Non-contrast imaging characteristics of papillary renal cell carcinoma: implications for diagnosis and subtyping

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BADRI AV, WAINGANKAR N, EDWARDS K, KUTIKOV A, PARSONS RB, CHEN DY, SMALDONE MC, VITERBO R, GREENBERG RE, UZZO RG. Non-contrast imaging characteristics of papillary renal cell carcinoma: implications for diagnosis and subtyping. *Can J Urol* 2019l26(5):9916-9921.

Introduction: *Current radiographic guidelines suggest unenhanced renal lesions < 20 Hounsfield Units (HU) are overwhelmingly benign, requiring no further evaluation. We evaluate our experience with papillary renal cell carcinoma (pRCC) presenting with low pre-contrast attenuation and the relationship of attenuation with histologic pRCC subtype.*

Materials and methods: *We reviewed our institutional kidney cancer database for patients with pT1 or pT2 pRCC between 2003-2017. Tumors were categorized by papillary subtype by expert uropathologists. Preoperative CT images were analyzed at six regional tumor locations. Low, presumably benign, unenhanced median attenuation was defined as ≤ 20 HU. We calculated the frequency of pRCC with low attenuation and assessed the relationship between attenuation and pRCC subtype using logistic regression.*

Results: *Sixty-one patients with evaluable imaging were included. Median tumor size was 6 cm (1.7 cm-15.3 cm) with 39% (n = 24) type-1 and 61% (n = 37) type-2. Half of all pRCC tumors (n = 30) exhibited very low pre-contrast attenuation (< 20 HU), risking misdiagnosis as benign using current guidelines. Of these, 80% (n = 24) were type-2 with significant biological potential. Overall, type-2 tumors demonstrated a lower pre-contrast attenuation than type-1 (median HU: 19.8 (1.5-42.3) versus 29.6 HU (10-45.8), p < 0.01; max HU: 25.3 versus 36.5 HU, p < 0.01). After adjustment, lower pre-contrast HU was an independent predictor of pRCC subtype associated with a 5.5-fold increase of being type-2 (OR = 5.47, p < 0.01).*

Conclusion: *pRCCs may exhibit very low attenuation on pre-contrast CT. This appears more common among the more aggressive type-2 subtype. These data suggest that low attenuation (< 20 HU) alone on non-contrast CT imaging is insufficient as a single parameter to rule out malignancy.*

Key Words: papillary, RCC, noncontrast, unenhanced, CT, radiomics

Introduction

Radiomics is the extraction of quantifiable features of an imaging modality intended to assist in non-invasive diagnosis, prognostication and risk stratification. It is an emerging area in genitourinary radiology. Quantifiable aspects of imaging data can include imaging signal features, such as density on computed tomography (CT), intensity on magnetic resonance imaging (MRI), and echogenicity on ultrasonography (US); physical features, such as size, volume, shape, lobularity, and architecture; anatomical features such as enhancement, tumor/organ relation, and texture or other features such as molecular imaging.[1] These data may be subject to high throughput extraction

Accepted for publication July 2019

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of mineable features and evolving AI algorithms[2] or combined with existing morphometric systems such as nephrometry scoring.[3,4]

Radiomics and computer aided diagnosis is particularly promising in the field of renal mass imaging, particularly as the frequency of incidentally detected lesions found on cross-sectional imaging for work up of other disease processes rise; increasingly, the modality of choice is the non-contrast CT.[5,6] Low attenuation renal contour abnormalities in this population are exceptionally common and therefore must be distinguished as cystic or potentially solid. Most guidelines, including some algorithms, advise that the majority of homogeneous masses with attenuation between -10 and +20 Hounsfield Units (HU) are overwhelmingly simple cysts (Bosniak I), with no further evaluation recommended.[7,8] In fact a recent position paper from the Incidental Findings Committee of the American College of Radiology recommends that homogeneous renal masses < 20 HU incidentally detected on non-contrast CT "require no further work up".[9] Conversely those lesions measuring between 20-70 HU on unenhanced CT scan have been deemed suspicious,[10,11] requiring further workup with pre/post imaging studies. As with any threshold, a specific cut off of < 20 HU on pre-contrast imaging may risk misdiagnosis and an opportunity for beneficial therapeutic intervention. To our knowledge, there is inconclusive literature that has addressed the likelihood of cancers in lesions that seem to be simple cysts, classically < 20 HU, on unenhanced CT.

Papillary renal cell carcinoma (pRCC), a histologic subtype that comprises 10%-15% of all RCC, is an optimal target for improving image-based risk stratification given that most lesions are homogenous with lower attenuation pre- and post-contrast and a flatter washout curve[12] and that there are noted prognostic differences between type-1 and type-2 pRCC; some studies have shown that type-1 pRCC portends a much more favorable prognosis than type-2 pRCC,[13] with significant cancer-specific mortality differences reported.[14] As such, the ability to accurately differentiate benign cystic lesions that need no further evaluation from pRCC with its subtypes preoperatively can mean the difference between a recommendation of "no further imaging required" and the patient undergoing potentially curative surgery for localized RCC. One aspect of CT-based radiomics, quantitative comparison of radiodensity, can provide useful prognostic data to assess biologic risk and optimize further management strategies, potentially without obtaining tissue.[15]

Here we reviewed the characteristics of pRCC presenting with very low pre-contrast attenuation and the relationship of attenuation with histologic pRCC subtypes.

Materials and methods

Patients

We reviewed our prospectively maintained comprehensive RCC database after obtaining Institutional Review Board (IRB) approval. We included all patients who were diagnosed with pT1 or pT2 papillary RCC after partial or radical nephrectomy by any approach from 2003-2017. Patients without available preoperative non-contrast CT scans in PACS were excluded. Patients with pT3, pT4 or N+ lesions were also excluded as these lesions were readily identifiable as likely malignant due to large size,

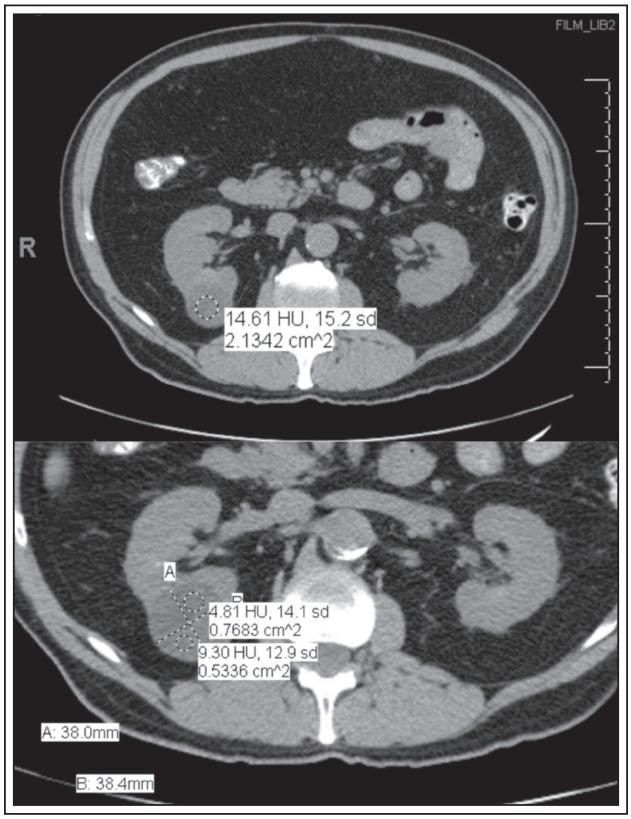

Figure 1. Representative axial slices of a preoperative unenhanced computed tomogram illustrating the heterogeneity technique employed. Above – single region of interest (ROI) used for the inferior attenuation measurement. Below – the center of the lesion is identified on axial imaging and bisected into four quadrants; four ROI measurements, one in each quadrant, are used for central measurements.

lesion complexity, and/or presence of local or nodal invasion. We excluded all cases of heterogeneity, septa, and nodularity present on preoperative non-contrast CT. Review by our institutional uropathologists confirmed the histology, stage (described by the 2010 TNM classification,[16]) and subtype of papillary type-1 versus 2. Although classification of papillary subtypes at some institutions accounts for mixed type 1 and 2, for the purposes of our study, we included all tumors that could be definitively classified as either papillary type 1 or 2. Other covariates of interest included age, gender, and laterality. Of the patients with pT1-pT2 pRCC in the database, 61 patients were identified for whom complete clinical and pathological data were available and for whom primary radiographs could be analyzed.

Imaging

Preoperative non-contrast CT images were reviewed by an experienced genitourinary radiologist. Maximum tumor diameter was measured in centimeters. To account for tumor heterogeneity, densities in HU were calculated in six distinct axial regions of interest (ROI) in each tumor: superior, inferior, and four central areas including right anterior, right posterior, left anterior, and left posterior. From these six ROI measurements, a median was calculated for each patient to provide a global HU determination for each patient's mass, Figure 1. We defined low attenuation as ≤ 20 HU and high attenuation as > 20 HU.

Statistical analysis

We quantified degree of tumor heterogeneity by calculating standard deviations for the attenuation measurements within each lesion. All comparative statistical tests evaluated differences between papillary type-1 and type-2 lesions. For univariate analyses, Student's t-test was used for comparison of continuous data while Chi-squared and Fisher's exact tests were used for comparison of categorical data. All covariates were entered into a logistic regression analysis with pRCC type-2 as the dependent variable. HU was

TABLE 1. **Baseline clinical and descriptive data of patient included with a comparison of type-1 and type-2 pRCC lesions by descriptive statistic**

	All pRCC (n = 61)	**Type-1 pRCC (n = 24)**	**Type-2 pRCC (n = 37)**	**p value**
Age (years)	64.9	66.8	63.8	0.279
Diameter (cm)	6.07	5.27	6.59	0.103
Median ROI (HU)*	23.7	29.6	19.8	*0.002
Max ROI (HU)*	29.7	36.5	25.3	*0.001
SD of ROI (HU)	4.87	4.04	5.33	0.07
Gender				0.744
Men	48	20	28	
Women	13	4	9	
Laterality				0.531
Left	33	14	19	
Right	28	10	18	
Surgery type				0.056
Partial Nx	46	15	31	
Open	30	13	17	
Robotic	16	2	14	
Radical Nx	15	8	7	
Open	1	0	1	
Laparoscopic	13	8	5	
Robotic	1	0	1	

*denotes statistical significance
pRCC = papillary renal cell carcinoma; ROI = regions of interest; HU = Hounsfield Units; SD = standard deviation; Nx = nephrectomy

TABLE 2. **Proportion of type-1 and type-2 pRCC lesions based on low versus high attenuation. (X^2 = 7.6, p = 0.006)**

ROI (HU)	Type-1	Type-2	Total
≤ 20	6	24	30
> 20	18	13	31
Total	24	37	61
Proportion (%) ≤ 20*	6/24 (25%)	24/37 (64.9%)	30/61 (49.1%)

*denotes statistical significance
ROI = regions of interest; HU = Hounsfield Units

separately modeled as a categorical variable (low versus high HU) and a continuous variable. All statistical analysis was performed using Stata v14 (College Station, TX, USA).

Results

There were 61 patients analyzed with papillary RCC, of whom 24 had type-1 and 37 had type-2 pRCC. There were 39 pT1 lesions (16 type-1, 23 type-2) and 22 pT2 lesions (8 type-1, 14 type-2). Comparison of the type-1 and type-2 pRCC cohorts revealed no significant differences in age (median 66.8 versus 63.8 years, p = 0.28) or clinical tumor diameter (median 5.27 versus 6.59 cm, p = 0.10). Type-2 tumors demonstrated a significantly lower attenuation than type-1 tumors (median HU: 19.8 versus 29.6 HU, p < 0.01; max HU: 25.3 versus 36.5 HU, p = < 0.01). There was no difference in heterogeneity of attenuation between type-1 (SD = 4.04) and type-2 (SD = 5.33, p = 0.07) tumors. Demographic and baseline clinical statistics are detailed in Table 1.

Thirty patients (49%) had low attenuation lesions < 20 HU on non-contrast imaging, of which 6 (20%) had type-1 pRCC and 24 (80%) had type-2 pRCC (X^2=9.2, p = 0.002). Categorical comparison of low (≤ 20 HU) and high (> 20 HU) attenuation lesions illustrates that a greater proportion of type-2 pRCC (24, 64.9%) were categorized as low-density lesions on non-contrast CT than type-1 pRCC (6, 25%, X^2 = 9.2, p = 0.002), Table 2.

After controlling for age, gender, laterality, and size, HU was identified as an independent predictor of pRCC subtype. Relative to high HU tumors, low HU tumors have a 5.5-fold increase of being type-2 pRCC (OR = 5.47, 95% CI 1.67-17.92, p < 0.01), Table 3. HU remained an independent predictor of subtype when used as a continuous variable. Each unit decrease in HU was associated with an 8% increase in the odds of the lesion being type-2 pRCC (OR = 1.08, 95% CI 1.02-1.14, p = 0.006), Table 3.

Discussion

The ability to provide an accurate, noninvasive, quantifiable risk assessment of a renal lesion can meaningfully impact medical management and patient counseling. Currently, decision-making is most commonly based on differences between pre and post contrast-enhanced CT scans and MRI, and in some centers, performance of a percutaneous biopsy. While patients present to urologists with varying degrees of imaging workup, often the first indication of a renal mass is an abnormality on a non-contrast low-dose screening CT obtained due to abdominal symptomatology.[7] According to current radiology guidelines, further evaluation of incidental low-density renal lesions on non-contrast CT is often deemed unnecessary whereas benign renal cysts are the most common cause of these lesions. Here we assess the unenhanced CT density of

TABLE 3. **Multivariable analysis of association between covariates of interest and finding of type-2 pRCC. HU analyzed as both a categorical (cat.) and continuous (cont.) variable.**

Variable	Odds ratio	95% CI	p value
Age	0.994	0.936-1.056	0.856
Gender	1.541	0.326-7.266	0.584
Surgical laterality	0.996	0.306-3.243	0.996
Diameter (cm)	1.159	0.939-1.429	0.168
ROI (HU) (cat.)*	5.471	1.671-17.922	*0.005
ROI (HU) (cont.)*	1.081	1.022-1.141	*0.006

*denotes statistical significance
ROI = regions of interest; HU = Hounsfield Units

a large series of pathologically confirmed pRCC and demonstrate that they often meet current criteria for benign cysts give their low density. Inasmuch, foregoing further evaluation risks disease progression.

Lesions with attenuation of less than 20 HU have historically been considered to harbor negligible malignant potential whereas they most commonly represent Bosniak I simple cysts;[11,17-22] as such, the true incidence of RCC harboring < 20 HU unenhanced attenuation is unknown. It has also been previously reported that RCC will rarely appear as a homogeneous solid mass less than 20 HU on an unenhanced CT.[23] Support for this cut-point comes from the work of Pooler and associates, who demonstrated in their study of 193 RCCs that all cancers had attenuation values in the 20-70 range on non-contrast imaging.[22] In our analysis, however, almost half of the patients with pathologically confirmed pRCC demonstrated average ROI less than 20 HU on pre-contrast imaging, even when accounting for variations in heterogeneity. Moreover, this finding of low attenuation was common among patients with the more aggressive type-2 pRCC subtype. Application of the traditional 20 HU cut off to our data risks misclassifying 23% (using max HU) to 49% (using average HU) of pRCC in this series as benign cysts despite their solid and potentially biological aggressive nature. It follows that the current ACR guidelines regarding incidental renal masses on non-contrast CT must be interpreted with caution.[9]

Our work expands upon the findings of Schieda and colleagues, who found in their series of 96 tumors that 8 (8.3%) had pre-contrast attenuation < 20 HU, of which all were clear cell RCC. Their series featured 27 pRCC with a mean non-contrast attenuation of 34 +/- 10 HU; one standard deviation below the mean approached the cusp of the 20 HU cut off. They conclude that perhaps a larger series may have identified tumors under 20 HU.[24] Our series has more than twice as many papillary tumors, and to our knowledge is among the first to demonstrate papillary tumors having similar pre-contrast attenuation as simple cysts on non-contrast CT imaging.

In addition to finding a high frequency of pRCC patients with low attenuation, we demonstrated the ability to begin to discriminate between papillary subtypes using non-contrast CT: for each unit decrease in HU, there was an 8% increase in the odds of harboring a type-2 pRCC. While some have suggested that there may be a difference in lesion heterogeneity between the two subtypes of papillary tumors, our data did not support this. Similar lesion heterogeneity may be due to (1) a true lack of difference in heterogeneity between type-1 and 2 pRCCs, (2) our small sample size being underpowered to detect a difference in heterogeneity, or (3) our approach of measuring attenuation in six regions failing to expose a difference in lesion heterogeneity. Despite this, the ability to discriminate by mean attenuation provides important clinical context for radiologists evaluating non-contrast images of the kidney and may be useful to urologists in potentially selecting candidates for biopsy, active surveillance, or those in whom treatment should be more aggressively pursued.

Limitations of our work include the retrospective nature of the study and inherent selection bias, along with our relatively small sample size. While the denominator in our study was all pathologically proven papillary RCCs, not all renal malignancies, so extrapolation beyond pRCCs is unwarranted. Furthermore, our work retrospectively addresses preoperative imaging findings after surgery, therefore we cannot comment on patients with renal lesions < 20 HU that did not undergo surgery. Additionally, although we work with expert GU uropathologists, our pathologic specimens were not re-reviewed with modern schemes for papillary classification. Importantly, there is no uniformly accepted methodology employed to account for heterogeneity of attenuation within lesions, with other investigators opting for continuous sampling for attenuation within the entire tumor,[23] or selection of a single circular region.[25] Our approach of averaging ROI across six regions accounts for attenuation differences within each lesion to provide an objective and expedient way for those in a busy clinical practice to address intra-lesion heterogeneity; we further plot our median and standard deviation measurements in Figure 1 as an additional surrogate to heterogeneity. This methodology will ultimately require future study, external validation, and assessment in other tumor types. Lastly, patients captured in this study were referred to a tertiary specialty care center with prior imaging in-hand, thereby adding non-standardization of CT scanning technique.

Finally, we would like to emphasize that a pre- and post- contrast-enhanced CT or MRI remain the imaging modalities of choice and mainstay for diagnosis of renal tumors. In this report, we are not promoting a reliance on unenhanced CT scans; rather, we simply report data that contradict current ACR guideline recommendations suggesting that incidental renal lesions < 20 HU need no further evaluation[10] and, in so doing, favor a more thorough analysis of pre-contrast HU attenuation, in conjunction with lesion heterogeneity, enhancement, and the presence of mural nodularity, calcifications, multiple septations, to aid in contextualizing post-contrast

findings in the workup and further management of these renal masses. With an increase in usage of radiologist workflow aides such as night-hawk reads, quick reads, and the advent of computer-aided radiographic detection software,[8,26] a small change in pre-set attenuation parameters could have a drastic change in radiographic interpretations and specialist referrals. The majority (17/30, 57%) of our cohort with < 20 HU attenuation resided between 15-20 HU and would risk misclassification and under diagnosis if a 20 HU lower-limit attenuation parameter were set.

Conclusion

Here we demonstrate that nearly half of all pRCC lesions in our cohort had a pre-contrast attenuation of ≤ 20 HU. Moreover, we note a significant attenuation difference existed between type-1 and type-2 pRCC lesions with type-2 lesions exhibiting even lower non-contrast HU suggesting that the biologically more aggressive lesions are at highest risk for being overlooked as benign lesions using current ACR guidelines. Additionally, we noticed that HU independently predicted papillary subtype, but this finding will need further validation in external cohorts. While non-contrast CT does not replace pre/post contrast-enhanced imaging in the ability to discriminate between benign and malignant lesions, our analysis of differential attenuation can further inform the risk stratification of patients with renal lesions and better contextualize post-contrast findings in the workup and further management of these renal masses. □

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