA). P-value < 0.05 was defined as significant.

Results

Participants

We included 163 patients in the study. Significant differences existed in age ($p < 0.001$), sex ($p < 0.001$), and preoperative serum creatinine ($p = 0.008$) between histological subgroups, Table 1.

TABLE 1. **Patient characteristics and tumor imaging morphology**

	CC-RCC (n = 92)	Pa-RCC (n = 43)	Ch-RCC (n = 6)	OC (n = 11)	AML (n = 11)	p value
Mean age ± SD, yrs	64 ± 10.5	59 ± 11.7	60 ± 8.3	69 ± 8.6	51 ± 16.4	< 0.001
Sex						< 0.001
Male	75 (85.2%)	33 (78.6%)	6 (100%)	8 (72.7%)	3 (27.3%)	
Female	13 (14.8%)	9 (21.4%)	0 (0%)	3 (27.3%)	8 (72.7%)	
Race						0.151
Caucasian	53 (63.9%)	24 (61.5%)	2 (33.3%)	10 (90.9%)	5 (50%)	
Other	30 (36.1%)	15 (38.5%)	4 (66.7%)	1 (9.1%)	5 (50%)	
Mean BMI ± SD, kg/m^2	29 ± 5.5	27.7 ± 6.5	28.1 ± 3.3	27.8 ± 4.4	25.5 ± 4.8	0.400
Smoking history	54 (64.3%)	24 (63.2%)	1 (16.7%)	3 (42.9%)	1 (33.3%)	0.123
Preoperative creatinine (IQR)	0.99 (0.85-1.1)	0.96 (0.8-1.1)	0.96 (0.8-1.2)	1.2 (0.8-1.4)	0.79 (0.7-0.9)	0.008
Tumor size, cm (IQR)	4.9 (2.9-7.2)	2.7 (1.7-5.5)	3.6 (3-5.3)	1.8 (1.2-3.2)	1.7 (1.2-5)	< 0.001
Borders						0.413
Well defined	79 (85.9%)	39 (90.7%)	5 (83.3%)	11 (100%)	11 (100%)	
Ill defined	13 (14.1%)	4 (9.3%)	1 (14.3%)	0	0	
Composition						< 0.001
Heterogeneous	87 (94.6%)	11 (25.6%)	0 (0%)	5 (45.5%)	6 (54.5%)	
Homogeneous	5 (5.4%)	32 (74.4%)	6 (85.7%)	6 (54.5%)	5 (45.5%)	
Calcification	17 (18.5%)	5 (11.6%)	2 (33.3%)	0	0	0.146
Lymphadenopathy	2 (2.2%)	3 (7%)	0 (0%)	0	0	0.502
Necrosis	67 (77.9%)	9 (20.9%)	0 (0%)	0	0	< 0.001
Cystic	3 (3.5%)	2 (4.7%)	0 (0%)	0	0	0.870

CC = clear cell; RCC = renal cell carcinoma; Pa = papillary; Ch = chromophobe; OC = oncocytoma; AML = angiomyolipoma; BMC = body mass index

Imaging characteristics

Tumor size was largest among CC-RCC and smallest among AML ($p < 0.001$). Heterogeneous composition was most common among CC-RCC, and homogeneous composition was more common among Pa-RCC and Ch-RCC ($p < 0.001$), Table 1. After administration of contrast, CC-RCC, OC, and AML enhanced to significantly greater magnitude compared to Pa-RCC and Ch-RCC within all post-contrast phases ($p < 0.001$). Overall 25 (15.3%) of tumors had washout < 0. Median washout value for CC-RCC was 0.54 (IQR 0.47-0.61), and similarly for OC was 0.54 (IQR 0.44-0.7). Median washout for Ch-RCC (0.27, IQR 0.07-0.35) was significantly different from that of OC ($p = 0.05$). Tumors with washout value < 0 were Pa-RCC 24/43 (56%), and Ch-RCC 1/6 (14%). No patients with CC-RR, OC, or AML had washout value < 0. When the washout cut off was increased to 0.16 a total of 9 more papillary tumors were included, for a total of 33 papillary tumors (76.7%) included in the group < 0.16. Group assignment of other histologies was not affected by increasing the washout threshold to 0.16, Table 2. A distribution of tumor enhancement washout values is shown in Figure 2.

Additional enhancement analysis compared the relative enhancement of tumor to cortex in the corticomedullary phase for tumor subtypes. When difference in Mass minus Cortex in the corticomedullary phase was calculated, median difference (IQR) was -6.5 (-37 to 22.8) for CC-RCC; -123 (-160.3 to -87) for Pa-RCC; 28 for OC (-57. 8 to -18.3) and -20 (-44 to -1) for AML [p value < 0.001, overall and significant in pair-wise comparisons for CC-RCC versus Pa-RCC, Pa-RCC versus OC, and Pa-RCC versus AML, but not CC-RCC versus OC]. Therefore, on subset analysis, Pa-RCC, but not CC-RCC demonstrated a consistent difference in corticomedullary values between mass and cortex compared to OC.

TABLE 2. **Tumor attenuation values (HU) and washout**

	CC-RCC (n = 92)	Pa-RCC (n = 43)	Ch-RCC (n = 6)	OC (n = 11)	AML (n = 11)	p value
Non-contrast HU (IQR)	32 (27-37)	35 (28-40)	37 (28-44)	30 (25-35)	40 (31-52)	0.053
Corticomedullary HU (IQR)	161 (134-204)	54 (45-72)	- -	153 (131-186)	163 (127-181)	< 0.001*
Nephrographic HU (IQR)	145 (130-172)	64 (51-84)	71 (62-75)	158 (132-190)	144 (134-149)	< 0.001*
Delayed HU (IQR)	86 (75-98)	65 (57-78)	62 (55-68)	85 (79-100)	91 (82-106)	< 0.001*
Washout (IQR)	0.54 (0.47-0.61)	-0.04 (-0.35-0.13)	0.27 (0.07-0.35)	0.54 (0.44-0.7)	0.44 (0.42-0.57)	< 0.001*
Washout (# tumors)						< 0.001*
< 0.16	0	33 (76.7%)	1 (16.7%)	0	0	
≥ 0.16	92 (100%)	10 (23.3%)	5 (83.3%)	11 (100%)	11 (100%)	
Washout (# tumors)						< 0.001*
< 0	0	24 (55.8%)	1 (16.7%)	0	0	
≥ 0	92 (100%)	19 (44.2%)	5 (83.3%)	11 (100%)	11 (100%)	

CC = clear cell; RCC = renal cell carcinoma; Pa = papillary; Ch = chromophobe; OC = oncocytoma; AML = angiomyolipoma

Statistical measures of performance

Washout value < 0 had a specificity of 99.2% for Pa-RCC and 100% for non-CC-RCC. Washout value ≥ 0 had sensitivity and NPV of 100% for CC-RCC, OC, and AML. Washout value ≥ 0 had a specificity of 35.2% and a PPV of 66.7% for CC-RCC, Table 3. After increasing the washout threshold to 0.16, for washout < 0.16 the sensitivity for Pa-RCC increased to 77%. Washout value ≥ 0.16 had a specificity of 52.1% and PPV of 71.3% for CC-RCC.

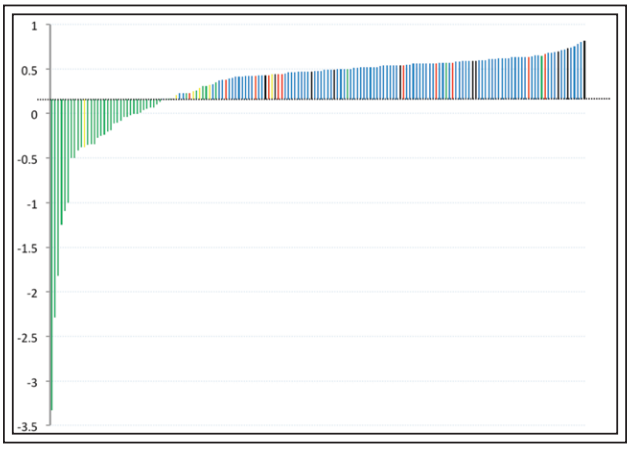

Figure 2. Waterfall plot demonstrating distribution of enhancement washout values among all tumors in the study. A value of 0.16 was chosen to maximize cutoff between clear cell and non-clear cell renal cell carcinoma. Histologies are Pa-RCC (green), Ch-RCC (yellow), CC-RCC (blue), AML (red), and OC (black).

Discussion

Herein we demonstrate an efficient method that provides an additional tool to aid with diagnosis of renal mass histology. This method may be easily applied in clinical practice, as it 1) uses existing technology and imaging practices, and 2) applies a contrast washout evaluation analogous to that radiologists and urologists may be familiar with for evaluation of adrenal masses. Most substantial, we demonstrated that enhancement washout value < 0 was 100% specific for non-clear cell RCC in our cohort. As defined in our study, to obtain an enhancement washout value < 0 the mass must enhance greater on the delayed phase compared to the nephrographic phase on contrast-enhanced CT images.

These findings are similar to a recent report by Shebel et al, who investigated enhancement washout of renal masses in 97 patients, but noted a greater degree of enhancement for Ch-RCC and substantially less for OC compared to our study.[17] While Shebel et al utilized multiple thresholds for relative and absolute washout, we designed our analysis around a washout value of < 0

TABLE 3. **Statistical measures of performance for each histology when compared to all others; a) washout value of < 0 and ≥ 0, b) washout value of < 0.16 and ≥ 0.16.**

	CC-RCC (n = 92)	Pa-RCC (n = 43)	Ch-RCC (n = 6)	OC (n = 11)	AML (n = 11)
a) Washout < 0					
Sensitivity	0%	56%	17%	0%	0%
Specificity	64.8%	99.2%	84.7%	83.6%	83.6%
PPV	0%	96%	4.0%	0%	0.0%
NPV	33.3%	86.2%	96.4%	92%	92.0%
Washout ≥ 0					
Sensitivity	100%	44%	83%	100%	100%
Specificity	35.2%	0.8%	15.3%	16.4%	16.4%
PPV	66.7%	13.8%	3.6%	8.0%	8.0%
NPV	100.0%	4.0%	96.0%	100.0%	100.0%
b) Washout < 0.16					
Sensitivity	0%	77%	17%	0%	0%
Specificity	52.1%	99.2%	79%	77.6%	77.6%
PPV	0%	97.1%	2.9%	0%	0.0%
NPV	28.7%	92.2%	96.1%	91.5%	91.5%
Washout ≥ 0.16					
Sensitivity	100%	23%	83%	100%	100%
Specificity	47.9%	0.8%	21%	22.4%	22.4%
PPV	71.3%	7.8%	3.9%	8.5%	8.5%
NPV	100.0%	2.9%	97.1%	100.0%	100.0%

CC = clear cell; RCC = renal cell carcinoma; Pa = papillary; Ch = chromophobe; OC = oncocytoma; AML = angiomyolipoma; PPV = positive predictive value; NPV = negative predictive value

versus ≥ 0 for. We were able to determine that increasing the threshold to 0.16 aided in differentiation of Pa-RCC from CC-RCC, which is closer to the value of 0.14, or 14% as reported by Shebel et al. Further analysis and validation studies would be necessary to determine the thresholds with highest accuracy for differentiation between tumor types.

We find that application of washout formula to differentiate between clear and non-clear cell RCC may be a practical adjunct to current diagnostic methods as our field marches towards improved risk assessment of renal masses and efficacy of individualized medical and surgical therapies. Distinct histologic types of renal masses have varying risks of progression to metastatic disease, with clear cell having the highest rate of visceral metastases,[5,6,18] and patients with metastatic disease demonstrate differential responses to systemic medical therapy based on tumor type.[19-22] Currently there is substantial clinical interest in differentiating between benign and malignant masses using CT parameters, however potentially applicable results have not been validated. In this study we also performed a secondary analysis to determine if we could validate results of other groups who have suggested that enhancement patterns may be able to differentiate between OC and RCC in the corticomedullary phase.[13,14] We found that there was no significant difference in the relative attenuation between tumor and cortex for OC and CC-RCC in the corticomedullary phase, though we did note a significantly greater median washout for OC than Ch-RCC. Interestingly, the study by Gakis et al reports higher attenuation values for CC-RCC, while the study by Bird et al reports higher values for OC, and similarly each of these studies include small cohorts of OC. Although Bird et al also reported that only OC has a washout greater than 50%;[14] these findings are not consistent with our study or the results of Shebel et al, wherein washout values were nearly identical for OC and CC-RCC.

Diagnostic methods should also aim to limit morbidity of treatment in those who may harbor benign or less aggressive lesions. With increased interest in active surveillance in renal masses, further measures of risk assessment are necessary.[23,24] We would not recommend omission of renal mass

biopsy in the setting of active surveillance, however application of contrast washout and enhancement patterns could aid in the setting of a non-diagnostic or equivocal biopsy, where for example, the finding of 'oncocytic neoplasm,' which may indicate OC or Ch-RCC, may be placed in the context of a washout value to aid in risk stratification. Further studies with a larger cohort are necessary to confirm our findings with respect to difference between Ch-RCC and OC, yet our finding is tantalizing and warrants further investigation.

Incorporation of imaging features to differentiate renal mass histology has been an emerging area of interest in recent years.[10-13,25,26] Limitations of utilizing raw enhancement as the primary predictor have been acknowledged, as enhancement may be significantly affected by intrinsic factors such as cardiac output which varies between individuals—although intrinsic factors may be adjusted for with additional measurements and mathematics, practices to correct for intrinsic factors are not widely utilized but may improve correlation of radiology to pathology.[10,11] Despite limitations, magnitude of enhancement has historically been the greatest predictor to differentiate between tumor types.[11,17] Additionally, other features may prove informative; we found that heterogeneous enhancement was significantly more common in CC-RCC compared to Pa- or non-CC-RCC. This finding has previously been reported by Zhang et al in an analysis of 198 renal tumors, two separate image interpreters found heterogeneous enhancement in 79% and 88% of CC-RCC.[11] Vikram et al described differential enhancement of CC-RCC and Pa-RCC on CT imaging. They noted that Pa-RCC enhances less than CC-RCC on all phases of imaging, and explain this effect as relative hypovascularity of Pa-RCC compared to CC-RCC.[25] However, we note in our study that while CC-RCC tends to have more abrupt de-enhancement or washout of contrast, many Pa-RCC will continue to increase the enhancement through delayed images–this is how a washout value < 0 is obtained, Figure 1. While Pa-RCC magnitude of enhancement may be less than CC-RCC, it is important to note the differences in the timing of maximal enhancement. These findings where similarly reported by Shebel et al.[17]

Investigations of imaging for differentiation of renal masses are not limited to CT imaging. Wang et al noted in a retrospective analysis of 85 tumors that diffusion-weighted magnetic resonance imaging (MRI) may have greater than 90% sensitivity and specificity for differentiation of CC-RCC and non-CC-RCC. The authors were unable to differentiate among other subtypes.[12] A potential hindrance of diffusion weighted MRI is substantial variability between institutions secondary to MRI systems used and the specific sequence parameters.[12,27] Vargas et al recently reported a retrospective study analyzing utility of multiphasic contrast-enhanced MRI to differentiate between malignant and benign histologic subtypes in 152 renal cortical masses which had undergone surgical extirpation. The authors utilized calculations of change in signal intensity between pre-contrast imaging and post-contrast phases. Similar to our findings, they demonstrated that Pa-RCC and Ch-RCC demonstrated less enhancement (significantly lower %SI change ($p < 0.0001$-0.0120) than CC-RCC in all three post-contrast phases, while CC-RCC was not significantly different from OC at any post-contrast phase ($p = 0.2081$-0.6000).[26] Many of these imaging modalities and techniques for interpreting images are promising, and we look forward to future validations and prospective investigations to compare effectiveness of different imaging modalities in differentiating renal masses.

One limitation of our study is the retrospective study design—as CT scan was not the only modality utilized to characterize renal cortical tumors at our institution; furthermore, not all patients who had CT scan for renal mass underwent surgical extirpation. Our analysis is limited to those patients with pre-existing imaging and pathology, thus limiting our ability to test the true utility of these imaging parameters for diagnosis, as may be performed in a prospective consecutive manner. Furthermore, this study was not limited to small renal masses—which present more of a diagnostic and clinical dilemma--however the range in tumor size represents a more natural distribution at presentation, and consequently imaging characteristics that reflect tumor histology throughout its growth. Also, patients must be able to receive intravenous contrast--this diverts application away from those with chronic kidney disease and who may theoretically benefit the most from individualized treatment plans. In addition the duration of the time during which CT studies where performed in resulted heterogeneity in the techniques utilized for CT imaging. To our knowledge, this is the second report primarily investigating contrast washout formula to differentiate between clear and non-CC-RCC on CT.[17] Although our findings are similar to the previous study, there were substantial differences in measured enhancement of Ch-RCC and OC, which would affect thresholds used for washout value to differentiate between masses. Furthermore, while neither study supports the difference in OC and CC-RCC washout recently reported by Bird et al,[14] and all of these studies are limited by a small number of OC,

we nonetheless noted a difference in median washout between OC and Ch-RCC which may hold promise as an adjunct to indeterminate oncocytic neoplasm biopsy findings, and therefore warrants further investigation. Washout and enhancement analysis will likely undergo continued refinement as more data emerge and are applied towards developing a test with high accuracy for differentiation between renal tumors.

Conclusion

Enhancement washout value < 0 on CT imaging is highly specific for Pa-RCC and non-CC-RCC. CC-RCC is essentially excluded for renal tumors that progressively enhance on all post-contrast phases. Washout value ≥ 0 is highly sensitive for CC-RCC, OC, and AML, while there was a significant difference in median washout between OC and Ch-RCC. Additional validation and prospective analysis is warranted to confirm these findings and develop washout thresholds with the highest accuracy prior to consideration of widespread application in clinical decision making. □

References

1. Kane CJ, Mallin K, Ritchey J et al. Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer* 2008; 113(1):78-83.
2. Pallwein-Prettner L, Flory D, Rotter CR et al. Assessment and characterisation of common renal masses with CT and MRI. *Insights Imaging* 2011;2(5):543-556.
3. Campbell SC, Novick AC, Belldegrun A et al. Guideline for management of the clinical T1 renal mass. *J Urol* 2009;182(4): 1271-1279.
4. Derweesh IH, Herts BR, Motta-Ramirez GA et al. The predictive value of helical computed tomography for collecting-system entry during nephron-sparing surgery. *BJU Int* 2006;98(5): 963-968.
5. Frank I, Blute ML, Cheville JC et al. Solid renal tumors: an analysis of pathological features related to tumor size. *J Urol* 2003;170(6 Pt 1):2217-2220.
6. Pahernik S, Ziegler S, Roos F et al. Small renal tumors: correlation of clinical and pathological features with tumor size. *J Urol* 2007;178(2):414-417.
7. Lane BR, Samplaski MK, Herts BR et al. Renal mass biopsy--a renaissance? *J Urol* 2008;179(1):20-27.
8. Leveridge MJ, Finelli A, Kachura JR et al. Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. *Eur Urol* 2011;60(3):578-584
9. Menogue SR, O'Brien BA, Brown AL et al. Percutaneous core biopsy of small renal mass lesions: a diagnostic tool to better stratify patients for surgical intervention. *BJU Int* 2013;111(4 Pt B): E146-E151.
10. Ruppert-Kohlmayr AJ, Uggowitzer M, Meissnitzer T et al. Differentiation of renal clear cell carcinoma and renal papillary carcinoma using quantitative CT enhancement parameters. *AJR Am J Roentgenol* 2004;183(5):1387-1391.
11. Zhang J, Lefkowitz RA, Ishill NM et al. Solid renal cortical tumors: differentiation with CT. *Radiology* 2007;244(2):494-504.
12. Wang H, Cheng L, Zhang X et al. Renal cell carcinoma: diffusion-weighted MR imaging for subtype differentiation at 3.0 T. *Radiology* 2010;257(1):135-143.
13. Gakis G, Kramer U, Schilling D et al. Small renal oncocytomas: differentiation with multiphase CT. *Eur J Radiol* 2011;80(2):274-278.
14. Bird VG, Kanagarajah P, Morillo G et al. Differentiation of oncocytoma and renal cell carcinoma in small renal masses (<4 cm): the role of 4-phase computerized tomography. *World J Urol* 2011; 29(6):787-792.
15. Reuter VE, Tickoo SK. Differential diagnosis of renal tumours with clear cell histology. *Pathology* 2010;42(4):374-383.
16. Szolar DH, Korobkin M, Reittner P et al. Adrenocortical carcinomas and adrenal pheochromocytomas: mass and enhancement loss evaluation at delayed contrast-enhanced CT. *Radiology* 2005;234(2):479-485.
17. Shebel HM, Elsayes KM, Sheir KZ et al. Quantitative enhancement washout analysis of solid cortical renal masses using multidetector computed tomography. *J Comput Assist Tomogr* 2011;35(3):337-342.
18. Remzi M, Ozsoy M, Klingler HC et al. Are small renal tumors harmless? Analysis of histopathological features according to tumors 4 cm or less in diameter. *J Urol* 2006;176(3):896-899.
19. Tannir NM, Plimack E, Ng C et al. A phase 2 trial of sunitinib in patients with advanced non-clear cell renal cell carcinoma. *Eur Urol* 2012;62(6):1013-1019.
20. Silberstein JL, Millard F, Mehrazin R et al. Feasibility and efficacy of neoadjuvant sunitinib before nephron-sparing surgery. *BJU Int* 2010;106(9):1270-1276.
21. Stroup SP, Raheem OA, Palazzi KL et al. Does timing of cytoreductive nephrectomy impact patient survival with metastatic renal cell carcinoma in the tyrosine kinase inhibitor era? A multi-institutional study. *Urology* 2013;81(4):805-811.
22. Choueiri TK, Plantade A, Elson P et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol* 2008;26(1):127-131.
23. Derweesh IH, Novick AC. Small renal tumors: natural history, observation strategies and emerging modalities of energy based tumor ablation. *Can J Urol* 2003;10(3):1871-1879.
24. Kunkle DA, Crispen PL, Chen DY et al. Enhancing renal masses with zero net growth during active surveillance. *J Urol* 2007;177(3):849-853.
25. Vikram R, Ng CS, Tamboli P et al. Papillary renal cell carcinoma: radiologic-pathologic correlation and spectrum of disease. *Radiographics* 2009;29(3):741-754.
26. Vargas HA, Chaim J, Lefkowitz RA et al. Renal cortical tumors: use of multiphasic contrast-enhanced MR imaging to differentiate benign and malignant histologic subtypes. *Radiology* 2012;264(3):779-788.
27. Zhang JL, Sigmund EE, Chandarana H et al. Variability of renal apparent diffusion coefficients: limitations of the monoexponential model for diffusion quantification. *Radiology* 2010;254(3):783-792.