The Role of Multiphasic Contrast Enhanced Computed Tomography in the Differentiation of Histopathological Subtypes of Renal Cell Carcinoma

[1]Boutros I. Hanna, [1]Manal H. Wahba, [2]Hany ElFayoumy, [1]Marie N. Grace*

[1]Diagnostic and Intervention Radiology Department, Cairo University Hospitals, Kasr Al-Ainy, Cairo, Egypt

[2]Urology department, Cairo University Hospitals, Kasr Al-Ainy, Cairo, Egypt

Correspondence to
Name: Marie N, Grace
Address: Diagnostic and Intervention Radiology Department, Cairo University Hospitals, El-Manial, 11956 Cairo, Egypt.
Tel: 002-01200338625
Fax: 002-02-23634717
Email: drmariegv@gmail.com

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ABSTRACT

Aim: Our aim is to assess the diagnostic potential of multiphasic contrast enhanced computed tomography for differentiation of the histological subtypes of renal cell carcinoma.

Patients and Methods: We prospectively evaluated 50 patients with renal masses previously detected by ultrasound. Multiphasic CT of the kidneys and urinary tract was done. The degree of enhancement was measured by calculating the difference in the HU between the corticomedullary and unenhanced phase scans and between the excretory and unenhanced phase scans. We assessed other parameters as size of the lesion, presence of hemorrhage and calcifications, pattern of enhancement, and lymphadenopathy. CT findings were compared with the histopathological results.

Results: In corticomedullary phase clear RCC had significantly higher CT HU measurement than papillary (107HU vs 41HU, p value=0.001) and chromophobe (107HU vs 71HU, p value=0.003), papillary RCC had significantly lower CT attenuation value than chromophobe (41HU vs 71HU, p value=0.022 .(In nephrograhic phase clear RCC had significantly higher CT HU measurement than papillary (94HU vs 51HU, p value=0.001) and chromophobe (94HU vs 74HU, p value=0.031), papillary RCC had significantly lower CT HU measurement than chromophobe (51HU vs 74HU, p value=0.015). In corticomedullary phase, a cut-off value of ≥ 76 showed 87% sensitivity and 74% specificity for the discrimination between clear and non-clear RCC.

Conclusion: Multiphasic CT is capable of differentiating clear-cell RCC from papillary and chromophobe subtypes for preoperative assessment in patients with renal masses. It is considered a safe and confident method for local staging and prediction of the histological grade of RCC.

Key words:
Multiphasic CT; renal cell carcinoma; histological subtypes; density; HU

Abbreviations:
HU: Housefield Unit

INTRODUCTION

Renal cell carcinoma is constituting 3-4% of all neoplasms worldwide [1]. It is categorized into several types, which have various characteristics and clinical behaviors. The incidence of renal malignancy surged significantly in the past few decades, owing to the increased use of cross-sectional imaging [2]. The histologic type of RCC represents one of the most important prognostic factors. The most common histologic type is the clear cell RCC, representing about 65–70%, with high metastatic potential. Papillary RCC accounts for 10–15% of RCCs, while chromophobe RCC represents 5% of RCCs, and both have a low metastatic potential. The other malignant types represent about 5 to 6% of the histologic types. Roughly; 20% of renal lesions are benign, and oncocytoma represents 5% of all renal tumors. [1]

Computed tomography (CT) is believed to be the modality of choice as it is the most widely accessible and the most effective for the diagnosis and staging of RCC. Multidetector CT brings further improvement in the assessment of RCC. The improvement of spatial resolution and the ability to obtain multiphase imaging, multi-planar and three-dimensional reformatting are the key for such improvement. The CT enhancement characteristics of the masses were found to be linked to the histologic subtype of RCC, the nuclear grade, and

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the cytogenetic characteristics of clear cell RCC. [3] The different histologic subtypes show distinct enhancement patterns at multiphasic CT; therefore, preoperative multiphasic CT imaging can provide useful information regarding the pathologic diagnosis before selecting treatment regime. [2] In our study, we compared contrast-enhanced multiphasic CT findings in the different subtypes of renal cell carcinoma and studied the most useful CT findings that could help characterize these subtypes.

Our aim was to assess the diagnostic potential of multiphasic contrast-enhanced computed tomography for the characterization of histological subtypes of renal cell carcinoma.

PATIENTS AND METHODS

Patients

The study was approved by hospital ethical committee. Informed consents were acquired from all patients. During three-year duration from February 2016 to February 2019 we prospectively evaluated 50 patients with renal masses formerly detected by ultrasound. Multiphasic CT examinations were done in Radiology department. We prospectively evaluated 32 males and 18 females; the patients' age ranged from 11 to 83 years old.

Twenty patients complained of visible hematuria, the rest of the patients (n=30) presented with non-specific symptoms including anorexia and weight loss (n=21) as well as fever of unknown origin (n=9). Patients with poor renal function were excluded from the study.

CT Examination

The examinations were performed using two CT machines; Philips brilliance 64 section multi–detector row CT scanner (Brilliance 64, Philips Healthcare, Cleveland, OH, USA); and 64 section multidetector CT scanner (Canon Medical Systems, Aquillion). All patients underwent multiphasic CT scanning for the kidneys and urinary tract that included non-contrast phase, corticomedullary phase (CMP), nephrograhic phase (NP) and excretory phase (EP) scanning. Contrast injection was done using automatic pump with approximately 100-120 ml of a nonionic contrast material was injected at a rate of 3-4 ml/sec through a 16/18-gauge cannula placed in a superficial vein. Cortico-medullary Phase CMP was done with smart preparation and auto injection. Nephrographic phase (NP) was obtained 70-80 seconds after contrast injection while breath holding. Excretory phase (EP) then obtained 3 minutes up to 8-10 minutes post contrast injection.

Image Analysis

Images were transferred to independent work station. ROI was placed on the most homogenous part of the lesion in the non-contrast phase, corticomedullary phase (CMP), nephrograhic phase (NP) and excretory phase (EP) to measure the CT density in HU. The degree of enhancement was assessed by calculating the difference in the HU between the corticomedullary and unenhanced phase scans and between the excretory and unenhanced phase scans. Additionally we assessed other parameters as size of renal lesion, presence of hemorrhage and calcifications, pattern of enhancement, tumoral spread patterns including perinephric changes, venous infiltration and pathological lymph nodes.

Standard of references:

CT findings were compared with the results of the histopathological examinations after nephrectomy or partial nephrectomy.

Statistical Analysis

Chi-squared test was used in assessment of qualitative data to determine whether there is a significant difference between different categories. Independent t test was used to compare the means of parametric quantitative data between two groups and ANOVA test in case of multiple comparisons. Mann-Whitney U test and Kruskal-Wallis H test was used to compare non-parametric quantitative data. Correlation coefficient for correlation analysis and ROC curve for diagnostic accuracy.

RESULTS

Lesion characteristics:

We prospectively evaluated 32 males and 18 females; the patients' age ranged from 11 to 83 years old.

28 patients (56%) have right sided lesions while 22 patients (44%) have left sided lesions.

According to histopathological findings almost third of the patients (30%) had clear cell RCC, 26% had papillary RCC, and 36% had Chromophobe RCC; only 2 patients had either Mucinous tubular or Xp 11.2 translocation/tfe3 gene fusion RCC.

CT characteristics:

Lesions assessment

According to their size, lesions are classified as two groups: group A: 32% of patients (n=16) had tumor size ranging from 2.5 to 7 cm (n= 16, 32%), and group B: lesions > 7cm in size (n= 34, 68%). 90 % of lesions demonstrated heterogeneous enhancement. There was a washout in 80% of the lesions and hemorrhage in 14% of the lesions. Thirty percent of the lesions had calcification. The presence of perinephric invasion was more in lesion size > 7cm (group B) than lesion size of 2.5-7 cm (group A), with statistically significance difference (p value =0.015). In contrary, there were no statistically significant differences between groups A (2.5-7cm) and B (>7cm) in terms of enhancement, washout, hemorrhage, calcification, difference of mean attenuation values between the corticomedullary and unenhanced phase scans and difference in mean attenuation value between the excretory and unenhanced phase scans.

Quantitative assessment

There were statistically significant differences between different histological types in terms of CT HU measurement in the Cortico-medullary phase (p value <0.001) and Nephrographic phase (p value <0.001). In the corticomedullary phase clear RCC had significantly

higher CT HU measurement than papillary (p value =0.001) and chromophobe (p value =0.003). Papillary RCC had significantly lower CT attenuation value than chromophobe (p value =0.022) **(Figure 1)**. In the nephrographic phase clear RCC had significantly higher CT HU measurement than papillary (p value =0.001) and chromophobe (p value=0.031). Papillary RCC had significantly lower CT HU measurement than chromophobe (p value =0.015) **(Table 1)**.

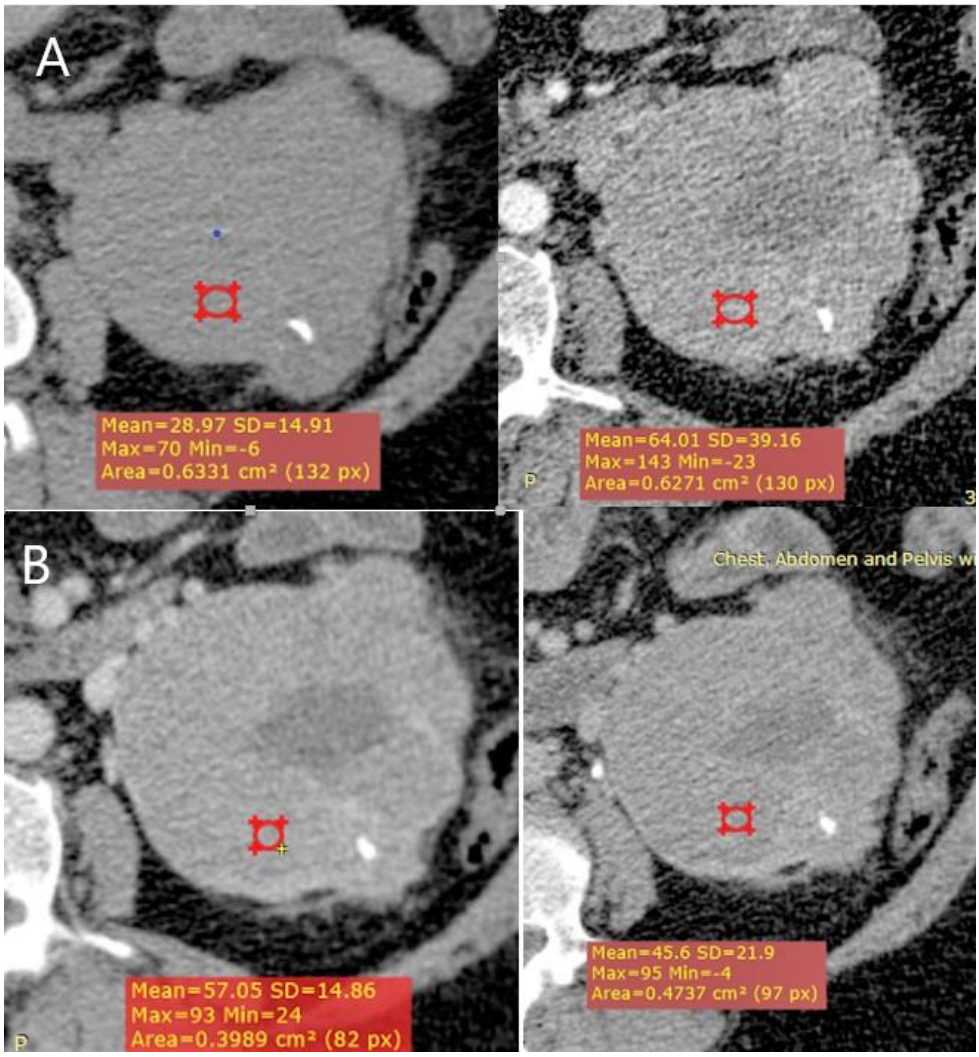


Fig 1: a 56-year-old female with Chromophobe cell carcinoma grade III

Multiphasic enhancement of a chromophobe RCC at axial multidetector CT. A representative ROI was placed on the lesion in each phase.
Degree of enhancement A [difference between the corticomedullary and unenhanced phase scans] = 36 HU.
Degree of enhancement B [difference between the excretory and unenhanced phase scans] = 17 HU.
CT findings are matched with the pathological findings of non-clear cell carcinoma subtype.

Table 1: CT density "HU" according to pathological types of renal lesions.

Variables	Pathological Types					P-value
	Clear (N =15)	**Papillary (N = 13)**	**Chromophobe (N =17)**	**Mucinous (N =2)**	**Xp 11.2 (N =2)**	
Non-contrast						
- Mean (SD)	33.1 (16.8)	28.6 (7.6)	35.9 (13.9)	23.5 (9.2)	25 (12.7)	0.44
- Median (IQR)	30 (22 – 40)	27 (22.5 – 34.5)	33 (29 – 40.5)	23.5 (17 – 23.5)	25 (16 – 25)	
Cortico-medullary						
- Mean (SD)	107.6 (35.2)[a]	41.4 (13.8)	71.9 (21.6)[b, c]	63 (19.8)	62.5 (33.2)	<0.001
- Median (IQR)	103 (79- 136)	37 (31.5 – 45)	68 (55 - 88.5)	63 (49 – 63)	62.5 (39 – 62.5)	
Nephrographic						
- Mean (SD)	94.3 (21.5)[a]	51.6 (11.7)	74.2 (17.5)[b,c]	98.5 (9.5)	93 (36.7)	<0.001
- Median (IQR)	95 (81-107)	51 (43.5 – 61)	73 (61.5 – 87)	98.5 (95 – 98.5)	93 (67 – 93)	
Excretory						
- Mean (SD)	58.2 (16.3)	44.6 (11.7)	49.5 (16.7)	60.5 (10.7)	52.5 (9.3)	0.17
- Median (IQR)	54 (48 – 63)	41 (34.5 – 53.25)	52.5 (34 – 54)	60.5 (53 – 60.5)	52.5 (47 – 52.5)	

a: significant difference between clear and papillary.
b: significant difference between clear and chromophobe.
c: significant difference between papillary and chromophobe.

Using CT density in the differentiation of clear cell and non-clear cell RCC: In the corticomedullary phase, a cut-off value of ≥ 76, showed sensitivity of 87% and specificity of 74% for the discrimination between clear and non-clear RCC **(Figure 2)**. Similarly, in the nephrographic phase a cut-off value of ≥ 76.5 showed sensitivity of 87% and specificity of 66% for the discrimination between clear and non-clear RCC **(Figure 3, Table 2)**.

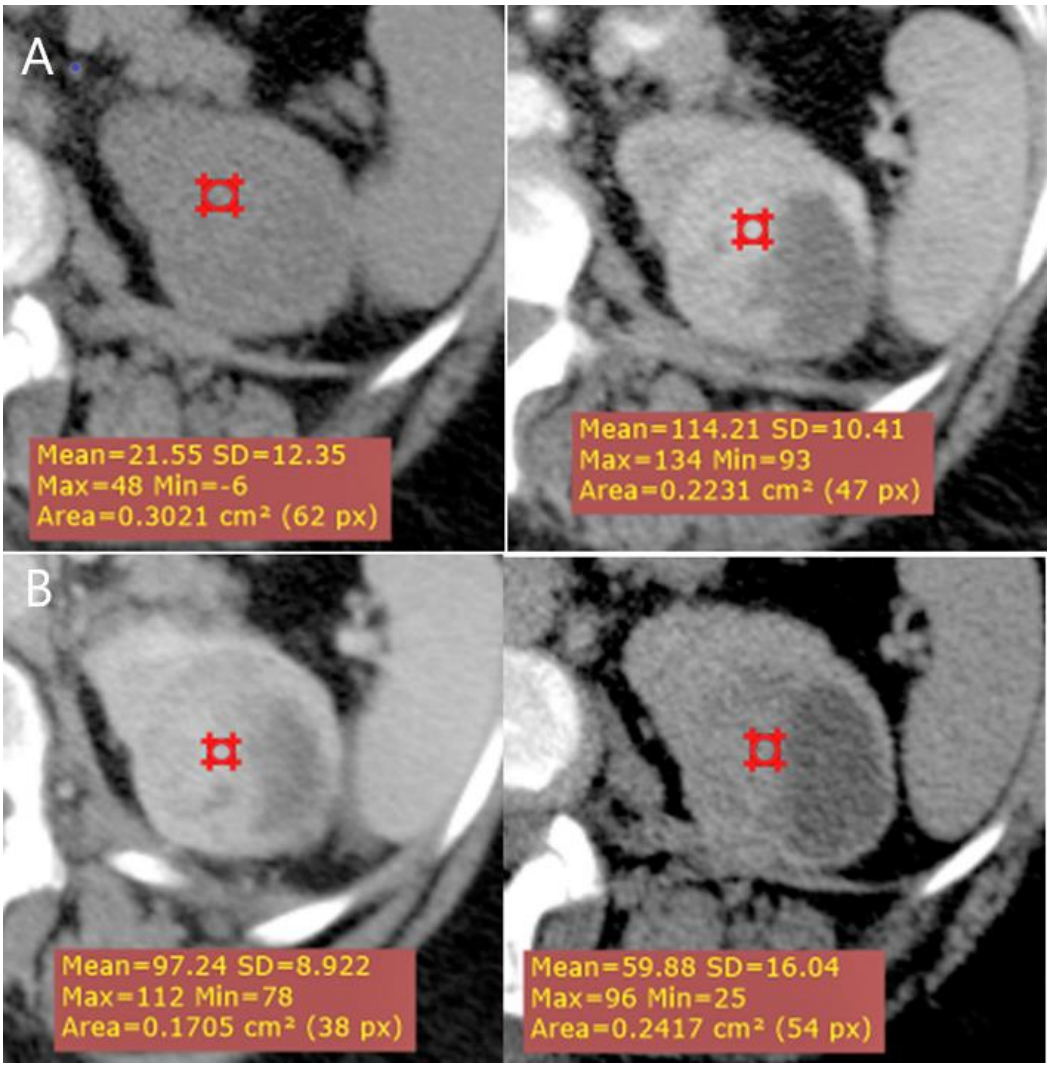
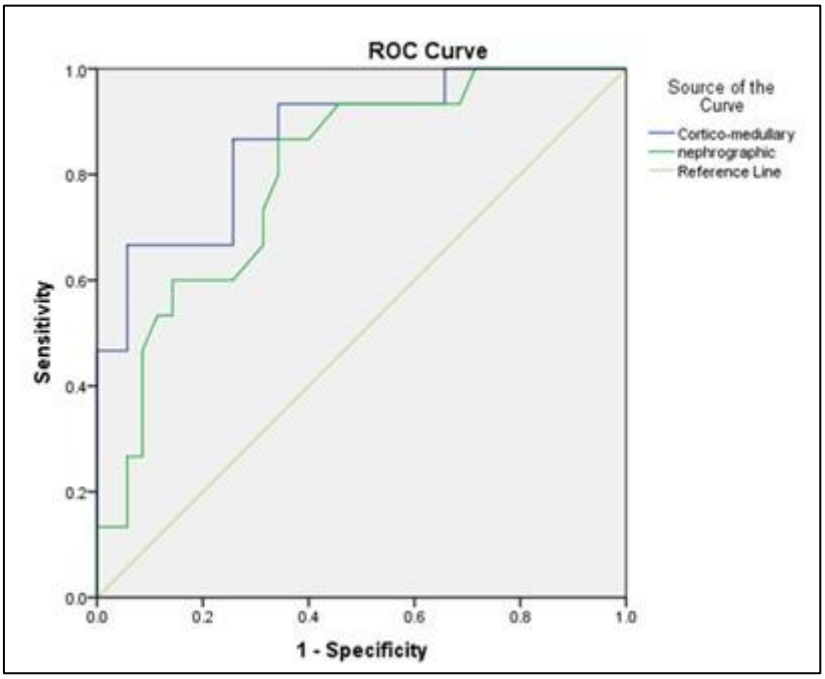


Fig 2: A 53-year-old female with Clear cell carcinoma subtype grade I

Multiphasic enhancement clear RCC at axial multidetector CT in. A representative ROI was placed on the lesion in each phase.
Degree of enhancement A [difference between the corticomedullary and unenhanced phase scans] = 93 HU.
Degree of enhancement B [difference between the excretory and unenhanced phase scans] = 38 HU
CT findings are matched with the pathological findings of clear cell subtype RCC.

Table 2, Fig. 3: ROC curve for CT density in the differentiation between clear RCC and non-clear RCC. AUC= area under the curve, CI= confidence interval.

	AUC	**95% CI**	**P-value**	**Cut-off**	**Sensitivity**	**Specificity**
Cortico-medullary	0.87	0.76 - 0.97	0.001	≥ 76	87%	74%
Nephrogenic	0.79	0.67- 0.93	0.001	≥ 76.5	87%	66%



Using CT density in the differentiation of chromophobe and non chromophobe RCC: The ROC curve showed that cortico-medullary and nephrogenic parameters were not significant discriminator of chromophobe RCC.

Using CT density in the differentiation of papillary and non-papillary: The ROC curve showed that cortico-medullary and nephrogenic parameters were significant discriminator of papillary RCC: at cut-off value of ≥ 64.5, the cortico-medullary parameter yielded a sensitivity of 56% and specificity of 38% for the discrimination between papillary and non- papillary RCC. Similarly, at cut-off value of ≥ 66.5, the nephrogenic phase yielded a sensitivity of 50% and specificity of 20% for the discrimination between papillary and non- papillary RCC.

There were statistically significant differences between different histological types and their degree of enhancement [difference of mean attenuation values between the corticomedullary and unenhanced phase scans (p value = <0.001) and difference in mean attenuation value between the excretory and unenhanced phase scans (p value =0.009)] **(Table 3)**.

Table 3: The degree of enhancement according to pathological types.

Variables	Pathological Type					P-value
	Clear (N =15)	Papillary (N = 13)	Chromophobe (N =17)	Mucinous (N =2)	Xp 11.2 (N =2)	
Difference between the corticomedullary and unenhanced phase scans						
1. Mean (SD)	74.5 (31.2)	12.8 (17.8)	35.9 (16.3)	39.5 (10.6)	37.5 (20.5)	<0.001
2. Median (IQR)	73 (61- 89)	5 (2 – 17.5)	36 (22 – 53)	39.5 (32 – 39.5)	37.5 (23 – 37.5)	
Difference in the HU between the excretory and unenhanced phase scans						
1. Mean (SD)	25 (12.9)	16.5 (12.9)	13.7 (8.5)	37 (1.4)	28.5 (5.6)	0.009
2. Median (IQR)	27 (19 – 33)	13 (7.5 – 25)	15 (5 – 19)	37 (36 – 37)	28.5 (28 – 28.5)	

The degree of enhancement was used to differentiate between clear cell and non-clear cell RCC. Using a cut-off value of ≥ 40.5, the difference between the corticomedullary and unenhanced phase scans yielded a sensitivity of 87% and specificity of 69%. Using a cut-off value of ≥ 18, the difference in the HU between the excretory and unenhanced phase scans yielded a sensitivity of 80% and specificity of 60%. When used to differentiate between chromophobe and non

chromophobe as well as the papillary RCC, the degree of enhancement yielded a poor sensitivity.

DISCUSSION

Computed tomography (CT) is favored as the most appropriate first-line examination for patients presenting with unexplained visible hematuria. [4] It is a non-invasive technique that can predict the pathological diagnosis of renal neoplasms, therefore having a great influence on the management of patients. [5, 6] Clear cell RCCs have a worse prognosis and a greater probability of metastasis, thus noninvasive means of characterizing these tumors can be of great clinical value. [7] Patient condition, treatment accessibility, and neoplastic characteristics are the bases of clinical decision for the management of renal cancer cases. Although, the most important prognostic factors are tumor stage, nuclear grade, and pathologic subtype. [8]

Our aim is to assess the efficacy of multiphasic contrast enhanced CT as a non-invasive technique for preoperative discrimination of the histological subtype of renal cell carcinoma. According to final histopathological diagnosis, 30% of the study group had clear cell RCC, 26% had papillary RCC, and 36% had chromophobe RCC. Based on our findings, the tumor morphological characteristics like heterogeneity, growth pattern cystic area or calcification were not useful for characterization of tumor histology. This was similar to the findings of Pierorazio PM et al., 2013. Additionally, there was no statistically significant differences between groups A (lesions measuring 2.5-7cm) and B (lesions measuring >7cm) in terms of enhancement pattern (p value =0.494).

In this study there were statistically significant differences between different histological types in terms of CT HU enhancement in the cortico-medullary and nephrographic phases. In the cortico-medullary phase clear cell RCC had significantly high CT HU measurement than papillary (p value =0.001) and chromophobe RCC (p value =0.003). This was similar to study by Ishigami K et al., 2015 who have found that clear cell RCC typically show avid arterial enhancement and non-clear cell RCC shows lesser degrees of enhancement. Additionally, Pierorazio PM et al., 2013 reported highest peak HU of clear cell RCCs (117 HU) compared to the other types. According to our findings clear cell RCCs have demonstrated significantly greater mean enhancement in the corticomedullary phase (107.0 HU) than papillary RCCs (41.4 HU), and chromophobe RCCs (71.9 HU). This was in agreement to Young et al., 2013 who have reported greater enhancement of clear cell RCCs in the corticomedullary phase (125.0 HU) than oncocytomas (106.0 HU), papillary RCCs (53.6 HU), and chromophobe RCCs (73.8 HU) and was in accordance to Tsili AC & Argyropoulou MI., 2015 have demonstrated high peak HU of clear cell RCC (117 HU) with peaking in the corticomedullary phase.

In our study the cortico-medullary phase was able to discriminate between clear and non-clear RCCs with cut-off value of ≥ 76 HU showed a sensitivity of 87% and specificity of 74%. Similarly, in the nephrogenic phase a cut-off value of ≥ 76.5 HU yielded a sensitivity of 87% and specificity of 66%. Pierorazio PM et al., 2013 have reported that rapid, high attenuation enhancement that quickly washes out in the delayed phase is indicative of clear cell RCC or oncocytoma, while papillary RCC had relatively low levels of peak enhancement and relatively little fluctuation in attenuation from corticomedullary through the delayed phase, however this pattern does not exclude other tumor histology. Our study showed that the degree of enhancement of clear cell RCCs was significantly higher than that of chromophobe RCCs in the corticomedullary and excretory phases, the mean HU enhancement of papillary RCCs peaked in the nephrograhic phase measuring 51.6 HU and this was similar to the findings of Young et al., 2013 and Ishigami K et al., 2015.

Muglia F and Prando A., 2015 have reported that papillary RCC was hypovascular compared to the adjacent renal parenchyma in the corticomedullary phase with a mean density ranging between 50-60 HU. However, it showed progressive uptake in the nephrographic phase with mean density of 65-75 HU, this was similar to our results, as the papillary RCC had mean density of 41.4 HU and 51.6 HI in the corticomedullary phase, and nephrographic phase respectively. Young et al., 2013 have reported high accuracy of multiphasic enhancement threshold levels in discriminating clear cell RCC from papillary RCC (accuracy of 85%) as well as clear cell RCC from chromophobe RCC (accuracy of 84%).

In the nephrographic phase, clear cell RCC had significantly higher CT HU measurement then papillary "p value = 0.001" and chromophobe "p value = 0.031" RCC. Also, the papillary RCC had significantly lower CT HU measurement values than chromophobe "p value = 0.015". This was similar to the findings of Sankineni S et al., 2016. They have reported greater enhancement of clear cell RCC than papillary RCC in the arterial, nephrographic and excretory phases with greater enhancement than chromophobe RCC in arterial and excretory phases.

Pierorazio PM et al., 2013 have stated that the difference between the non-contrast and corticomedullary phase (absolute enhancement) is the strongest predictor of histology. In this study we have measured the degree of enhancement between clear and non-clear cell RCC and we have found that clear cell RCC could be distinguished from other subtype by attenuation difference above 40.5 HU between the corticomedullary and unenhanced phases with 87% sensitivity and 69 % specificity. This was in disagreement with the findings of Kim et al., 2002 who have reported an absolute attenuation of 84 HU in difference between the corticomedullary and unenhanced phases of a multiphasic CT, above which clear RCC could be distinguished from other subtypes, with 74% sensitivity and 100% specificity. The difference in measurements in different studies can be attributed to factors that alter the tumor density on CT

like the patient's renal function, state of patient hydration and rate of contrast injection. [2]

There are few limitations to our study. First, there was no adjustment for contrast density as it depends on several parameters as the rate of contrast injection, renal function and hydration state of the patient. Second, there is a developing knowledge of hybrid lesions with mixed histologies. Lastly, few number of other tumor subtypes, like mucinous and xp 11.2 translocation renal cell carcinoma.

CONCLUSIONS

In conclusion, based on our studies, multiphasic multidetector CT is of great value in the differentiation of clear-cell RCC from papillary and chromophobe subtypes for preoperative assessment in patients with renal masses. It is considered a safe and confident method for local staging and prediction of the histological grade of renal cell carcinoma.

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