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Original Article

Can multiphase CT scan distinguish between papillary renal cell carcinoma type 1 and type 2?

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ABSTRACT

Objective: To investigate the utility of multiphase computed tomography (CT) and percutaneous renal mass biopsy (PRMB) in differentiating between papillary renal cell carcinoma (pRCC)–Type 1 and –Type 2, as emerging data have suggested differential enhancement patterns in different renal tumor histologies.

Material and methods: Retrospective analysis of 51 patients (23 pRCC-Type 1/28 pRCC-Type 2) who underwent multiphase CT followed by surgery from July 2011 to April 2016 was performed. Data were analyzed between subgroups based on histology. Multiphase CT was analyzed for tumor size, and attenuation [Hounsfield Units (HU)]. Change in HU (ΔHU) was calculated between noncontrast (NC), corticomedullary (CM), nephrographic (N), and delayed (D) phases. Subset analysis was carried out on patients who underwent PRMB prior to surgery.

Results: There was no difference in median tumor size (pRCC-Type 1 2.8 vs. pRCC-Type 2 2.6 cm, p=0.832). In addition to tumor size being similar between groups, distribution of tumor stages between groups was also similar (p=0.651). Greater proportion of high-grade tumors (III/IV) was noted in pRCC-Type 2 (42.9% vs. 8.7%) (p=0.011). There was no difference in HU values for NC (p=0.961), CM (p=0.118), N (p=0.277), and D (p=0.256) phases, and in ΔHU between CM-NC (p=0.278), N-NC (p=0.316), and D-NC (p=0.103). Thirteen patients underwent percutaneous biopsy, 11 of whom had diagnostic samples. Examination of 10/11 (90.9%) samples accurately predicted correct histology, and of 6/11 (54.5%) samples correctly identified high-vs. low-grade histology.

Conclusion: Our findings suggest substantial overlap of CT findings, despite pRCC-Type 2 having greater proportion of high-grade tumors. Utility of CT is limited in the differentiation between pRCC subtypes. Patients with suggested pRCC on CT imaging being considered for a non-extirpative strategy should undergo PRMB for risk stratification.

Keywords: Computed tomography; Hounsfield unit; nephrectomy; papillary renal cell carcinoma; renal cell carcinoma; renal mass biopsy.

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Introduction

An increasing number of individuals are diagnosed with renal cell carcinoma (RCC) each year, with more cancers diagnosed at earlier stages.[1,2] Papillary RCC (pRCC) is the second most frequent RCC subtype, accounting for approximately 13%-15% of all known RCC lesions.[3] In comparison with clear cell RCC (ccRCC), at presentation pRCC has a hypovascular appearance, and tends to have smaller tumor size of lower stage, though it may also have worse prognosis in the setting of metastatic disease.[4] Delahunt and Eble further defined pRCC into two subtypes, Type 1 and Type 2, on the basis of histology.[5] These two subtypes show different clinicopathologic behaviors with pRCC-Type 2 generally having worse prognosis than pRCC-Type 1.[6] Knowledge of the differential biological potential of different papillary subtypes may therefore impact follow-up strategy after de-

finitive treatment, and also potentially influenced the decision to offer definitive management as opposed to active surveillance.[7]

Computed tomography (CT) is currently the reference standard method for identification and clinical staging of renal masses.[1,2] However, preoperative pathological risk in a substantial number of patients with localized renal masses identified on CT who undergo surgery has been inaccurately or incompletely predicted. [8] Few radiologic studies have evaluated the differences between pRCC-Type 1-and pRCC-Type 2, and the issue of differentiation between two subtypes remains unresolved.[9]

While current guidelines of American Urological Association and European Association of Urology recommend percutaneous renal mass biopsy (PRMB) as part of ablative protocol and for consideration in active surveillance,[1,2] PRMB has gained increasing impetus as a first line-management option to delineate tumor histology and to inform therapeutic strategy, with emerging reports suggesting high accuracy and low morbidity and oncologic risk.[7,10]

We sought to investigate imaging characteristics of pRCC-Type 1 and Type 2 tumors, and examine utility of multiphasic CT and PRMB in distinguishing between the two subtypes in a cohort of patients with pRCC who underwent extirpative surgery.

Material and methods

Study patients

Institutional Ethics Review Board approved retrospective analysis of pRCC patients who underwent multiphase CT prior to surgical extirpation from July 2011 to April 2016. Fifty-one patients with pathologically confirmed pRCC whose pathological specimens were confirmed by one of two dedicated uropathologists (AS, DEH) were ultimately analyzed. Our cortical renal neoplasm workup, imaging evaluation and follow-up had been described previously.[11] Briefly, multiphasic CT were obtained as part of a work up for renal tumors suspicious for malignancy prior to management. Patients were counseled as to management options [Radical nephrectomy (RN), partial nephrectomy (PN), ablation, active surveillance (AS)] based on tumor size/stage, and patient baseline performance status and co-morbidities.

Patients who ultimately underwent RN or PN were included in this analysis. In this context patients were offered PRMB in the context of prior history of malignancy, or for risk stratification prior to therapeutic choice. Patients who opted for ablation or AS were not included in the analysis, and neoplasms not diagnosed by renal mass protocol CT and without confirmed pRCC diagnosis were excluded from analysis.

CT imaging evaluation

CT was performed with 64-detector row helical scanners (GE Medical Systems, Milwaukee, WI, USA). CT images were acquired with following parameters: 120 kVp, 200 mA-600 mA depending on size of the patient. Pitch varied from 0.75-1.5. Section thickness measured 0.625 mm reconstructed at 5 mm. Patients were scanned using renal mass protocol that included 4 phases: non-contrast, corticomedullary (35 sec delay), nephrographic (80 sec delay), and a delayed (180 sec) phases. All patients received 140cc of nonionic intravenous (IV) 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. Two radiologists (LA, FH) were blinded to tumor histology while interpreting imaging. When there was discordance in image interpretation, final decision was reached by consensus.

PRMB protocol and histologic evaluation

Our PRMB technique had been described previously.[12] All PRMB were performed by an interventional radiologist (G R-S) under CT guidance, utilizing 16- or 18-gauge needle and obtaining 2 cores. Uropathologists (VD, AS, DEH) were blinded to the clinical information/CT findings when they reviewed slides and classified biopsies and tumor specimens into pathologic subtypes of pRCC. In case of disagreement in interpretation, final decision was reached by consensus. Pathologic tumor stage (pT) and grade were recorded according to TNM and WHO classifications.[13,14]

Image analysis

The following parametres were interpreted: tumor size (maximal diameter, cm), categorical measurements of heterogeneous or homogeneous composition, well- or ill-defined borders, involvement of collecting system, presence of calcifications, necrosis, cystic components, and associated findings (lymphadenopathy or venous thrombus), and attenuation values [Hounsfield Units, (HU)].[11] Attenuation measurements were carried out by determination, and placement of region of interest (ROI) over the area with the highest attenuation detected during corticomedullary and/or nephrographic phase(s). Matching ROI were placed in the same location on non-contrast and delayed phases. ROI covered maximal measurable area that demonstrated highest enhancement. If the mass enhanced homogeneously, ROI covered one-half to two-thirds of the mass. Cystic, calcified, or necrotic areas were not included in ROI determination.[11]

Statistical analysis

Data concerning clinical, and demographic (age, sex, race, body mass index, history of smoking) characteristics and clinical/surgical/pathological tumor characteristics [tumor size (cm), type of surgery (radical/partial nephrectomy), and tumor grade (I/II

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vs. III/IV)], imaging characteristics (mass borders, composition, collecting system involvement, calcification, necrosis, cystic component, lymphadenopathy, or venous thrombus), and attenuation measurements [Hounsfield Units (HU), for noncontrast (NC), corticomedullary (CM), nephrographic (N) and delayed (D) Phases] were collected.

Data were comparatively analyzed between pRCC subtypes. Among clinicopathological characteristics, categorical variables were compared using Fisher's exact or Pearson's *chi*-square test for, Student's t-test for normally, and Mann-Whitney U test for non-normally distributed continuous variables. Absolute enhancement (HU) washout value for the mass was calculated by the formula (nephrographic-delayed)/(nephrographic–non contrast) and reported as a raw value.[15] Previously reported data using an absolute washout value <0 was highly specific for pRCC and therefore this value was also used as a threshold for comparison within pRCC subtypes.[11] Subgroup analysis of patients who underwent PRMB prior to surgical resection was also carried out for overall accuracy of histopathological evaluation of biopsy material in predicting final tumor histology and grade (high vs. low-grade). Statistical analysis was performed with IBM Statistical Package for the Social Sciences version 17.0 (IBM SPSS Statistics; Armonk, NY, USA). P value <0.05 was defined as significant.

Table 1. Demographics and clinical characteristics

Variable	pRCC-Type 1 (n=23)	pRCC-Type 2 (n=28)	p
Mean Age±SD, years	62.9±11.5	62.5±13.1	0.889
Sex (%)			
Male	15 (65.2%)	21 (75%)	
Female	8 (34.8%)	7 (25%)	0.542
Race			
Caucasian	13 (57.4%)	22 (78.6%)	
Other	10 (45.3%)	6 (32.4%)	0.131
Mean BMI±SD, kg/m^2	29.3±7.3	28.0±6.0	0.118
Smoking History (Yes)	15 (65.2%)	15 (53.6%)	0.568
Median clinical Tumor Size (IQR, cm)	2.8 (1.3-16.0)	2.6 (1.2-13.0)	0.832
Surgery type			
Partial nephrectomy	15 (65.2%)	19 (67.9%)	
Radical nephrectomy	8 (34.8%)	9 (32.1%)	1.000
Pathological staging			
pT1	19 (82.6%)	23 (82.1%)	
pT2	3 (13.0%)	1 (7.1%)	
pT3	1 (0.4%)	4 (10.7%)	0.651
Tumor grade			
1/2	21 (91.3%)	16 (57.1%)	
3/4	2 (8.7%)	12 (42.9%)	0.011

pRCC: papillary renal cell carcinoma; BMI: body mass index; SD: standard deviation; IQR: interquartile range

Results

Fifty-one patients met inclusion criteria (23 pRCC-Type 1, 28 pRCC-Type 2). Table 1 demonstrates demographics and clinical characteristics of the patients There was no difference noted with respect to demographic parameters, median clinical tumor size (pRCC-Type 1 2.8 cm vs. pRCC-Type 2 2.6 cm, p=0.832) and distribution of pathological stage (p=0.651). Nonetheless, pRCC-Type 2 had significantly higher proportion of high-grade (III/IV) tumors (42.9% vs. 8.7%, p=0.011).

Table 2. Imaging characteristics

Variable	pRCC-Type 1 (n=23)	pRCC-Type 2 (n=28)	p
Mass borders on CT			
Well defined	21 (91.3%)	24 (85.7%)	
Ill-defined	2 (8.7%)	4 (14.3%)	0.677
Composition			
Heterogeneous	4 (17.4%)	8 (28.6%)	
Homogeneous	19 (82.6%)	20 (71.4%)	0.510
Collecting System Involvement			
Yes	11 (47.8%)	13 (46.4%)	
No	12 (52.2%)	15 (53.6%)	1.000
Calcifications			
Yes	3 (13.0%)	4 (14.3%)	
No	20 (87.0%)	24 (85.7%)	1.000
Necrosis			
Yes	3 (13.0%)	8 (28.6%)	
No	20 (87.0%)	20 (71.4%)	0.305
Cystic component			
Yes	1 (4.3%)	1 (3.6%)	
No	22 (95.7%)	27 (96.4%)	1.000
Lymphadenopathy			
Yes	1 (4.3%)	3 (10.7%)	
No	22 (95.7%))	25 (89.3%)	0.617
Venous thrombus			
Yes	0 (0%)	3 (10.7%)	
No	23 (100%)	25 (89.3%)	0.242

pRCC: papillary renal cell carcinoma; CT: computed tomography

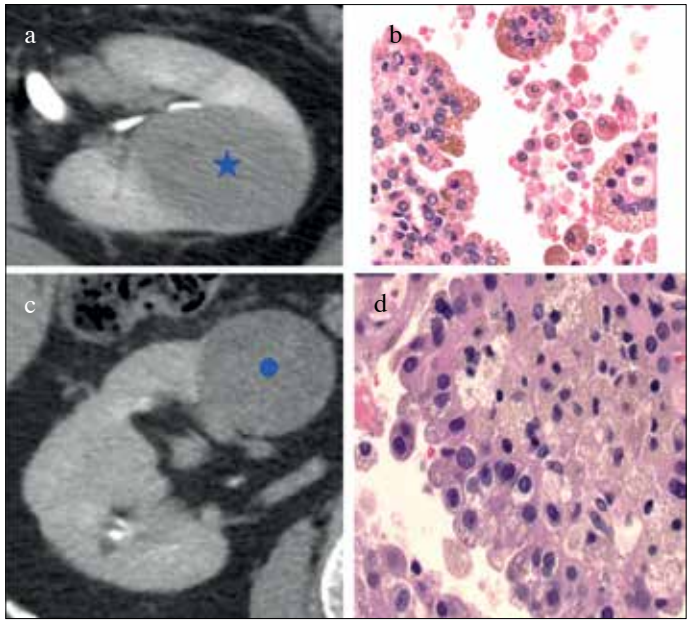

Figure 1.a-d. CT imaging of pRCC-Type 1 [a and b] and pRCC-Type 2 [c and d] and respective pathological correlates: (a) CT: Left renal mass, 4.7 cm, delayed phase HU 70, tumor washout-0.34; (blue star) (b) pathology revealed Type 1 pRCC, grade 3 (H&E, 40x); (c) CT: right renal mass, 3.8 cm, delayed phase HU 60, tumor washout-0.3; (blue circle) (d) pathology revealed Type 2 pRCC, grade 3 (H&E, 40x)

Imaging characteristics are demonstrated in Table 2. There were no differences between pRCC-Type 1-and pRCC-Type 2 with respect to irregular borders (5.6% vs. 14.3%, p=0.677), necrosis (13.0% vs. 28.6%, p=0.247), calcifications (p=1.000), collecting system involvement [abuts, displaces, effaces (p=1.000)], heterogeneous vs. homogenous enhancement on imaging (p=0.510), or presence of associated findings (lymphadenopathy, p=0.617; venous thrombus, p=0.242; Figure 1).

Attenuation measurements for different phases and washout calculations are demonstrated in Table 3. There were no differences between pRCC-Type 1 and pRCC-Type 2 for mean attenuation values (HU) of noncontrast (p=0.923), corticomedullary (58.1 vs. 67.6, p=0.118), nephrographic (65.4 vs. 73.1, p=0.227), and delayed phases (67.8 vs. 75.5, p=0.256). Moreover, there were no differences in delayed HU between corticomedullary–non contrast (23.5 vs. 32.8, p=0.278), nephrographic–noncontrast (30.8 vs. 38.3, p=0.103), and delayed–noncontrast (33.2 vs. 40.7, p=0.103) phases. Mean washout was comparable between Type 1, and 2 (Type 1-0.07 vs. Type 2-0.05, p=0.721). Almost similar proportions of pRCC-Type 1 and Type 2 had washout <0 (60.9% vs. 53.6%, p=0.777).

Table 4 demonstrates subgroup analysis of patients who underwent PRMB (n=13) prior to surgery. Indications for biopsy included presence of prior malignancy and need to rule out metastatic involvement of kidney in 7 and patients' request prior to proceeding with definitive management (to exclude benign histology) in 6 cases. Overall 11 patients had diagnostic samples. In 10/11 (90.9%) patients examination of the biopsy sample predicted correct histology (in one patient PRMB was suggestive of oncocytic neoplasm favoring chromophobe RCC, however final pathology was pRCC-Type 2), and correct grade (high-vs. low-grade) was identified in 6/11 (54.5%) samples. In 4 (36.4%) samples, grade could not be determined. In 2 samples, grade was underestimated (in both patients histopathological examination of the biopsy material accurately diagnosed pRCC-Type 1).

Discussion

We present the largest scale comparative study between pRCC-Type 1 and Type 2 tumors which examied imaging characteristics of these types on CT scan and the first to analyze utility of PRMB. While earlier reports have demonstrated that pRCC may have a distinct appearance from ccRCC and other renal cortical tumor histologies,[10,15] our findings suggest that multiphasic CT does not distinguish between pRCC subtypes, and that PRMB can accurately distinguish between these histological variants, and may have utility in patients in whom accuracy of risk stratification is sought prior to definitive management.

Our data suggest that pRCC-Type 1-and Type 2 tumors have substantial overlap in key CT findings including tumor size, definition of borders, heterogeneity, collection system involvement, presence of calcifications, and necrosis, enhancement pattern and values and washout. Our findings are in contrast to those of Yamada et al.[9], who conducted a retrospective analysis of 12 pRCC-Type 1 and 8 pRCC-Type 2 tumors, and noted that pRCC-Type 1 tumors had more distinct margins whereas pRCC-Type 2 showed more indistinct margins, infiltrative growth pattern, and increased heterogeneity. Unlike our cohort, the tumors in their series were not well-matched for size, with a median size of 3.3 cm for Type 1 vs. 5.1cm for pRCC-Type 2 (p=0.037). Herts et al.[15] compared triphasic CT enhancement patterns in 90 patients and found that pRCC is more likely to be homogeneous in comparison with other renal cell carcinomas (p=0.001), although size was not accounted for in this study. Conversely, when comparing RCC enhancement patterns on CT and controlling for tumor size, Kim et al.[16] found that both pRCC and ccRCC tumors larger than 3 cm were predominantly heterogeneous with areas of necrosis. Thus, Yamada et al.[9] findings may be attributed more to tumor size and histology.

CT washout formula is commonly used to evaluate the enhancement patterns of adrenal masses[17] and has been previously found by our group and others to differentiate ccRCC from non-ccRCC, with a washout value <0 being 100% specific for non-ccRCC.[11,18] When using the CT enhancement washout formula

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in our current analysis, we found no difference in washout values between the two pRCC subtypes, which further substantiates our findings that while CT may be specific in determining non-ccRCC histology, it may not be a reliable imaging modality to distinguish between pRCC subtypes.

Table 3. Attenuation measurements

Variable	pRCC-Type 1 (n=23)	pRCC-Type 2 (n=28)	p
HU (Mean±SD)			
Noncontrast	34.6±8.4	34.8±10.9	0.961
Corticomedullary	58.1±13.4	67.6±19.7	0.118
Nephrographic	65.4±16.8	73.1±23.4	0.227
Delayed Phase	67.8±14.0	75.5±21.4	0.256
Delayed HU between phases			
Corticomedullary-Noncontrast	23.5±10.1	32.8±19.2	0.278
Nephrographic-Noncontrast	30.8±14.1	38.3±22.1	0.316
Delayed-Noncontrast	33.2±9.0	40.7±17.1	0.103
Mean washout (± SD)*	-0.07 (±0.41)	-0.05 (±0.32)	0.721
Washout mass*			
<0	14 (60.9%)	15 (53.6%)	
≥0	9 (39.1%)	13 (46.4%)	0.777

pRCC: papillary renal cell carcinoma; SD: standard deviation; HU: Hounsfield units,

*Calculated by formula: (nephrographic-delayed)/(nephrographic–non contrast)

Similar findings have been observed in differentiation between pRCC and ccRCC tumors but magnetic resonance imaging (MRI) could not distinguish between pRCC subtypes.[19-22] Oliva et al.[19] compared contrast-enhanced MRI tumor signal intensity (SI) ratios (tumor SI/renal cortex SI) of 21 pRCC and 16 ccRCC lesions and found that tumor SI ratios on T1-weighted images were similar for the two RCC subtypes, although on T2-weighted images pRCC had a significantly lower SI ratio compared to ccRCC tumors (p<0.01). On qualitative assessment authors reported T2-weighted hypointense (SI≤0.66) tumors had a specificity of nearly 100% for pRCC, whereas SI of a hyperintense tumor was 100% specific for cRCC. Similarly, Young et al.[20] conducted a study to investigate the performance of contrast enhancement on multiphasic MRI to differentiate ccRCC from other RCC subtypes and reported that relative corticomedullary signal intensity differentiated ccRCCs from other RCC subtypes with an AUC of 0.93 and 90% accuracy, 90% sensitivity, and 90% specificity. Additionally, Vargas et al.[21] compared change in MRI SI between pre-contrast and post-contrast phases, and demonstrated that pRCC had significantly less enhancement than ccRCC in all three post-contrast phases (p<0.000-0.012). However, similar to CT findings, MRI imaging characteristics of Type I-and Type II-pRCC demonstrated substantial overlap. When comparing contrast enhanced MRI characteristics of 15 pRCC-Type 1 and 6 Type II-pRCC-Type 2 tumors, Egbert et al.[22] revealed no difference in definition of margins, presence of necrosis, lymphadenopathy, or signal

Table 4. Summary of characteristics of patients who underwent PRMB prior to surgery

				Tumor Specimen		Agreement Between PRMB and Tumor Specimen	
Patient Age (years)	Tumor Size (cm)	PRMB Histology	Grade	Histology	Grade	Histology	Grade
59	2.3	pRCC-Type 1	ND	pRCC-Type 1	1	Yes	No
51	4.2	pRCC-Type 2	High	pRCC-Type 2	3	Yes	Yes
64	2.9	Non-diagnostic	ND	pRCC-Type 1	1	No	No
69	1.8	Chromophobe RCC	ND	pRCC-Type 2	2	No	No
67	2.3	pRCC-Type 2	High	pRCC-Type 2	3	Yes	Yes
58	2.1	pRCC-Type 1	Low	pRCC-Type 1	1	Yes	Yes
73	2.3	Non-diagnostic	ND	pRCC-Type 2	2	No	No
43	3.4	pRCC-Type 2	High	pRCC-Type 2	3	Yes	Yes
59	2.7	pRCC-Type 1	Low	pRCC-Type 1	3	Yes	No
62	2.4	pRCC-Type 1	Low	pRCC-Type 1	3	Yes	No
67	2.3	pRCC-Type 2	High	pRCC-Type 2	3	Yes	Yes
66	2.5	pRCC-Type 1	Low	pRCC-Type 1	3	Yes	No
63	2.9	pRCC-Type 2	High	pRCC-Type 2	3	Yes	Yes

PRMB: percutaneous renal mass biopsy: pRCC: papillary renal cell carcinoma; ND: not determined

intensity on T1-, and T2-weighted images between subtypes, and, therefore, concluded that pRCC subtype classification is likely not possible using MRI.

Although our pRCC subtype groups had a similar median tumor size and stage distribution, we found a significantly proportion of higher grade (3/4) tumors in the pRCC-Type 2 group (42.9% vs. 8.7%, p=0.011), which is consistent with previous reports.[4,9] Given what we know about identified differences in biological potentials of different histologic subtypes of pRCC,[3-6] and the limitations in differentiating between subtypes by either CT or MRI, it is not enough to declare a small non-ccRCC appearing renal mass safe for surveillance. Thus, in a patient where consideration is being given for active surveillance versus treatment, and where presence of aggressive histological features may spur definitive management, PRMB may be useful to stratify oncologic risk, whether imaging findings are suggestive or not of ccRCC.

Halverson et al.[23] assessed accuracy of a biopsy-directed treatment algorithm in correctly assigning AS vs. treatment in patients with small renal masses, in a retrospective analysis of 151 patients with cT1a renal masses who underwent biopsy and subsequent surgical excision. Overall agreement between biopsy and final pathology was 92%. When analyzing for pRCC, 25 patients were noted to have pRCC as detected by preoperative histopathological examination of biopsy materials, while 27 patients had pRCC on final histopathological examination with an overall diagnostic accuracy of 93%. When categorized by histological subtype, pRCC-Type 1 diagnoses were made based on 10 preoperative biopsy materials, and 16 on final pathology (diagnostic accuracy, 62.5%). Histopathological examination of preoperative biopsy materials predicted diagnosis of pRCC-Type 2 in 4 patients compared to diagnosis of pRCC-Type 2 in 5 patients based on final pathology (diagnostic accuracy of 80%). Furthermore, preoperative histopathological examination of biopsy materials predicted 10/12 (83.3%) grade 1/2 pRCC-Type 1. The authors in their analysis included papillary RCC not otherwise specified in 11 preoperative and 6 postoperative specimens. The authors' findings suggest a high degree of accuracy in predicting pRCC histology overall, pRCC-Type 2 histology, and distinguishing between low-, and high-grade pRCC-Type 1 histology. While conduction of larger –scale studies with greater number of case series is necessary so as to correlate preoperative biopsy, imaging and final pathology findings. Findings of Halverson et al. [23] are similar to our findings and suggest that PRMB may be an effective and accurate predictor of papillary subtype and grade, accurately reflect oncologic risk and thus contribute to risk stratification.

Our study is limited by its retrospective design and inherent selection bias towards treatment for patients who were perceived to have appropriate risk from a medical and surgical standpoint. Furthermore, we excluded patients with non-pRCC pathology, and focused only on multiphasic CT findings. Indeed, while our analysis is limited by numbers and potential applicability, it stands as the largest comparison in imaging and pathological characteristics between the two subtypes of pRCC, and is unique in being well-matched in terms of tumor size. Given that our analysis is limited to those patients with pre-existing imaging and pathology results, our ability to test true utility of these imaging parameters for diagnosis was inherently limited, and prospective investigation is a requisite.

In conclusion, in this well-matched cohort study with respect to tumor size and stage, there was substantial overlap of key radiographic findings, despite pRCC-Type 2 having greater proportion of high-grade tumors. While multiphase CT scan was not able to differentiate between pRCC subtypes, in patients where PRMB was obtained, accurate histologic diagnosis was made in >90% of the patients. While further investigation is a requisite, in patients with imaging criteria suggestive of non-clear cell RCC in which further diagnostic refinement is sought, PRMB may add further risk stratification information that multiphasic CT scan is not able to achieve.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of California San Diego.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – I.D., D.E.H., L.A.; Design – A.B., A.T.B., M.L.M., I.D.; Supervision – I.D., D.H., F.H.; Resources – M.L.M., A.T.B., G.R.S., A.S.; Materials – A.B., M.L.M., F.H., L.A., D.E.H., I.D.; Data Collection and/or Processing – A.B., M.L.M., A.T.B., G.R.S., A.S., F.H., L.A., D.E.H., I.D.; Analysis and/or Interpretation – A.B., M.L.M., A.T.B., A.S., I.D.; Literature Search – M.L.M., A.T.B., F.H., D.E.H.; Writing Manuscript – A.B., M.L.M., A.T.B., D.E.H., I.D.; Critical Review – A.B., F.H., L.A., D.E.H., I.D.

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