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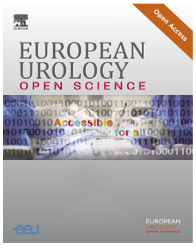

European Association of Urology

Kidney Cancer

Differentiating Oncocytic Renal Tumors from Chromophobe Renal Cell Carcinoma: Comparison of Peak Early-phase Enhancement Ratio to Clinical Risk Factors and Rater Predictions

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Article info

Article history:
Accepted October 5, 2022

Associate Editor:
M. Carmen Mir

Keywords:
Kidney cancer
Renal cell carcinoma
Oncocytoma
Oncocytic renal neoplasms
Nephrectomy
Computed tomography
Contrast enhancement

Abstract

Background: Most surgically resected benign renal tumors are found to be oncocytomas or indolent hybrid oncocytic tumors, which are difficult to differentiate from chromophobe renal cell carcinoma (chRCC) on renal mass biopsy. Both often exhibit CD117^{+} staining.
Objective: To evaluate the ability of the peak early-phase enhancement ratio (PEER) to distinguish oncocytomas from chRCC and compare its discrimination to traditional clinical risk factors and blinded clinical raters.
Design, setting, and participants: This was a diagnostic case-control study of patients (2006–2020) with oncocytoma or chRCC according to surgical pathology.
Intervention: Partial or radical nephrectomy.
Outcome measurements and statistical analysis: Three clinical raters blinded to histology measured the PEER and the presence of stellate scar and predicted the final histology for each tumor. Averaged and individual PEER values were compared to surgical pathology and assessed for interobserver variability. Subanalyses were conducted for patients with confirmed CD117^{+} status.
Results and limitations: For the 76 patients identified, PEER was higher among the 32 (42.1%) oncocytomas than among the 44 (57.9%) chRCCs (median 0.81 vs 0.43; $p < 0.001$), with high correlation across raters (correlation coefficients $\geq$0.85). A PEER cutoff of <0.60 was strongly associated with identification of chRCC (OR 95.7 (95% CI 19.9–460.8), $p < 0.001$). In the overall and CD117^{+} cohorts, sensitivity was 93.2% and 97.0%, the negative predictive value was 90.3% and 95.5%, and the area under the receiver operating characteristic curve (AUC) on multivariable modeling was 95.0% and 98.1%, respectively. PEER outperformed models with clinical risk factors alone (AUC 70.4%) and histology predictions by three raters (AUC

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https://doi.org/10.1016/j.euros.2022.10.006

51.6%, 62.5%, and 63.1%). Limitations include reliance on surgical pathology and inclusion of a mix of early contrast-enhanced phases.
Conclusions: PEER reliably differentiated benign renal oncocytomas and indolent hybrid tumors from malignant chRCC with excellent diagnostic performance. A diagnostic pathway with biopsy, CD117 staining, and PEER deserves further study to potentially avoid unnecessary surgery for oncocytic renal tumors.
Patient summary: We assessed a measurement called PEER on computed tomography (CT) scans and found higher values for benign and lower values for malignant kidney masses, so we were able to tell these apart. PEER was reliable for identifying tumors with positive staining for the CD117 protein biomarker as well as in the overall patient group. Our results show that PEER could be considered for use with biopsy and CD117 staining to potentially avoid unnecessary surgery for benign kidney masses.

1. Introduction

The incidence of kidney cancer increased through the early 2000s because of greater use of cross-sectional imaging, with 70% of patients now diagnosed with early-stage cT1 disease [1,2]. However, clinical stage migration and an increase in surgical resection of localized renal tumors has led to a greater number of potentially unnecessary surgeries for benign and low-grade tumors [3,4]. Most patients diagnosed with localized renal tumors undergo resection without histologic confirmation of malignancy on renal mass biopsy, leading to removal of an estimated 3300 benign and 5400 very low-risk small renal masses each year in the USA [4].

Oncocytoma represents the most common surgically resected benign renal tumor. Traditional evaluation of enhancement on computed tomography (CT) or magnetic resonance imaging is unable to reliably differentiate oncocytoma from renal cell carcinoma (RCC) [5]. In addition, while a positive renal mass biopsy can confirm a diagnosis of RCC, the negative predictive value (NPV) may be as low as 63.3%, suggesting that one-third of patients with a negative biopsy may still harbor cancer [6]. A primary problem with biopsy is an oncocytic renal neoplasm result, which may indicate an oncocytoma but has histologic overlap with chromophobe RCC (chRCC) [7,8]. Some oncocytic neoplasms may also exhibit hybrid or borderline features but are generally considered indolent tumors and could be managed similarly to oncocytomas [9].

A recent approach that combines immunohistochemical staining for CD117 with a novel measurement of the peak early-phase enhancement ratio (PEER) between the tumor and cortex on CT was suggested for perfect differentiation of $CD117^+$ benign oncocytomas from chRCC [10]. Given the clinical implication of reducing the resection of benign renal tumors, we aimed to externally validate the ability of PEER to distinguish benign oncocytomas and indolent hybrid tumors from chRCC. In addition, we sought to evaluate interobserver variability and compare the discrimination of PEER with that of traditional clinical risk factors and the overall impressions of three blinded clinical raters.

2. Patients and methods

2.1. Study design

After obtaining institutional review board approval, we identified all patients undergoing radical or partial nephrectomy at Loyola University Medical Center from 2006 to 2020 who were found to have benign oncocytoma or chRCC on surgical pathology for a diagnostic case-control study. Indolent hybrid oncocytic tumors were included and grouped with benign oncocytomas. Candidate patients were initially identified via a natural language search of pathology reports using CoPath. Patients with preoperative CT imaging (early-phase contrast-enhanced and noncontrast scans) allowing calculation of PEER were included. Patients with multiple concurrent tumors were excluded. The primary analysis included all patients, and a subgroup analysis was conducted for $CD117^+$ tumors.

2.2. Radiographic assessment

Three separate blinded raters (two radiologists, one urologist) measured the parameters needed to calculate PEER, evaluated the presence of a stellate scar, and provided an overall radiographic prediction classifying the tumor as an oncocytoma or chRCC. The blinded clinical raters for imaging studies consisted of two radiologists and one urologist. Rater #1 was a radiology resident (D.L.T.), rater #2 was a urology resident (N.E.), and rater #3 was an expert genitourinary radiologist (D.B.). The diversity of raters was chosen to evaluate reproducibility of measurements.

PEER was calculated as previously described and shown in Figure 1 [10]. For the tumor, a circular 1-cm diameter region of interest (ROI) was used to measure Hounsfield units (HU) in the brightest region of the tumor on a cortical (arterial) or nephrogenic (venous) phase. For small and heterogeneous tumors, a small 1-cm × 0.5-cm ellipse was used. The same tumor ROI was then measured on the noncontrast phase. For the cortex, an ellipsoid ROI was used for HU measurements on both the contrast-enhanced and noncontrast phases. The net enhancement of the tumor was then divided by the net enhancement of the cortex to obtain the PEER value.

2.3. Pathology review

For patients with unknown CD117 status, an expert genitourinary pathologist (M.M.P.) re-reviewed slides as available to determine CK7 and CD117 status, and provided an overall pathologic interpretation based on hematoxylin and eosin stains and immunohistochemistry.

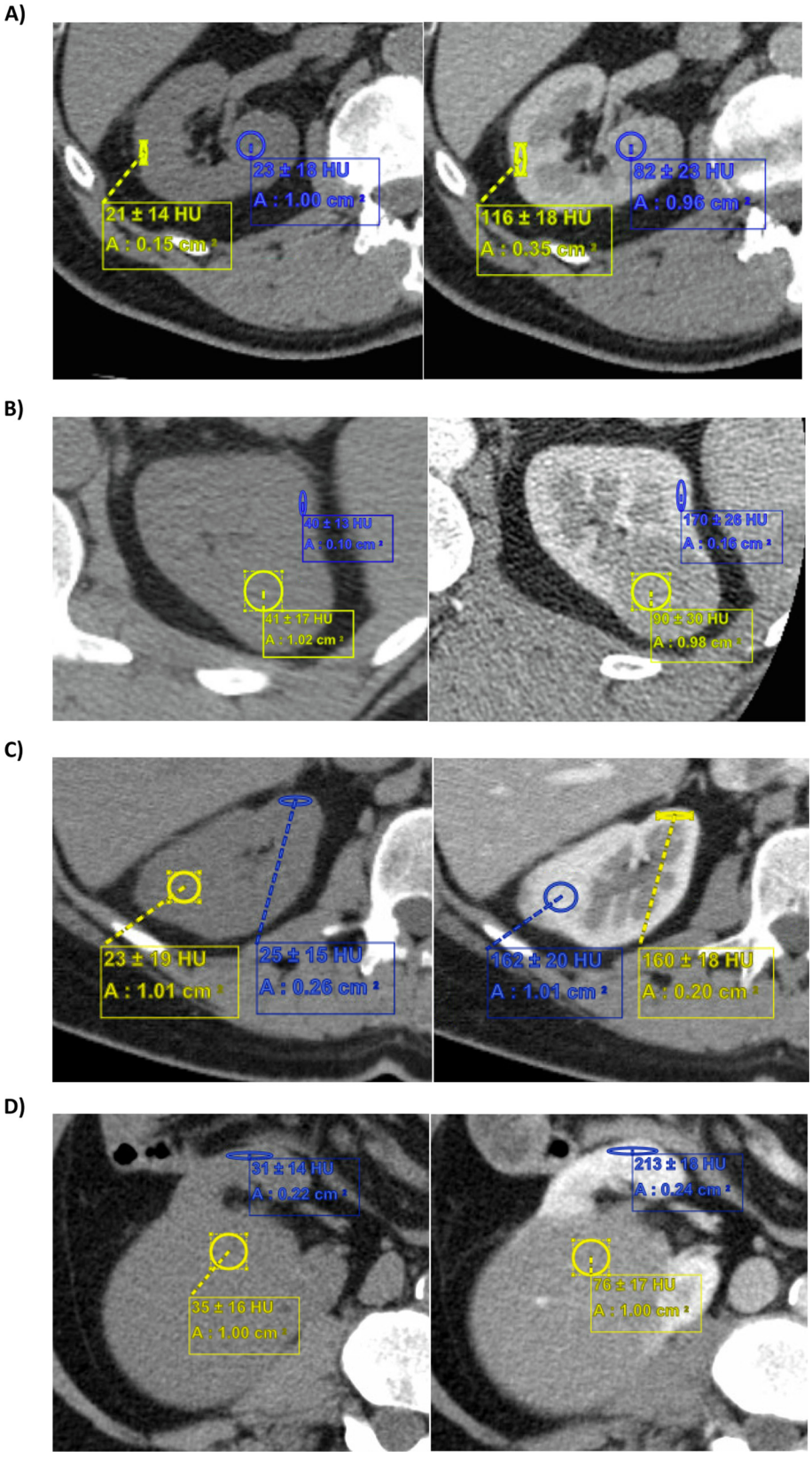

Fig. 1 – Computed tomography images demonstrating calculation of PEER for patients with (A) an oncocytoma with PEER value of 0.62, (B) a chromophobe renal cell carcinoma with PEER value of 0.38, (C) an oncocytoma with PEER value of 1.02, and (D) a chromophobe renal cell carcinoma with PEER value of 0.23. PEER calculations were as follows: (A) PEER = (82 - 23)/(116 - 21) = 0.62; (B) PEER = (90 - 41)/(170 - 40) = 0.38; (C) PEER = (162 - 23)/(160 - 25) = 1.02; and (D) (76 - 35)/(213 - 31) = 0.23. PEER = peak early-phase enhancement ratio.

Table 1 – Baseline demographics and clinical characteristics stratified by the presence of oncocytoma or chromophobe RCC at surgical pathology

Parameter	Overall	Oncocytoma	Chromophobe RCC	*p* value
Patients (*n*)	76	32	44	
Median age, yr (IQR)	61.3 (53.4–68.0)	63.7 (59.7–68.0)	59.0 (48.5–68.0)	0.03
Sex, *n* (%)				
Female	40 (52.6)	16 (50.0)	24 (54.5)	0.70
Male	36 (47.4)	16 (50.0)	20 (45.5)	
Laterality				
Left	40 (52.6)	18 (56.3)	22 (50.0)	0.59
Right	36 (47.4)	14 (43.8)	22 (50.0)	
Surgical approach				
Open	18 (23.7)	6 (18.8)	12 (27.3)	0.52
Laparoscopic	13 (17.1)	7 (21.9)	6 (13.6)	
Robotic	45 (59.2)	19 (59.4)	26 (59.1)	
Surgery type				
Radical nephrectomy	36 (47.4)	12 (37.5)	24 (54.5)	0.14
Partial nephrectomy	40 (52.6)	20 (62.5)	20 (45.5)	
Median radiographic size, cm (IQR)	3.9 2.4-6.6	2.9 (2.3–4.9)	5.5 (2.8–7.6)	0.01
Median pathologic size, cm (IQR)	4.1 (2.3–6.7)	3.4 (1.9–4.8)	5.4 (2.6–8.3)	0.01
CD117 status				
Negative	5 (6.6)	2 (6.3)	3 (6.8)	0.95
Positive	58 (76.3)	25 (78.1)	33 (75.0)	
Unknown	13 (17.1)	5 (15.6)	8 (18.2)	

IQR = interquartile range; RCC = renal cell carcinoma.

Tumors with borderline or discordant PEER measurements were also re-reviewed as available. Additional details on pathology review are provided in the Supplementary material.

2.4. Statistical analysis

The primary outcome was the presence of oncocytoma or chRCC according to surgical pathology. Demographic and clinical data were compared for patients with oncocytoma and chRCC. PEER values were averaged across the three raters to obtain an overall value. The overall PEER and individual rater PEER values were evaluated as continuous measures and for an optimal cutoff near the previously suggested range of 0.50–0.55 [10]. The sensitivity, specificity, positive predictive value (PPV), and NPV were calculated. Receiver operating characteristic (ROC) curves were constructed based on multivariable logistic regression models to estimate the area under ROC curve (AUC) and compare PEER to known clinical risk factors and prediction by raters. Statistical analyses were performed using Stata version 15.0 (Stata Corp., College Station, TX, USA). Additional cohort and analysis details are presented in the Supplementary material.

3. Results

3.1. Patient cohort

Of 118 patients with unifocal tumors and CT imaging identified, 41 were excluded because of missing suitable

Table 2 – PEER measurements and radiographic interpretations by three blinded clinical raters with stratification by the presence of oncocytoma or chromophobe RCC at surgical pathology

	Overall	Oncocytoma	Chromophobe RCC	*p* value
Patients (*n*)	76	32	44	
Median overall PEER (IQR)[a]	0.55 (0.41–0.79)	0.81 (0.70–0.88)	0.43 (0.33–0.54)	<0.001
Rater #1				
Stellate scar, *n* (%)				
Absent	58 (76.3)	22 (68.8)	36 (81.8)	0.19
Present	18 (23.7)	10 (31.3)	8 (18.2)	
Prediction, *n* (%)				
Oncocytoma	27 (35.5)	16 (50.0)	11 (25.0)	0.03
Chromophobe RCC	49 (64.5)	16 (50.0)	33 (75.0)	
Median PEER (IQR	0.59 (0.42–0.83)	0.85 (0.78–0.97)	0.48 (0.38–0.58)	<0.001
Rater #2				
Stellate scar, *n* (%)				
Absent	72 (94.7)	28 (87.5)	44 (100.0)	0.02
Present	5 (6.6)	4 (12.5)	0 (0.0)	
Prediction, *n* (%)				
Oncocytoma	36 (47.4)	20 (62.5)	16 (36.4)	0.02
Chromophobe RCC	40 (52.6)	12 (37.5)	28 (63.6)	
Median PEER (IQR)	0.55 (0.37–0.73)	0.74 (0.64–0.81)	0.41 (0.33–0.52)	<0.001
Rater #3				
Stellate scar, *n* (%)				
Absent	64 (84.2)	27 (84.4)	37 (84.1)	0.97
Present	12 (15.8)	5 (15.6)	7 (15.9)	
Prediction, *n* (%)				
Oncocytoma	20 (26.3)	9 (28.1)	11 (25.0)	0.76
Chromophobe RCC	56 (73.7)	23 (71.9)	33 (75.0)	
Median PEER (IQR)	0.55 (0.37–0.76)	0.77 (0.65–0.88)	0.41 (0.31–0.54)	<0.001

IQR = interquartile range; RCC = renal cell carcinoma; PEER = peak early-phase enhancement ratio.
[a] Average PEER across all three raters.

contrast-enhanced or noncontrast phase images precluding PEER calculation (Supplementary Fig. 1). One additional patient was excluded after pathologic re-review because of findings consistent with succinate dehydrogenase–deficient RCC rather than oncocytoma or chRCC (Supplementary material). Of the 76 patients included, 32 (42.1%) had oncocytoma and 44 (57.9%) had chRCC (Table 1). Patients with chRCC were younger and had larger tumors. CD117 status was positive for 58 (76.3%), unknown for 13 (17.1%), and negative for five (6.6%) patients.

3.2. PEER differentiation of benign oncocytoma from chRCC

Median PEER vales were higher for oncocytomas (0.81, interquartile range [IQR] 0.70–0.88) than for chRCCs (0.43, IQR 0.33–0.54; $p < 0.001$), with similar findings by rater (Table 2). Pairwise correlation coefficients were high (Pearson's: 0.85–0.88; Spearman's 0.87–0.90). A scatterplot for PEER comparing oncocytoma to chRCC in the overall cohort is shown Figure 2A. PEER cutoffs between 0.50 and 0.70 were evaluated on the basis of a previously suggested cutoff of ~0.55 and the performance characteristics of these cutoffs are outlined in Supplementary Table 1 [10]. A PEER value of <0.60 was identified as an optimal cutoff for the present cohort and was strongly associated with identification of chRCC (odds ratio [OR] 95.7, 95% confidence interval [CI] 19.9–460.8; $p < 0.001$) with sensitivity of 93.2%, specificity of 87.5%, PPV of 91.1%, and NPV of 90.3% (Supplementary Table 1). A cutoff of <0.55 was strongly associated with identification of chRCC (OR 59.9, 95% CI 7.43–482.9; $p < 0.001$) but with lower sensitivity and NPV (sensitivity 81.8%, specificity 93.8%, PPV 94.7%, NPV 78.9%).

In the CD117$^+$ subset, similar associations were observed, with performance characteristics of 97.0% sensitivity, 84.0% specificity, 88.9% PPV, and 95.5% NPV for a PEER cutoff of <0.60 (Fig. 2B, Supplementary Table 1). A scatter plot for the 18 patients with unknown or negative CD117 status is shown in Supplementary Figure 2. Notably, among the 32 patients included in the oncocytoma group, three had hybrid features known to exhibit an indolent nature; PEER values were consistent and similar to those for pure oncocytoma in all three cases (PEER 0.79, 0.92, and 0.92).

3.3. Comparison of PEER to clinical risk factors and rater predictions

Raters identified stellate scars in 6.6–23.7% of cases; stellate scar presence was associated with oncocytoma only for rater #2 (Table 2). Rater #1 correctly identified 50% of oncocytomas and 75% of chRCCs ($p = 0.03$), while rater #2 correctly identified 62.5% of oncocytomas and 63.6% of chRCCs ($p = 0.02$). Predictions by rater #3 were not associated with surgical pathology.

A predictive model based on clinical risk factors (age, sex, tumor size) outperformed rater #3 (AUC 70.4% vs 51.6%; $p = 0.003$) but its performance was not significantly different ($p > 0.05$) from that of rater #1 (AUC 62.5%) or rater #2 (AUC 63.1%). Models based on PEER alone (AUC 92.1%) and PEER combined with age and tumor size (AUC 95.0%) outperformed clinical risk factors and all raters

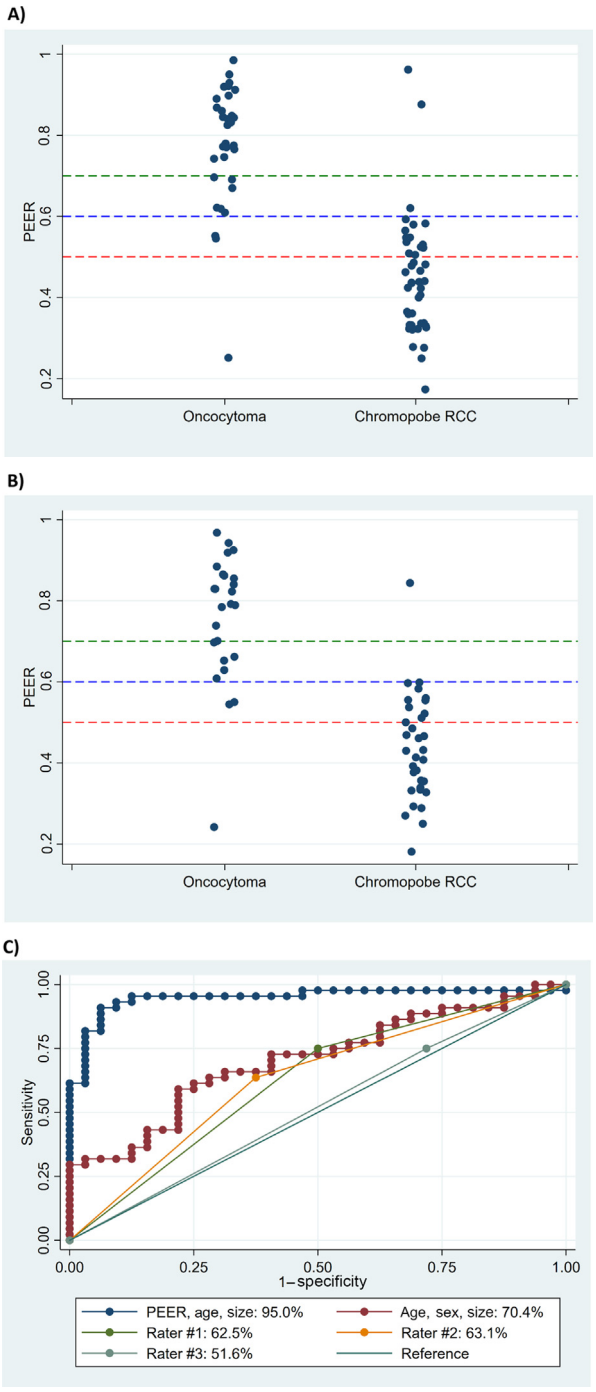

Fig. 2 – Scatter plots for (A) PEER in the overall cohort and (B) PEER in the CD117$^+$ subgroup and (C) receiver operating characteristic curves showing discrimination for models with PEER, clinical risk factors, and histologic predictions by individual clinical raters. PEER = peak early-phase enhancement ratio.

($p < 0.001$ for all; Table 3, Fig. 2C). AUCs were similarly high for models in the CD117$^+$ subset for PEER alone (AUC 92.3%) and PEER combined with age and tumor size (AUC 98.1%).

In a subgroup analysis of patients with tumors ≤4 cm (20 oncocytoma, 19 chRCC), PEER performed similarly, with OR of 0.39 (95% CI 0.22–070; $p = 0.002$), while age and tumor size were not statistically significant on multivariable analysis (AUC 90.8%). Further restriction to ≤4 cm

Table 3 – Multivariable logistic regression models evaluating associations with identification of chromophobe renal cell carcinoma versus oncocytoma on surgical pathology

	Univariable[a]		Multivariable (overall cohort)		Multivariable (CD117$^+$)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95%CI)	*p* value
PEER (per 0.1)	0.32 (0.20–0.51)	<0.001	0.31 (0.18–0.51)	<0.001	0.12 (0.03–0.52)	0.005
PEER <0.60 (vs ≥0.60)	95.7 (19.9–460.8)	<0.001	–	–	–	–
TSI (per cm)	1.23 (1.04–1.46)	0.02	1.37 (1.01–1.85)	0.04	2.36 (1.18–4.71)	0.02
Age (per year)	0.96 (0.92–1.00)	0.04	0.94 (0.85–1.03)	0.18	0.75 (0.57–1.00)	0.05
Male sex (vs female)	0.83 (0.33–2.08)	0.70	–	–	–	–
Right laterality (vs left)	1.28 (0.52–3.21)	0.59	–	–	–	–
Stellate scar (vs absent)[b]	0.49 (0.17–1.43)	0.19	–	–	–	–

PEER = peak early-phase enhancement ratio; OR = odds ratio; CI = confidence interval; TSI = tumor size on imaging AUC = area under the receiver operating characteristic curve.
[a] AUC was 92.1% for PEER alone; AUC for PEER plus age and tumor size was 95.0% in the overall cohort and 98.1% in the CD117$^+$ subgroup.
[b] Based on the interpretation of rater #1.

and CD117$^+$ tumors (16 oncocytoma, 13 chRCC) improved the AUC to 96.2%.

4. Discussion

In the present study, PEER reliably differentiated benign renal oncocytomas and indolent hybrid oncocytic tumors from malignant chRCC with excellent diagnostic performance. Importantly, PEER was far superior to known clinical risk factors and radiographic predictions by three blinded clinical raters. Given that a primary limitation of renal mass biopsy is the clinical dilemma of oncocytic neoplasms, the reproducibility and performance of PEER may augment biopsy sufficiently to increase adoption in the diagnostic pathway for localized renal masses.

Renal mass biopsy is only used in 15% of patients harboring cT1a renal tumors, but is associated with a reduction in surgery, especially among older patients and those with comorbidities [11]. Observation with active surveillance is a guidelines-based management option for small renal tumors, with favorable data for older patients now being complemented by data for younger and unselected cohorts [12–15]. Therefore, improving renal mass biopsy with PEER has the potential to decrease unnecessary surgery for benign tumors and, at the same time, promote consideration of an initial period of active surveillance for lower-grade tumors diagnosed on biopsy, with delayed intervention as needed [16].

In addition to oncocytoma and chRCC, a rare subset of renal tumors may exhibit hybrid features, with several terminologies emerging because of overlapping morphologic and immunophenotypic features [17,18]. However, these tumors are generally indolent and can be managed similarly to benign oncocytomas. Recent recommendations by the Genitourinary Pathology Society and other experts have suggested use of the term "low-grade oncocytic tumor" to compress the confusing terminology and distinguish these tumors from syndromic renal neoplasia [17,18]. Notably, the few cases of indolent hybrid oncocytic tumors in the present study had PEER values comparable to those for pure oncocytomas.

While an ideal study would include blinding for both biopsy data and PEER results for comparison to surgical pathology, such a design would not be practical given the invasiveness of biopsy, with no benefit to the patient in avoiding surgery. In addition, while the results have clear implications for patients with CD117$^+$ status on biopsy with sensitivity and NPV >95%, the data suggest that PEER could still be used for tumors interpreted as oncocytic neoplasms on biopsy without CD117 immunohistochemistry. Finally, cases deemed CD117$^-$ but with strong evidence suggesting an oncocytic neoplasm on biopsy according to hematoxylin and eosin evaluation deserve further study; PEER may still be of benefit despite potential biopsy tissue limitations for immunohistochemistry. A potential diagnostic algorithm is outlined in Supplementary Figure 3.

The optimal PEER cutoff of 0.60 in the present study is slightly higher than previously suggested thresholds. Amin et al. [10] initially identified a cutoff between 0.50 and 0.55 for perfect classification of 14 CD117$^+$ oncocytomas from five CD117$^+$ chRCC tumors in a retrospective analysis, as well as 12 CD117$^+$ oncocytomas from ten CD117$^+$ chRCC tumors in a prospective validation. Notably, when excluding the nephrogenic phase and only including PEER calculated from the cortical phase, the separation between oncocytomas and chRCC increased, with equal performance for CD117$^+$ tumors across a full range of PEER values from 0.50 and 0.60. Therefore, the ideal PEER threshold may vary slightly according to the contrast-enhanced phase available. Kahn et al. [19] suggested that the optimal cutoff varied from 0.49 to 0.56, depending on whether PEER was calculated from nephrogenic, excretory, or nonspecific phases, but the authors did not assess the cortical phase. Amin et al. [10] and Kahn et al. [19] included a total of 41 and 12 CD117$^+$ tumors, respectively, while the present analysis includes the largest sample to date, with 58 CD117$^+$ tumors. For the goal of optimizing identification of chRCC for treatment, erring on a slightly higher cutoff may be reasonable and would still lead to fewer benign resections.

Another emerging approach for distinguishing oncocytoma from chRCC is use of a gene expression classifier [20]. While the classifier was based on surgically resected specimens, tissue from renal mass biopsy may be sufficient to evaluate whether the gene signature resembles oncocytoma or chRCC. It is possible that sampling on renal mass biopsy and intratumoral heterogeneity could have a greater impact on the accuracy of a genomic classier in comparison to a single immunohistochemical stain for CD117 as required to use PEER. However, an augmented approach

with both a gene expression classifier and freely available radiographic information to calculate PEER may provide more reassurance, especially in situations in which CD117 status is negative or cannot be determined on biopsy.

Limitations of our study include the use of a retrospective design, surgical specimens, and a mix of early contrast-enhanced phases (cortical or nephrogenic) on CT. The need for contrast enhancement may preclude applicability to some patients with pre-existing renal dysfunction who could have benefited from avoidance of surgery and further compromise of renal function. Comparisons of diagnostic approaches with PEER to novel options such as genomic classifiers on biopsy tissue and noninvasive options such as ^{99m}Tc-sestamibi single-photon emission CT/CT deserve further study [20,21].

5. Conclusions

PEER reliably differentiated benign renal oncocytomas and indolent hybrid tumors from malignant chRCC with excellent diagnostic performance. Further study of PEER in a diagnostic pathway with biopsy and CD117 staining should be conducted given the potential to avoid nephrectomy for benign and indolent oncocytic renal tumors.

Author contributions: Hiten D. Patel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Patel, Huai, Gupta.
Acquisition of data: Patel, Huai, Elliott, Thorson, Picken, Bova.
Analysis and interpretation of data: Patel.
Drafting of the manuscript: Patel, Huai, Elliott, Thorson, Rac, Picken, Quek, Bova, Gupta.
Critical revision of the manuscript for important intellectual content: Patel, Huai, Elliott, Thorson, Rac, Picken, Quek, Bova, Gupta.
Statistical analysis: Patel.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Picken, Quek, Bova, Gupta.
Other: None.

Financial disclosures: Hiten D. Patel certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.10.006.

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