Identification and Validation of Radiographic Enhancement for Reliable Differentiation of CD117(+) Benign Renal Oncocytoma and Chromophobe Renal Cell Carcinoma

Jay Amin1, Bo Xu2, Shervin Badkhshan1, Terrance T. Creighton1, Daniel Abbotoy1, Christine Murekeyisoni1, Kristopher M. Attwood3, Thomas Schwaab1,4,5, Craig Hendler6, Michael Petroziello6, Charles L. Roche6, and Eric C. Kauffman1,5,7

Abstract

Purpose: The diagnostic differential for CD117/KIT(+) oncocytic renal tumor biopsies is limited to benign renal oncocytoa versus chromophobe renal cell carcinoma (ChRCC); however, further differentiation is often challenging and requires surgical resection. We investigated clinical variables that might improve preoperative differentiation of CD117(+) renal oncocytoa versus ChRCC to avoid the need for benign tumor resection.

Experimental Design: A total of 124 nephrectomy patients from a single institute with 133 renal oncocytoma or ChRCC tumors were studied. Patients from 2003 to 2012 comprised a retrospective cohort to identify clinical/radiographic variables associated with renal oncocytoa versus ChRCC. Prospective validation was performed among consecutive renal oncocytoa/ChRCC tumors resected from 2013 to 2017.

Results: Tumor size and younger age were associated with ChRCC, and multifocality with renal oncocytoma; however, the most reliable variable for ChRCC versus renal oncocytoa differentiation was the tumor:urea peak early-phase enhancement ratio (PEER) using multiphase CT. Among 54 PEER-eligible tumors in the retrospective cohort [19 CD117(+), 13 CD117(-), 22 CD117-untested], PEER classified each correctly as renal oncocytoma (PEER >0.50) or ChRCC (PEER <0.50), except for four misclassified CD117(-) ChRCC variants. Prospective study of PEER confirmed 100% accuracy of renal oncocytoma/ChRCC classification among 22/22 additional CD117(+) tumors. Prospective interobserver reproducibility was excellent for PEER scoring (intraclass correlation coefficient, ICC = 0.97) and perfect for renal oncocytoma/ChRCC assignment (ICC = 1.0).

Conclusions: In the largest clinical comparison of renal oncocytoa versus ChRCC to our knowledge, we identified and prospectively validated a reproducible radiographic measure that differentiates CD117(+) renal oncocytoa from ChRCC with potentially 100% accuracy. PEER may allow reliable biopsy-based diagnosis of CD117(+) renal oncocytoa, avoiding the need for diagnostic nephrectomy. Clin Cancer Res; 24(16); 3898–907. ©2018 AACR.

Introduction

Historically, renal tumors have been treated as renal cell carcinoma (RCC) until proven otherwise by surgical resection using partial or radical nephrectomy. Yet, at least 10% of resected renal masses are benign (1, 2). The majority of resected benign tumors are asymptomatic renal oncocytoas with typically small size amenable to partial nephrectomy. However, partial nephrectomy is associated with overall and high-grade complication rates of 25% to 30% and 10% to 15%, respectively, in addition to a small decline in renal function and an estimated healthcare cost of $24,000 per resection ($30,000 if complicated; refs. 3–7). On the basis of >60,000 new kidney tumor diagnoses in the United States annually (8) of which >90% are RCC (9), and a 5% incidence (range 3–7%) of renal oncocytoa among resected renal cell tumors (10, 11), renal oncocytoa resection can be estimated to incur an annual health care cost in the United States of nearly 100 million dollars. Reliable preoperative renal oncocytoa diagnosis would allow significant reductions in surgical resections, patient morbidity, and healthcare costs.

Currently, preoperative differentiation of renal oncocytoa from RCC is aided by renal tumor biopsy, which has a high diagnostic rate, a low incidence of predominantly low-grade complications, and a miniscule (<1:10,000) estimated risk of tumor seeding in contemporary studies (12–17). Yet, biopsy is still commonly deferred because RCC cannot be definitively ruled out when the biopsy favors renal oncocytoa (18). The most common diagnostic challenge in this regard is the differentiation of renal oncocytoa from chromophobe RCC (ChRCC; refs. 18–21). Renal oncocytoa and ChRCC share classic...
oncocytic histology and also a remarkably similar molecular biomarker profile (19, 20, 22, 23). In addition, eosinophilia that is characteristic of renal oncocytoma can be mimicked by ChRCC, which has a predominant eosinophilia in 40% of cases and at least some eosinophilic foci in most remaining cases (20). Both tumor subtypes are relatively indolent and appropriate for active surveillance management. However, whereas renal oncocytoma is benign, ChRCC has occasional metastatic potential and resection is warranted for select patients (24).

Biopsy differentiation of renal tumor subtypes has been aided by contemporary immunohistochemical biomarker panels. Most (≥70%) but not all renal oncocytoma and ChRCC tumors express the protein biomarker, CD117KIT, which is absent in other RCC subtypes and therefore narrows the differential diagnosis to renal oncocytoma versus ChRCC (23). Similarly, both renal oncocytoma and ChRCC lack classic biomarkers (e.g., CAIX, vimentin, AMACR) of clear cell RCC (CcRCC) and/or papillary RCC (PRCC; refs. 22, 23). Accordingly, although the diagnostic differential for an oncocytic renal tumor includes many renal cell tumor subtypes (18), contemporary immunostain panels incorporating CD117 and other biomarkers reliably differentiate renal oncocytoma and ChRCC from other oncocytic RCC variants, including CcRCC and PRCC. When the diagnostic differential has been narrowed to renal oncocytoma versus ChRCC, the CK7 protein biomarker is commonly used to support ChRCC diagnosis. However, CK7 is occasionally inaccurate in this role (22, 25, 26), and more reliable approaches are needed (21). Radiographic approaches, such as CT contrast enhancement measurement, have not yet shown utility in aiding preoperative renal oncocytopathy diagnosis. However, most prior radiographic studies have focused on the differentiation of renal oncocytoma from RCC subtypes collectively, overlooking the specific comparison of renal oncocytoma with the ChRCC subtype and the potential impact of occasional CD117(−) variants (27–29).

Here we report the largest study to our knowledge comparing clinical features of renal oncocytoma and ChRCC, and the first study to also consider the impact of CD117 positivity. We hypothesized that certain clinical and/or radiographic features might allow reliable preoperative differentiation of these two renal tumor subtypes, particularly among classic CD117(+) tumors for which the ChRCC/renal oncocytoma question on biopsy is most relevant. Using both a retrospective discovery cohort and prospective validation cohort, we identified a simple CT enhancement measure that differentiated renal oncocytoma from ChRCC with 100% accuracy and perfect interobserver reproducibility whenever CD117 was expressed; occasional inaccuracy was limited strictly to CD117(−) tumor variants. This generalizable approach may facilitate renal oncocytoma versus ChRCC diagnosis among CD117(−) oncocytic tumor biopsies and negate the need for CD117(+) renal oncocytoma resection to rule out malignancy.

**Translational Relevance**

Current inability to reliably differentiate benign renal oncocytoma from renal cell carcinoma (RCC) using needle core biopsy remains the primary reason behind routine surgical resection of these benign tumors, which is associated with frequent perioperative morbidity and an estimated annual health care cost approaching $100 million in the United States alone. Historically, the greatest challenge for preoperative renal oncocytoma diagnosis using biopsy has been the difficult differentiation of this benign tumor from the chromophobe RCC (ChRCC) subtype due to significant histologic and molecular overlap, including common expression of the CD117 biomarker. Here we retrospectively identified and prospectively validated a simple radiographic measurement ("PEER") that achieved 100% (41/41 cases) accuracy in differentiating CD117(+) renal oncocytoma from CD117(+) ChRCC. In the setting of a CD117(+) renal tumor biopsy, a high PEER value may reliably confirm renal oncocytoma diagnosis without the need for surgical resection, allowing significant reductions in patient morbidity and health care costs.

**Materials and Methods**

**Retrospective patient cohort**

Institutional review board approval at Roswell Park Cancer Institute, a National Comprehensive Cancer Network institute, was obtained for this study. A prospectively maintained nephrectomy database was queried to identify all patients who underwent partial or radical nephrectomy for pathologically confirmed renal oncocytoma or ChRCC between August 2003 and December 2012. One patient with four hybrid renal oncocytoma-ChRCC tumors was excluded from analyses due to indeterminate malignant versus benign pathology (30, 31). CD117 and CK7 immunostain results were obtained from pathology reports, and classified as positive for moderate-to-strong/diffuse membranous stain, or as negative for absent or weak/focal (<10%) stain (25). Hematoxylin- and eosin-stained slides from a subset of ChRCC tumors were scored retrospectively for eosinophilia tissue percentage (0%–100%) and eosinophilia intensity (0–3+) by a genitourinary pathologist (B. Xu).

**Radiographic tumor measurements**

Preoperative cross-sectional radiographic imaging for each tumor in the retrospective cohort was evaluated by two members of a committee comprised of three radiologists (C. Hendler, M. Petroziello, and C.L. Roche) and one urologic oncologist with kidney cancer specialization (E.C. Kauffman) while blinded to tumor histologic subtype. Scans were acquired from several different radiology facilities and no standardized imaging protocol was used. CT signal intensity (Hounsfield units, HU) of each tumor was measured in an early (arterial/cortical or venous/nephrogenic) contrast phase and a delayed/excretory contrast phase for the peak enhancing portion of each tumor using a 1.0-cm diameter region-of-interest (ROI) circle; or a 1.0-cm × 0.5-cm elliptical ROI for small heterogeneous tumors to avoid hypoenhancing portions. When multiple early CT phases were available for a patient, the earliest phase was used. Signal intensity of renal cortex adjacent to the tumor was measured using an elliptical ROI without specified dimensions. Tumor heterogeneity was estimated using a subjective 3-point scale (1, homogenous; 2, mild heterogeneity; 3, high heterogeneity).

**Prospective validation**

Clinical/radiographic variables that were significantly associated with renal oncocytoma or ChRCC in the retrospective analysis were evaluated prospectively between January 2013 and
February 2017. All resected tumors from this period were stained prospectively for CD117 and CK7. Preoperative radiographic imaging for each resected tumor was evaluated independently by three observers (E.C. Kaufmann, M. Petroziello, C.L. Roche), who assigned ChRCC or renal oncocytoma classification based on radiographic assessment while blinded to the actual tumor subtype histology.

**Results**

**Retrospective evaluation**

A total of 87 patients (93 tumors) comprised the retrospective cohort, which included 53 renal oncocytoma patients (59 tumors) and 34 ChRCC patients (34 tumors). Renal oncocytoma and ChRCC patients were similar for most preoperative features (Table 1). Younger age (<50 years) was significantly associated with ChRCC (80% specific), but only 24% sensitive for this subtype (Table 1A). Multifocality was significantly associated with renal oncocytoma (100% specific), but only 27% sensitive for this subtype (Table 1B). Smaller tumor sizes were enriched for renal oncocytoma, whereas larger tumor sizes and higher nephrometry scores were enriched for ChRCC (Table 1B).

The variable most reliably associated with renal oncocytoma versus ChRCC diagnosis was the CT peak signal intensity within a tumor, particularly when expressed as a tumor:cortex ratio (Table 1B). Differences in tumor:cortex peak signal intensity between renal oncocytoma and ChRCC were greater when measured using net enhancement (i.e., contrast phase signal intensity minus noncontrast phase signal intensity; Fig. 1; Supplementary Fig. S1A) compared with absolute signal intensity using the contrast phase only (Supplementary Fig. S1B and S1C); and when measured using an early (arterial/cortical or venous/nephrogenic) contrast phase (Fig. 1; Supplementary Fig. S1B) compared with a delayed/excretory contrast phase (Supplementary Fig. S1A and S1C). Combining these observations, we identified the most discriminating radiographic measurement to be the peak early-phase enhancement ratio (PEER) of the tumor:cortex (Fig. 1). All renal oncocytoma tumors were relatively hypoenhancing with a tumor:cortex PEER <0.50 (Figs. 1 and 2A–D). In contrast, all but four ChRCC tumors were relatively hyperenhancing with a tumor:cortex PEER >0.50 (Figs. 1 and 2E–H). Intriguingly, all four ChRCC tumors with a tumor:cortex PEER >0.50 were CD117(+) variants (Fig. 1; Supplementary Fig. S2). Thus, a tumor:cortex PEER threshold value of 0.50 reliably separated renal oncocytoma (PEER <0.50) from ChRCC (PEER >0.50) for all tumors that were either CD117(+) or CD117-untested (Fig. 1).

**Prospective validation**

Variables of age, tumor size, multifocality, and tumor:cortex PEER were next evaluated prospectively over a 4-year period for ability to classify 40 additional tumors (20 renal oncocytoma, 20 ChRCC) from 37 consecutive nephrectomy patients with renal oncocytoma or ChRCC. A total of 28/40 (14 renal oncocytoma, 14 ChRCC) tumors had preoperative multiphase CT scans available for PEER measurement, 22 of which were CD117(+) and six of which were CD117(−). All 22 CD117(+) tumors were correctly classified using a PEER threshold value of 0.50 by each of the three independent reviewers, whereas 3/6 CD117(−) tumors were misclassified by each reviewer using this approach (Fig. 3A and B). Interobserver reliability was excellent for PEER scoring (ICC = 0.97), and perfect for renal oncocytoma versus ChRCC classification (ICC = 1.0; Fig. 3A). Multifocality correctly classified 6/6 CD117(+) tumors as renal oncocytoma, age <50 years correctly classified 4/5 CD117(+) tumors as ChRCC, size <2 cm correctly classified 4/5 CD117(+) tumors as renal oncocytoma, and size >7 cm correctly classified 4/5 CD117(+) tumors as ChRCC.

In a combined analysis of the prospective and retrospective cohorts, PEER classified renal oncocytoma versus ChRCC correctly in 63/63 (100%) tumors without evidence of CD117(−) staining, including 41/41 cases confirmed to be CD117(+) (Table 2; Fig. 3C). In contrast, the CK7 biomarker occasionally misclassified CD117(+) tumors, including 17% of CD117(+) ChRCC tumors (Table 2; Supplementary Fig. S3). Neither PEER nor CK7 performed well among CD117(−) variants (Table 2). Although CD117(+) renal oncocytoma and CD117(+) ChRCC tumors were reliably separated by PEER using either the arterial/cortical or venous/nephrogenic phase, the former phase allowed greater separation (Fig. 3D). Among CD117(+) ChRCC tumors evaluated by PEER, eosinophilia of moderate-to-strong intensity was present diffusely (>80% of tissue) in close to one third of cases and at least focally in most cases; however, eosinophilia tended to be more prevalent among CD117(−) tumors (Supplementary Table S1). PEER values of four tumors from the excluded hybrid patient ranged from 0.44 to 0.47, each of which was CD117(+).

**Discussion**

Currently, most benign renal oncocytoma tumor patients continue to undergo unnecessary partial or radical nephrectomy because biopsy alone is inadequate to definitively rule out cancer. Improved preoperative diagnosis of benign renal oncocytoma tumors would avoid a need for diagnostic renal oncocytoma resection and thereby allow significant reductions in patient morbidity and healthcare costs (3–7). The greatest challenge for nonsurgical diagnosis of renal oncocytoma has been the difficult differentiation of renal oncocytoma from ChRCC on percutaneous needle-core biopsy, due to significant overlap in histology and biomarker profile, including common expression of CD117 (19–23). Although both tumor types confer excellent candidacy for active surveillance management, the latter has occasional lethal potential and warrants resection in select patients.

This study investigated clinical variables which might facilitate nonoperative diagnostic differentiation of renal oncocytoma from ChRCC, including the potential impact of CD117 expression status. In the largest clinical comparison of ChRCC versus renal oncocytoma to our knowledge, we retrospectively identified a simple CT enhancement measure (tumor:cortex PEER) that differentiated renal oncocytoma from ChRCC whenever
Table 1. Clinicopathologic features of the retrospective cohort

| A. Patient features | ChRCC | RO | P      |
|---------------------|-------|----|--------|
| Total patients, n (%) | 34 (39%) | 53 (61%) | 0.16   |
| Age, mean (range) | 61.2 (28–84) | 66.2 (35–89) | 0.012  |
| <50, n (%) | 8 (24%) | 2 (4%) |        |
| Gender, n (%) |  |  |  |
| Male | 20 (59%) | 37 (70%) | 0.36   |
| Female | 14 (41%) | 16 (30%) |        |
| Race, n (%) |  |  |  |
| White | 32 (94%) | 49 (92%) | 1.00   |
| Black | 1 (3%) | 3 (6%) |        |
| Other | 1 (3%) | 1 (2%) |        |
| BMI, n (%) |  |  |  |
| ≥ 30 | 16 (47%) | 32 (62%) | 0.27   |
| < 35 | 10 (29%) | 10 (19%) | 0.31   |
| Smoking history |  |  |  |
| Never smoker, n (%) | 23 (68%) | 27 (51%) | 0.18   |
| Any smoking, n (%) | 11 (32%) | 26 (49%) |        |
| Pack years, mean (range) | 24.9 (1–100) | 25.6 (5–50) | 0.37   |
| Serum creatinine, mean (range) | 1.0 (0–1.9) | 1.1 (0.8–2.4) | 0.98   |
| Charlson index, mean (range) | 2.5 (0–8) | 2.5 (0–11) | 0.98   |

| B. Tumor features | ChRCC | RO | P      |
|---------------------|-------|----|--------|
| Total tumors, n (%) | 34 (37%) | 59 (63%) |        |
| Laterality, n (%) |  |  |  |
| Left | 22 (65%) | 35 (59%) | 0.66   |
| Right | 12 (35%) | 24 (41%) |        |
| Multifocality, n (%) |  |  |  |
| 0% | 0 (0%) | 0 (0%) | <0.001 |
| Synchronous RCC | 0 (0%) | 0 (0%) |        |
| Synchronous RO | 0 (0%) | 0 (0%) |        |
| Synchronous AML | 0 (0%) | 0 (0%) |        |
| Tumor diameter, cm |  |  |  |
| Mean (range) | 6.4 (1.8–20.0) | 3.4 (0.9–12.0) | <0.001 |
| ≤4, n (%) | 13 (38%) | 44 (75%) | <0.001 |
| 4.1–7, n (%) | 11 (32%) | 12 (20%) |        |
| >7, n (%) | 10 (29%) | 3 (5%) |        |
| RENAL score |  |  |  |
| Total, mean (range) | 8.3 (5–11) | 7.3 (4–11) | 0.022  |
| R, mean (range) | 1.9 (1–3) | 1.3 (1–3) | 0.001  |
| E, mean (range) | 1.6 (1–3) | 1.7 (1–3) | 0.47   |
| N, mean (range) | 2.6 (1–3) | 2.2 (1–3) | 0.022  |
| A, n (%) |  |  |  |
| Anterior | 13 (38%) | 27 (46%) | 0.65   |
| Posterior | 11 (32%) | 14 (24%) |        |
| Neither | 10 (29%) | 18 (31%) |        |
| L, mean (range) | 2.2 (1–3) | 2.2 (1–3) | 0.76   |
| Endophytic %, mean (range) | 51.1 (5–100) | 56.2 (10–100) | 0.40   |
| Kidney pole, n (%) |  |  |  |
| Upper | 7 (21%) | 13 (22%) | 0.77   |
| Middle | 16 (47%) | 31 (53%) |        |
| Lower | 9 (26%) | 14 (24%) |        |
| N/A | 2 (6%) | 1 (2%) |        |
| Stellate scar, n (%) |  |  |  |
| Yes | 2 (6%) | 5 (8%) | 1.00   |
| No | 26 (76%) | 46 (78%) |        |
| Unknown | 6 (18%) | 8 (14%) |        |
| Heterogeneity score, mean (range) | 2.0 (1–3) | 1.9 (1–3) | 0.62   |
| CT signal intensity (HU), mean (range) |  |  |  |
| Tumor Early phase | 99.1 (53.5–186) | 133.4 (70–250) | 0.002  |
| Net<sup>a</sup> early phase | 63.7 (17.5–162) | 110.4 (48–225) | <0.001 |
| Delayed phase | 74.6 (39–146) | 94.9 (41–180) | 0.043  |
| Net<sup>a</sup> delayed phase | 42.7 (16–122) | 70.5 (15.5–155) | 0.009  |
| Tumor: cortex Early phase | 0.63 (0.32–100) | 0.80 (0.55–1.04) | 0.001  |
| Net<sup>a</sup> early phase | 0.45 (0.18–0.96) | 0.77 (0.50–1.00) | <0.001 |
| Delayed phase | 0.53 (0.36–0.86) | 0.70 (0.48–0.93) | <0.001 |
| Net<sup>a</sup> delayed phase | 0.39 (0.16–0.80) | 0.62 (0.23–0.95) | <0.001 |

<sup>a</sup>Net difference between contrast and noncontrast CT phases.
CD117(+) with 100% accuracy. All renal oncocytoma tumors in the retrospective cohort had hyperenhancement (PEER > 0.50) regardless of CD117 positivity, whereas ChRCC tumors typically had hypoenhancement (PEER < 0.50) except for a minority of cases which, to our surprise, were all CD117(−) variants. To validate this finding, all resected renal oncocytoma or ChRCC tumors in the past 4 years at our institution were evaluated prospectively by CD117/CK7 expression and PEER, as measured by three independent reviewers blinded to whether each tumor was renal oncocytoma or ChRCC. All CD117(+) tumors in this prospective cohort were correctly classified as renal oncocytoma or ChRCC by each reviewer using PEER; and as in the retrospective cohort, only CD117(−) ChRCC variants were misclassified. In combined retrospective and prospective cohort analyses, PEER classified renal oncocytoma versus ChRCC correctly when not CD117(−) in 63/63 (100%) evaluable cases, including 41/41 confirmed CD117(+) cases. These findings indicate PEER is an accurate tool for differentiating CD117(+) renal oncocytoma from ChRCC.

Currently, the CD117 biomarker is used in contemporary pathology to narrow the diagnostic differential of an oncocytic renal tumor to either renal oncocytoma or ChRCC (22, 23). Histomorphology is the gold-standard for renal oncocytoma versus ChRCC differentiation but may be inadequately represented in small biopsy tissues. Furthermore, eosinophilia present to some degree in most ChRCC tumors and predominant in 40% of cases (20), can mimic classic renal oncocytoma eosinophilia when captured on biopsy. In this scenario, the CK7 clinical biomarker can be helpful to support ChRCC diagnosis; however, some ChRCC variants lack CK7 expression (22, 25, 26).

Figure 1.
Tumor:cortex PEER values in renal oncocytoma (RO) versus ChRCC tumors of retrospective cohort patients according to CD117 expression. The contrast CT peak signal intensity (HU) of each tumor calculated as \( \frac{(tumor_{contrast} - tumor_{noncontrast})}{(cortex_{contrast} - cortex_{noncontrast})} \) is plotted according to RO versus ChRCC histology and stratified by CD117 immunostain result. An early contrast phase includes either an arterial/cortical phase or venous/nephrogenic phase.

Figure 2.
Representative early-phase contrast CT images of CD117(+) renal oncocytoma/ChRCC tumors. A–D, Four representative CD117(+) renal oncocytoma tumors with tumor hyperenhancement that is similar to the enhancement level of the adjacent cortex (tumor:cortex PEER scores = 0.96, 0.92, 0.93, 0.71, respectively). E–H, Four representative CD117(+) ChRCC tumors with hypoenhancement relative to the adjacent cortex (tumor:cortex PEER scores = 0.26, 0.27, 0.32, 0.27, respectively). Dotted circles and ellipses (ROI) denote the peak enhancing areas of the tumors and representative regions of renal cortex, respectively, used for tumor:cortex PEER calculation.
Figure 3.
Prospective validation of tumor:cortex PEER score for assignment of renal oncocytoma (RO) versus ChRCC histology. A, Comparison of PEER scores from three independent physician reviewers for 28 consecutive RO/ChRCC tumors in the prospective cohort, indicating high interobserver agreement (ICC = 0.97) and perfect agreement for the assigned histology (ICC = 1.0). B, The mean tumor:cortex PEER score for each tumor in the prospective cohort is plotted according to CD117 expression. C, PEER scores for all tumors in the combined retrospective and prospective cohorts are plotted according to CD117 expression. D, PEER scores from part C after exclusion of tumors measured using a venous/nephrogenic rather than arterial/cortical contrast phase show improved separation of CD117(+) renal oncocytoma and CD117(+) ChRCC tumors.
Accordingly, definitive renal oncocyto\text{ma} diagnosis cannot be confirmed on the basis of CK7 absence alone in a biopsy, and is often deferred to surgical resection pathology (20, 22, 26). In this study, PEER outperformed CK7, which misclassified 17\% of CD117(\text{+}) ChRCC cases as renal oncocyto\text{ma}, consistent with prior reports (22, 25, 26). Although neither PEER nor CK7 was very accurate among CD117(\text{+/-}) tumors, this scenario has less relevance to the clinical challenge of ChRCC versus renal oncocyto\text{ma}, because the diagnostic differential of a CD117(\text{-}) oncocyto\text{ma} biopsy is not limited to these two subtypes and includes several other RCC subtypes as well (18). Only when an oncocyto\text{ma} tumor is CD117(\text{+}) does the renal oncocyto\text{ma} versus ChRCC distinction become critical, and in this scenario PEER achieves high if not perfect accuracy.

**Figure 4.**

Management algorithm for an oncocyto\text{ma} renal tumor biopsy patient using CD117 immunostain and tumor:cortex PEER. An oncocyto\text{ma} renal tumor biopsy should undergo CD117 and CK7 immunostain; multiple biopsy cores should be obtained to differentiate diffuse versus focal expression. If CD117(\text{-}), the differential is large and includes CcRCC and PRCC, in addition to less common RCC subtypes, and resection is favored if tumor size and patient health are appropriate. If CD117(\text{+}), the differential is limited to ChRCC and RO, and a tumor:cortex PEER score can be measured using CT imaging that includes an early contrast phase and an unenhanced phase. For tumor:cortex PEER \textless{}0.50, the CD117(\text{+}) tumor is predicted to be ChRCC and can be resected or surveyed depending on tumor size and patient health/life expectancy. \*, Active surveillance may be appropriate in select patients with small tumors and/or limited life expectancy. **, A PEER score of 0.51 to 0.55 was not observed in this study for any CD117(\text{+}) tumor; a hypothetical CD117(\text{+}) tumor with PEER score falling within this range based on a venous/nephrogenic phase should undergo repeat CT imaging with a true arterial/cortical phase, which may yield a higher PEER value if the tumor is renal oncocyto\text{ma}. If PEER remains between 0.51 and 0.55 using an arterial/cortical phase, consider CK7 immunostain result and other clinical features (patient age, tumor size/focality) or defer to diagnostic resection.

| CD117 level | PEER (%) | CK7 (%) | PEER (%) | CK7 (%) | PEER (%) | CK7 (%) | PEER (%) | CK7 (%) |
|-------------|---------|---------|---------|---------|---------|---------|---------|---------|
| Not tested  | 5/5 (100)| 2/2 (100)| 17/17 (100)| 4/4 (100)| 22/22 (100)| 6/6 (100)| 17/17 (100)| 4/4 (100)|
| Positive    | 15/15 (100)| 15/18 (83)| 26/26 (100)| 28/28 (100)| 41/41 (100)| 43/46 (93)| 26/26 (100)| 28/28 (100)|
| Negative    | 3/10 (30)| 7/10 (70)| 9/9 (100)| 7/10 (70)| 12/19 (63)| 14/20 (70)| 9/9 (100)| 7/10 (70)|

Abbreviation: RO, renal oncocyto\text{ma}.

Amin et al.  
Clin Cancer Res; 24(16) August 15, 2018  
Clinical Cancer Research
Figure 4 illustrates a proposed algorithm that combines PEER with CD117 immunostain in the management of oncocytic renal tumor biopsy patients. PEER does not negate the need for biopsy in preoperative renal oncocytoma diagnosis, but may improve biopsy accuracy so that diagnostic resection can be avoided for CD117(+) renal oncocytoma tumors, which account for most renal oncocytoma cases. For CD117(−) renal oncocytoma tumors, PEER does not facilitate diagnosis and other novel diagnostic approaches are needed to avoid surgery. In our prospective series, CD117(−) tumors accounted for 21% of all renal oncocytoma/ChRCC cases, which is consistent with reported incidences (23).

Additional study is needed to validate the management algorithm in Figure 4 and confirm the added value of PEER in the clinic. Goals of this future research should include verification of the optimal PEER cut-off value for ChRCC versus renal oncocytoma differentiation. The cut-off PEER value of 0.50 in our prospective cohort was arbitrarily selected on the basis of our retrospective observations; however, a cut-off PEER value of 0.55 too would have achieved 100% diagnostic accuracy in both the retrospective and prospective cohorts. Because PEER measurements never fell within the 0.51–55 range for any CD117(+) tumor in this study, additional investigation is needed to determine whether this scenario ever occurs; and if so, whether such tumors are renal oncocytoma (in which case a 0.50 cut-off would be optimal) or ChRCC (in which case a cut-off of 0.55 would be optimal). In the interim, for a hypothetical CD117(+) tumor with PEER value of 0.51–0.55 based only on a venous/nephrogenic phase PEER protocol standardization. Although the cortical phase gave the best separation of renal oncocytoma from ChRCC tumors when CD117(+) (Figs. 3D and 4).

An association between CD117 positivity and radiographic enhancement level is not previously reported to our knowledge. Our discovery that CD117 absence correlates with frequent ChRCC hyperenhancement is unexpected on the basis of known CD117 function. CD117 is a tyrosine kinase membrane receptor for the ligand, stem cell factor (SCF), and positively regulates a diversity of cell processes, including proliferation, differentiation, migration, and angiogenesis (32, 33). CD117 interacts with several cell signaling pathways implicated in cancer development, such as those of PI3K/Akt, Src family kinases, and Ras-Erk (34). The role of CD117 in ChRCC/renal oncocytoma tumorigenesis, however, is unknown. Given its known function in increasing microvesSEL density and angiogenesis (33), absence of CD117 expression might be expected to decrease vascularity/enhancement, which is opposite to observations in this study. CD117 is a differentiation marker for the nephron distal renal tubule (35), from which renal oncocytoma and ChRCC tumors are believed to originate, and it is possible that its loss in ChRCC tumors might reflect dedifferentiation to a hypervascular and potentially more aggressive variant. Also worthy of note is our observation that CD117(−) tumors have a high rate of predominant eosinophilia. Together, these findings suggest the existence of a ChRCC biologic variant characterized by CD117 negativity, frequent atypical hypervascularity, and common eosinophilia. Study is currently ongoing to characterize the clinicopathologic features and prognostic significance of these CD117(−) ChRCC variants.

Prior studies that compared clinical features of renal oncocytoma and RCC have generally overlooked the direct renal oncocytoma versus ChRCC comparison (1, 36, 37), which is most relevant to the contemporary diagnostic challenge of a CD117(+) oncotic tumor biopsy (28). Furthermore, no study comparing radiographic features of renal oncocytoma and ChRCC has considered CD117 expression. Bird and colleagues studied CT enhancement in various renal cell tumor types, which included 12 renal oncocytoma and 5 ChRCC (29). Renal oncocytoma enhancement was three times higher than ChRCC enhancement, with greatest difference in the arterial phase, as in this study. Gorin and colleagues has reported that a sestamibi scan has high sensitivity for renal oncocytoma but cannot reliably rule out ChRCC, which occasionally gives a positive result (38). Canvasser and colleagues reported recently an algorithm using MRI signal intensity to predict CrRCC histology (39). A total of 9 ChRCC and 7 renal oncocytoma tumors of unspecified CD117 status were studied and showed overlap in MRI enhancement.

Novel molecular biomarkers may help differentiate renal oncocytoma and ChRCC on biopsy, but have not yet translated clinically (21, 40–44). Kauffman et al. reported CD82/KAI1 as a sensitive ChRCC marker that is typically absent in renal oncocytoma, a finding validated subsequently by Truong and colleagues (42, 45). Additional promising biomarker candidates to distinguish renal oncocytoma and ChRCC include S100A1 and cyclin D1 (46, 47), whereas other potential biomarkers involve more complicated definitions of positivity or molecular approaches (40, 41, 43, 44). In contrast, a PEER ratio can be determined rapidly and cheaply using routine multiphase CT imaging, which has already been obtained for many patients prior to the CD117(+) oncotic tumor biopsy. A strength of this study is that CT scans are done from different facilities without protocol standardization. Although the cortical phase gave the best separation of renal oncocytoma from ChRCC when CD117(+) , either the cortical or nephrogenic phase was 100% accurate. Hence, the specific CT protocol and precise timing of the early contrast phase does not appear to be critical, which should facilitate generalized PEER usage.

A historical concern with active surveillance of biopsy-favored renal oncocytoma is that the tumor might simultaneously harbor ChRCC, as in rare hybrid oncotic tumors (HOCT; ref. 48). However, to our knowledge, HOCT metastatic behavior has never been confirmed, raising the assertion by some investigators that these hybrid tumors might be benign (30). Consistent with this possibility, Pote and colleagues recently concluded that HOCT is genetically more similar to renal oncocytoma than ChRCC and may therefore be a renal oncocytoma variant (31). Regardless, given its indolent clinical behavior and lack of known metastatic potential, the rare possibility of HOCT should not justify routine resection of tumors with renal oncocytoma diagnosis favored on biopsy, because HOCT too is appropriate for surveillance (49).

In addition to PEER outcomes, we found that younger age and larger tumor size enriched for ChRCC, while multifocality and smaller tumor size enriched for renal oncocytoma. Although an age cutoff of <50 years had high specificity for ChRCC, the optimal age cutoff to discern these two subtypes needs to be better defined in larger studies with statistical analyses designed to identify this cutoff. The association of ChRCC with young age is consistent with recent observations from Daugherty and colleagues, who noted ChRCC tumors to be the most common nonclear RCC subtype in young white females (50). In contrast to PEER, however, each of these other variables (age, size, focality) was poorly sensitive for either renal oncocytoma or ChRCC in the current study; and with the exception of multifocality, none was 100%
specific. Nevertheless, these variables might be clinically helpful to corroborate PEER findings among CD117(+) tumors with a PEER value near the 0.50 threshold (Fig. 4). Caution must be exercised with multifocal tumors, because renal oncocytoma diagnosis for one tumor does not exclude malignancy in another (48). Additional biopsy should be considered for any synchronous tumor with radiographic features (e.g., PEER, size, growth rate) that are discordant from the biopsied renal oncocytoma tumor.

Consistently high PEER values for renal oncocytoma, regardless of CD117 positivity, suggest that a tumor:cortex PEER <0.50 might rule out renal oncocytoma without the need for biopsy. Fat-poor angiomyolipoma (AML) represents the other main benign renal tumor besides renal oncocytoma that often undergoes unnecessary diagnostic resection; although unlike renal oncocytoma, AML diagnosis by percutaneous biopsy is uncomplicated. Interestingly, AML is characterized by hypervascularity that might be expected to yield uniformly high PEER values, similar to renal oncocytoma. Future studies are therefore warranted to determine the accuracy of a low tumor:cortex PEER value to rule out any common benign histology (i.e., renal oncocytoma and fat-poor AML) without the need for biopsy.

A limitation of this study is that CD117 staining was determined with surgically resected tumors, whereas PEER is proposed to guide clinical management based on the CD117 status of biopsy tissues (Fig. 4). Additional investigation is therefore needed to confirm concordance between CD117 staining on biopsy tissue and resected specimens. In the interim, a CD117(+) stain result based on only a single biopsy core should be interpreted with caution because this result may not rule out a CD117(−) tumor with focal positivity. To avoid this scenario, multiple tumor biopsies are recommended to ensure adequate tumor sampling that reliably differentiates focal versus diffuse CD117 expression.

Additional study limitations include a single institute setting and lack of external validation. Although the study is the largest clinical comparison of ChRCC and renal oncocytoma to our knowledge, the cohort is nevertheless limited in size, and many patients were lacking preoperative multiphase CT scans necessary to measure PEER. Furthermore, MRI enhancement was not evaluated in this study due to a limited number of available cases at our institute and warrants future investigation. Finally, many tumors in the retrospective cohort were not tested for CD117(+) tumors. A historical challenge to reliable preoperative renal oncocytoma diagnosis used biopsy has been differentiation from ChRCC, which shares common CD117 biomarker expression with renal oncocytoma, but warrants resection in select cases due to occasional lethal potential. We identified and prospectively validated a reproducible and easily generalizable radiographic measure (tumor:cortex PEER) that uses standard multiphase CT imaging to differentiate CD117(+) renal oncocytoma from CD117(+) ChRCC with potentially 100% accuracy. Age, tumor size, focality, and CK7 immunostain may corroborate renal oncocytoma/ChRCC diagnosis but are alone not 100% reliable. In contrast, a high PEER value may reliably confirm renal oncocytoma diagnosis whenever an oncocytic renal tumor biopsy is CD117(+), and thereby allow diagnostic resection to be avoided. The number of patients in this study with known CD117(+) tumors that were evaluable with PEER was limited (41 cases), and external validation in larger cohorts will be helpful to confirm the clinical value of PEER for CD117(+) renal oncocytoma diagnosis.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: J. Amin, E.C. Kauffman
Development of methodology: J. Amin, S. Badkhshan, C. Hendler, E.C. Kauffman
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Amin, B. Xu, S. Badkhshan, T.T. Creighton, C. Murekeyisoni, T. Schaewb, C. Hendler, C.L. Roche, E.C. Kauffman
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Amin, B. Xu, S. Badkhshan, C. Murekeyisoni, K.M. Attwood, C. Hendler, M. Petrozzello, C.L. Roche, E.C. Kauffman
Writing, review, and/or revision of the manuscript: J. Amin, B. Xu, C. Murekeyisoni, C.L. Roche, E.C. Kauffman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Amin, S. Badkhshan, D. Abbotoy, C. Murekeyisoni
Study supervision: E.C. Kauffman

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