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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Radiology and Organ Imaging/Radyoloji ve Organ Görüntüleme

Diagnostic Performance of Multiphase Multidetector CT in the Differentiation of Renal Cell Carcinoma (RCC) Subtypes

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ABSTRACT

Purpose: This study aimed to determine the applicability of quantitative multiphase multidetector computed tomography (MDCT) enhancement parameters for diagnosing renal cell carcinoma (RCC) subtypes and evaluate their discriminating capability.

Methods: This retrospective study included 72 patients with histopathologically confirmed RCC from 2009 to 2013. The patients included 58 with clear-cell RCC (ccRCC), 7 with papillary RCC, and 7 with chromophobe RCC. Patients underwent multiphase MDCT for quantitative enhancement parameter calculations, including corticomedullary and excretory enhancement difference (ΔHU) and standardized enhancement ratios. Cutoff values for subtypes were determined using receiver operating characteristic (ROC) curve analysis.

Results: Corticomedullary ΔHU parameters showed best performance across all phases. The highest sensitivity, specificity, and accuracy (sensitivity 93%, specificity 100%, accuracy 94%) were associated with a ΔHU cutoff of > 47 HU. A standardized corticomedullary enhancement ratio of > 0.31 yielded 93% sensitivity, 93% specificity, and 93% accuracy. The washout enhancement pattern showed lower performance, with 79% accuracy and 92% specificity. The corticomedullary phase performed significantly better than the excretory phase ($p<0.05$).

Conclusion: Quantitative enhancement parameters from multiphase MDCT, particularly during the corticomedullary phase, provide a robust method for distinguishing ccRCC from non–clear cell subtypes with high diagnostic accuracy, supporting their routine clinical integration.

Keywords: Renal cell carcinoma; Multidetector computed tomography; Clear cell carcinoma; Papillary carcinoma; Chromophobe carcinoma; Diagnostic imaging

ÖZET

Amaç: Bu çalışma, renal hücreli karsinom (RCC) alt tiplerinin tanısında kantitatif çok fazlı çok dedektörlü bilgisayarlı tomografi (MDCT) kontrastlanma parametrelerinin uygulanabilirliğini belirlemeyi ve ayırt edici yeteneklerini değerlendirmeyi amaçladı.

Yöntemler: Bu retrospektif çalışma, 2009–2013 yılları arasında histopatolojik olarak doğrulanmış RCC tanılı 72 hastayı içermektedir. Hastaların 58'i berrak hücreli RCC (ccRCC), 7'si papiller RCC ve 7'si kromofob RCC idi. Hastalarda çok fazlı MDCT ile kortikomedüller ve ekskrezyon fazı kontrastlanma farkı (ΔHU) ve standardize kontrastlanma oranları dahil kantitatif kontrastlanma parametreleri hesaplandı. Alt tipler için eşik değerleri receiver operating characteristic (ROC) eğrisi analizi ile belirlendi.

Bulgular: Kortikomedüller ΔHU parametreleri tüm fazlar arasında en iyi performansı gösterdi. >47 HU'luk ΔHU eşik değeri, %93 duyarlılık, %100 özgüllük ve %94 doğruluk ile en yüksek tanısal performansı gösterdi. Standardize kortikomedüller kontrastlanma oranı >0,31 olduğunda %93 duyarlılık, %93 özgüllük ve %93 doğruluk olarak bulundu. Washout kontrastlanma paterni diğer parametrelerden daha düşük performans gösterdi (doğruluk %79, özgüllük %92). Kortikomedüller faz, ekskrezyon fazına kıyasla anlamlı derecede üstün performans gösterdi ($p < 0.05$).

Sonuç: Çok fazlı MDCT'den elde edilen kantitatif kontrastlanma parametreleri, özellikle kortikomedüller fazda, ccRCC'yi non–berrak hücreli alt tiplerden ayırmada yüksek tanısal doğruluk sağlayan güçlü bir yöntem sunmaktadır. Bu bulgular, söz konusu parametrelerin rutin klinik uygulamaya entegrasyonunu desteklemektedir.

Anahtar Kelimeler: Renal hücreli karsinom; Çok dedektörlü bilgisayarlı tomografi; Berrak hücreli karsinom; Papiller karsinom; Kromofob karsinom; Tanısal görüntüleme.

Renal cell carcinoma (RCC) comprises 90% of all kidney cancers and 2-3% of all cancers in adult patients across the globe(1). RCC has three major histological subtypes: clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC), account for 70-80%, 10-15%, and 5-7% of RCC cases, respectively(2, 3). Each subtype has its own distinct biological behavior, prognosis, and response to therapy. Of all subtypes, clear cell RCC is the most aggressive and highly responsive to anti-angiogenic agents. In contrast, papillary RCC responded to MET inhibitors (4). Calibration of subtype allocation into the clear cell and papillary RCC categories is crucial in determining precise relapse- and recurrence-free survival. Therefore, treatment can be tailored to patients with the most aggressive types of RCC, whereas patients with other subtypes are spared unnecessary treatments.

Multiphase computed tomography (MDCT) is a routine imaging technique used for the characterization of renal masses. The biology of the pathology provides a basis for subtype differentiation in ccRCC owing to its histopathologically abundant vascular networks that cause enhancement during the corticomedullary phase. In contrast, pRCC is poorly vascularized and has modest enhancement, whereas chRCC shows patterns that are intermediate (5, 6). The measurement of quantitative enhancement to improve diagnostic accuracy has been the focus of several studies. In 2002, Kim et al. set thresholds of 84 HU for the corticomedullary phase and 44 HU for the excretory phase and were able to achieve an accuracy range of 82-86% for distinguishing ccRCC from pRCC and chRCC (7). ccRCC was shown by Young et al. (2013) to be distinguishable from other subtypes with multiphasic thresholds of corticomedullary > 106 HU, nephrographic > 92 HU, and excretory > 68 HU, with an accuracy range of 84-85% (8). Ruppert-Kohlmayr et al. (2004) applied aortic normalization to remove other factors and achieved 95.7% accuracy in differentiating ccRCC and pRCC (9). Kim et al. (2016) determined the ratio of percentage enhancement to absolute washout ratio, which demonstrated 85% accuracy for ccRCC differentiation (10).

New interest in automated classification has emerged owing to advances in radiomics and machine learning (11, 12). However, these techniques anchor to the same enhancement patterns that underlie traditional quantitative measurements. In a multicenter cohort study renal cell carcinoma (RCC), Uhlig et al. (2024) worked with machine learning and radiomics features to achieve an AUC of 0.75, and the venous phase was the most informative (13). Uhm et al. (2021) created an end-to-end deep learning model and achieved an AUC of 0.889 internally and 0.855 externally (14). Despite these promising results, AI approaches face issues such as lack of external validation and high computational costs (15). It is noteworthy that well-reasoned traditional approaches achieve similar results with higher accuracy (85-96%) at a lower level of complexity (9, 10).

Despite its proven utility, several challenges persist. Chromophobe RCC differentiation remains difficult because of the overlapping enhancement patterns (16). Small renal masses present technical challenges for attenuation measurement (17). Protocol standardization across institutions is a source of variability. The present study aimed to comprehensively evaluate the quantitative multiphase MDCT enhancement parameters for differentiating the three major RCC subtypes, establishing an optimized, standardized framework that is readily implementable in routine clinical practice.

Materials and Methods

Study Population

This retrospective study included 86 patients who underwent multiphase multidetector computed tomography (MDCT) for renal mass evaluation between 2009 and 2013 at Eskisehir Osmangazi University Faculty of Medicine with subsequent histopathological confirmation via nephrectomy (n=77) or biopsy (n=9). For analysis, 72 RCC cases were grouped into clear-cell RCC (n=58) and non-clear-cell RCC (n=14, comprising seven papillary and seven chromophobe subtypes). The study was approved by the institutional ethics committee (Decision No: 06, May 28, 2013).

Exclusion criteria were as follows: (a) benign renal lesions including fat poor angiomyolipoma (n:1) and oncocytomas (n:4) and (b) small renal masses measuring less than 3 cm (n:9). Of the initial 86 patients, 14 were excluded based on these criteria, yielding a final study cohort of 72 patients with histopathologically confirmed RCC.

CT Protocol

All examinations were performed using a 64-detector CT scanner (Toshiba Aquilion) with standard renal mass protocol. Following intravenous contrast administration

(300 mg I/mL at 3.5-4 mL/s), three-phase imaging was performed: non-contrast, corticomedullary (30s), and excretory (180s) phases.

Image Evaluation

Raw DICOM images were jointly reviewed by two observers (one radiology specialist with 16 years of genitourinary imaging experience and one radiology resident), both blinded to histopathology. To characterize clear-cell RCC vs. non-clear-cell RCC groups, the following parameters were analyzed: age, sex, tumor size, enhancement pattern, and attenuation measurements.

Qualitative Assessment of Enhancement Pattern

Lesions were categorized visually according to the difference in attenuation between the corticomedullary and excretory phases: <20 HU was classified as washout pattern, >20 HU as progressive enhancement, and values between these thresholds as plateau pattern.

Quantitative Attenuation Measurements

Attenuation measurements were obtained in all three phases (non-enhanced, corticomedullary, and excretory). To account for hemodynamic variability, standardized enhancement ratios were calculated using aortic normalization at the celiac trunk level. Enhancement differences (delta-HU) were computed as the change from baseline noncontrast values. Circular ROIs ranging from 0.2 to 1.0 cm^2 were carefully positioned in the most homogeneously enhancing solid portion of each tumor, avoiding areas of necrosis, hemorrhage, calcification, or cystic change. For heterogeneous lesions, three separate ROI measurements were obtained and averaged to minimize sampling bias.

Standardized CM ratio = CM / Aortic HU (CM phase)

Standardized Excretory ratio = E / Aortic HU (excretory phase)

Enhancement differences (ΔHU) were calculated as:

CM enhancement difference (ΔHU) = CM - D

Excretory enhancement difference (ΔHU) = E - D

Statistical Analysis

All analyses were performed using SPSS version 20.0 (IBM, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are expressed as percentages. Data distribution and homogeneity were tested using Kolmogorov-Smirnov and ANOVA tests. Statistical significance was set at $P < 0.05$. Morphological characteristics were compared using the chi-squared test. Continuous variables (attenuation values) were analyzed using the t-test or Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values for differentiating RCC subtypes. From these thresholds, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were calculated.

Results

A total of 72 RCC cases were analyzed, comprising 58 clear-cell RCC (80.6%), 7 chromophobe RCC (9.7%), and 7 papillary RCC (9.7%). The demographic and clinical characteristics of the patients are summarized in Table 1. No significant differences were observed between the clear-cell and non-clear-cell RCC groups in terms of age, sex distribution, or tumor size (all $p > 0.05$).

Table 1. Demographic and Clinical Characteristics of RCC Subtypes

Characteristic	Clear-cell RCC (n=58)	Chromophobe RCC (n=7)	Papillary RCC (n=7)
Age (years), mean ± SD	56.5 ± 10.0	52.2 ± 7.5	59.4 ± 9.7
Male, n (%)	37 (63.8%)	5 (71.4%)	5 (71.4%)
Female, n (%)	21 (36.2%)	2 (28.6%)	2 (28.6%)
Tumor size (cm), mean ± SD	6.0 ± 2.9	5.4 ± 2.1	5.4 ± 2.1
p-value*	> 0.05	> 0.05	> 0.05

** Comparison between clear-cell RCC and non-clear-cell RCC groups (chromophobe + papillary).*

Analysis of contrast-enhancement patterns demonstrated that 75.9% of clear-cell RCC exhibited a washout pattern, while 92.9% of non-clear-cell RCC showed plateau or progressive enhancement. The washout pattern achieved 79% accuracy for identifying clear cell RCC, with 92% specificity and 97% positive predictive value (Table 2).

Clear-cell RCC demonstrated significantly higher enhancement across all quantitative parameters than non-clear-cell RCC (Table 3). Both absolute attenuation values and standardized enhancement ratios showed marked differences (all $p < 0.001$), with corticomedullary phase parameters exhibiting the greatest discrimination between the subtypes.

Table 2. Mean Attenuation Values and Enhancement Parameters by RCC Subtype

Parameter	Clear-cell RCC (n=58)	Non-clear-cell RCC (n=14)
Non-contrast (HU)	27.4 ± 7.5	34.0 ± 5.1
Corticomedullary (HU)	130.5 ± 38.0	58.9 ± 13.0
Excretory (HU)	89.8 ± 17.3	64.9 ± 13.6
Standardized CM ratio	0.54 ± 0.12	0.23 ± 0.05
Standardized excretory ratio	0.82 ± 0.17	0.61 ± 0.10
CM enhancement difference (ΔHU)	103.1 ± 32.1	24.9 ± 12.8
Excretory enhancement difference (ΔHU)	67.0 ± 23.0	38.8 ± 10.4

HU: Hounsfield Units; CM: Corticomedullary; ΔHU: Enhancement difference. All p < 0.001 for comparisons between clear-cell and non-clear-cell RCC.

Table 3. Distribution and Diagnostic Performance of Enhancement Patterns in RCC Subtypes

Histopathologic Subtype	Washout	Plateau/Progressive	Total
Clear cell RCC	44 (75.9%)	14 (24.1%)	58
Non-clear cell RCC	1 (7.1%)	13 (92.9%)	14
Total	**45**	**27**	**72**

Diagnostic Metric	Washout Pattern
Sensitivity	75%
Specificity	92%
Positive Predictive Value (PPV)	97%
Negative Predictive Value (NPV)	48%

Washout pattern: Enhancement decrease >20 HU between corticomedullary and excretory phases. Plateau/Progressive: Enhancement decrease ≤20 HU or increase between phases.

Table 4. Diagnostic Performance of Enhancement Parameters for Differentiating Clear-cell from Non-clear-cell RCC

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Standardized CM ratio (>0.31)	93	93	98	93	93
Standardized excretory ratio (>0.67)	81	79	94	50	80
CM ΔHU (>47 HU)	**93**	**100**	**100**	**77**	**94**
Excretory ΔHU (>40 HU)	84	71	92	52	81

CM: Corticomedullary; ΔHU: Enhancement difference in Hounsfield Units; PPV: Positive predictive value; NPV: Negative predictive value. Bold indicates highest diagnostic performance (94% accuracy with 100% specificity and PPV).

ROC Curve Analysis and Diagnostic Performance

ROC curve analysis identified the optimal cut-off values for RCC subtype differentiation (Tables 3-4). Among all the parameters, corticomedullary phase measurements achieved the highest diagnostic performance. Standardized corticomedullary ratio >0.31 yielded 93% accuracy (93% sensitivity, 93% specificity, 98% positive predictive value (PPV)), while a corticomedullary enhancement difference >47 HU achieved 94% accuracy with 100% specificity and 100% PPV. The excretory phase parameters demonstrated lower but still acceptable performance, with 80-81% accuracy.

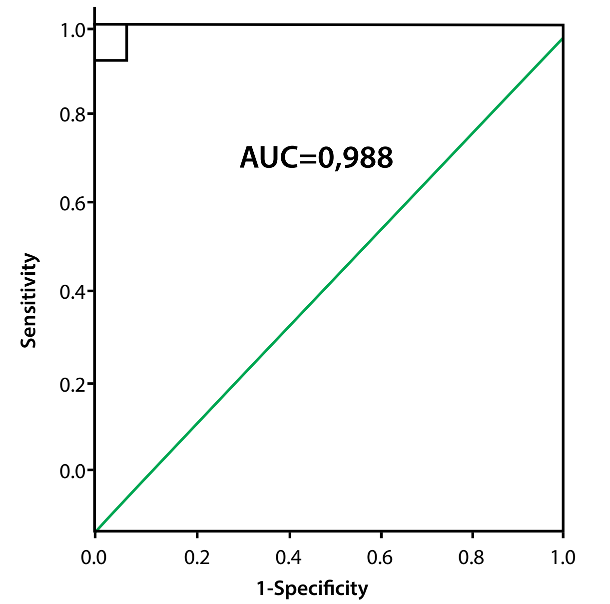

Figure 1. ROC curve for Corticomedullary HU demonstrating diagnostic performance.

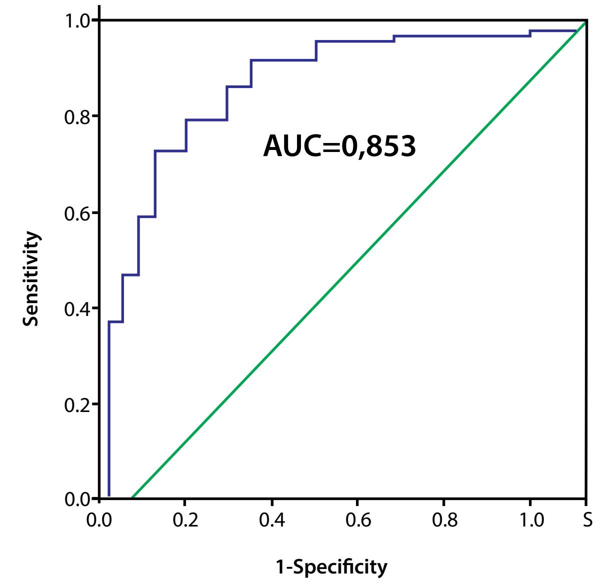

Figure 2. ROC curve for Excretory HU demonstrating diagnostic performance.

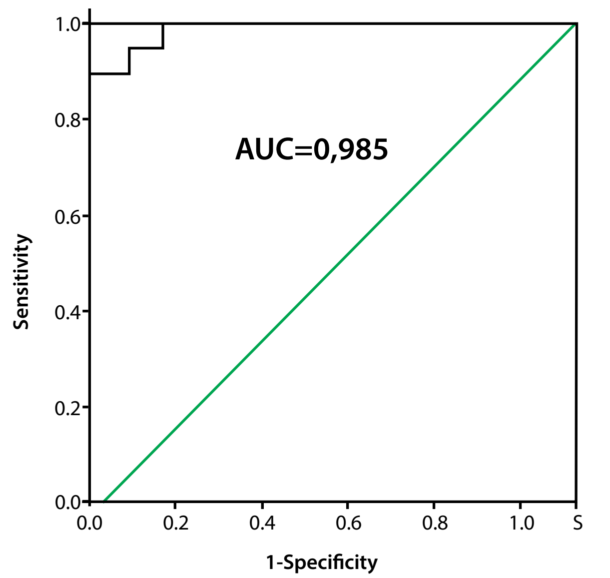

Figure 3. ROC curve for Corticomedullary Enhancement ΔHU demonstrating diagnostic performance.

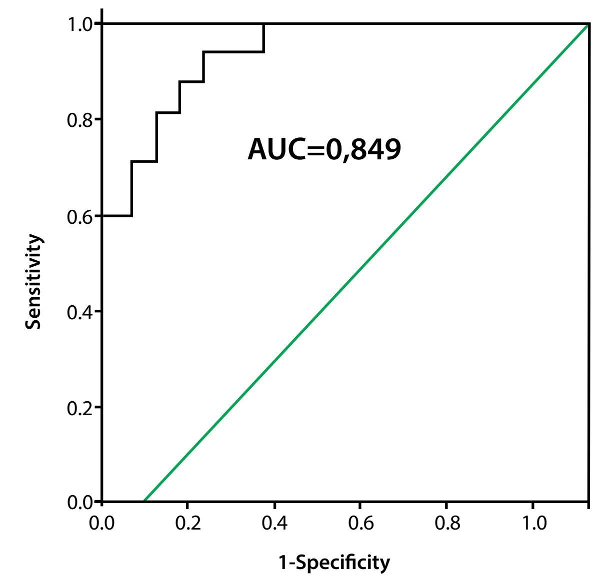

Figure 4. ROC curve for Excretory Enhancement ΔHU demonstrating diagnostic performance.
(AUC: Area Under the Curve)

Comparative analysis demonstrated that corticomedullary phase parameters (both standardized ratio and enhancement difference) significantly outperformed excretory phase parameters in diagnostic accuracy (93-94% vs. 80-81%, $p < 0.05$). The corticomedullary enhancement difference (delta-HU >47 HU) and standardized corticomedullary ratio (>0.31) emerged as the most discriminative parameters for differentiating clear-cell from non-clear-cell RCC.

Discussion

This study showed that the enhancement parameters of quantitative multiphase multidetector CT can accurately distinguish clear cell RCC from non-clear cell subtypes with high diagnostic accuracy. Of the parameters assessed, the difference in corticomedullary phase enhancement (ΔHU >47 HU) and the standardized corticomedullary enhancement ratio (>0.31) had the highest diagnostic accuracies of 94% and 93%, respectively. The corticomedullary phase was more accurate and decisive than the excretory phase. Moreover, the washout enhancement pattern was helpful in diagnosing clear cell RCC owing to its 79% accuracy and 92% specificity. These results indicate the importance of quantitative estimation of enhancement kinetics in RCC subtype classification.

Our findings are consistent with those of earlier studies that focused on quantitative CT-based RCC subtype differentiation. According to Kim et al. (2002), enhancement thresholds of 84 HU (corticomedullary) and 44 HU (excretory) differentiated conventional from non-conventional RCC with 82%-86% accuracy (7). In comparison, our corticomedullary enhancement difference (ΔHU) cut-off of 47 HU achieved superior performance at 94% accuracy, and this could be due to the fact that enhancement difference (ΔHU) is a more reliable means of measuring dynamic contrast uptake independent of baseline tissue density.

Young et al. (2013) achieved 85% accuracy using multiphasic thresholds (corticomedullary >106 HU, nephrographic >92 HU, excretory >68 HU) (8). Although comparable, our study shows that a single corticomedullary parameter can achieve the same or better result, which is clinically simple. The highest literature accuracy was reported by Ruppert-Kohlmayr et al. (2004), who used aortic normalization and achieved 95.7% accuracy (9). Our standardized corticomedullary ratio achieving 93% accuracy employed similar normalization, showing that the consideration of hemodynamic variability in the standardized ratio improves the accuracy of the diagnosis. Kim et al. (2016) demonstrated 85% accuracy using the percentage enhancement ratio and absolute washout ratio in 563 lesions, supporting the robustness of quantitative enhancement analysis (10).

The studies collectively built a case where quantitative enhancement parameters attain 82-96% for RCC subtype differentiation accuracy, which our results also retrieval (93-94%). The corticomedullary phase appears to be the most discriminative in all studies, illustrating the critical biological differences in tumor vascularity between clear- and non clear cell subtypes.

Subsequent developments in the field of machine learning and radiomics have led to a wide interest in the automatic classification of RCC subtypes. A critical comparison of the various approaches reveals that quantitative approaches still perform comparably or better. Uhlig et al. (2024) used extreme gradient boosting on 127 radiomic features in a multicenter cohort and obtained an AUC of 0.75, the most informative, in venous phase-independent testing (13). Zhang et al. (2021) relied on 105 features to build a 3D multiphase radiomic model and achieved 80% accuracy in three-way classification and an AUC of 0.89 in differentiating ccRCC from non-ccRCC (18). Chen et al. (2021) developed combined models by integrating 296 texture and 43 non-texture features and obtained an AUC of 0.864-0.900 (19). While these models utilized hundreds of features, most achieved a diagnostic accuracy of 75-90% which is lower and in some scenarios or comparable to our two-parameter semi-analytical model of 93-94% accuracy.

Similar patterns were observed using advanced deep-learning techniques. Uhm et al. (2021) created a completely autonomous, end-to-end processing pipeline that, after being internally validated, achieved an AUC of 0.889 and 0.855 after being externally validated on an independent dataset.(20) Although such automation offered by AI-based approaches applied by Wang et al. and Myers et al. represent considerable steps forward, their "black-box" nature that demands heavy computational power, bespoke architecture, and extensive training data continue to impact their clinical utility (21, 22). Ultimately, these advanced artificial neural networks are built with the same enhancement features that can be identified using far less complicated quantitative frameworks. Moldovanu et al. (2020) showed that quantitative

MDCT enhancement parameters with standardized ratios achieved an AUC of 0.976 for differentiating clear cells from papillary RCC(15). This confirms that high discriminative power fundamentally emanates from the features of enhancement rather than the complexity of the algorithm.

This study features the unique corticomedullary enhancement difference (ΔHU > 47 HU) and the standardized corticomedullary enhancement ratio (st> 0.31) as two parameters achieving diagnostic accuracy (93-94%) on par with or exceeding the performance of complex AI systems. They do this while maintaining unparalleled simplicity and ease of use without the dependence on sensitive software or AI computing resources. This is a notable advantage for its practical use in daily clinical workflows.

The results of our study show that RCC subtype differentiation is most accurate in the corticomedullary phase, achieving–93-94% accuracy, in comparison to the 80-81% accuracy of the excretory phase. This is also in line with biology: clear cell RCC has a predilection for early enhancement in vascular regions, while papillary and chromophobe RCC lack vascularity (5, 6). Similar results have also been reported in other studies. . These results are in agreement with those of other studies. Kim et al. (2002) described the corticomedullary phase as the most discriminative (7), whereas Uhlig et al. (2024) described the venous phase as the most informative(13). The agreement between traditional quantitative methods and AI approaches focusing on early phase imaging emphasizes the critical role of dynamic contrast enhancement patterns in illustrating the histopathological differences between RCC subtypes.

Our findings have several significant clinical implications. Two quantitative metrics, corticomedullary enhancement difference and standardized enhancement ratio, are readily obtainable from routine multiphase CT scans using standard PACS workstations. Specialized software or AI are not required. Hence, radiologists can offer assessments that are objective and reproducible, thereby directing treatment planning. Due to the varying targeted therapy responses with different RCC subtypes (4), precise preoperative classification can lead to more tailored and effective treatment and avoid unnecessary treatment. The method's simplicity and transparency, coupled with its high diagnostic accuracy, offer the best chances for widespread use in clinical practice. It is reasonable to expect that a clinical facility with limited resources and no advanced AI systems in place will find a useful method for clinically differentiating RCC subtypes.

This study has some limitations need to be addressed. First, the retrospective and single-center design may limit generalizability. Second, the small sample sizes for non–clear cell subtype cases (seven papillary, seven chromophobe) may impact precision, but the primary aim was to classify the lesions as clear cell or non-clear cell. Third, the differentiation of chromophobe and papillary RCC is problematic because of overlapping enhancement features(16). Fourth, oncocytomas and benign lesions were excluded, narrowing the applicability of the findings to other clinical situations. Fifth, we did not include small renal masses (<3 cm) that were tenuously enhanced. Finally, the differences in CT scanners and protocols necessitate a prospective multicenter study to confirm these findings. Additionally, formal inter- and intra-observer variability assessments were not performed in this study, which limits the evaluation of measurement reproducibility. However, all measurements were performed by consensus between two observers, which may partially mitigate this limitation.

Subsequent investigations can look at prospective multicenter validation of different patient demographics and imaging techniques. For difficult cases, a hybrid method that combines basic quantitative metrics with AI may enhance diagnostic precision while still being clinically feasible. Assessment of small renal masses and prediction of response to treatment require special attention.

Conclusion

This study showed that the use of quantitative multiphase MDCT enhancement parameters can differentiate clear-cell RCC from other non-clear-cell subtypes with a high degree of accuracy. Especially during the corticomedullary phase, the enhancement difference and standardized enhancement ratio were the most discriminative parameters. Systematic quantitative enhancement kinetic assessments can be performed with any radiology PACS workstation, which helps in producing objective and consistent RCC subtype assessments to guide personalized therapy.

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