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Original Article

Radiology Section

Association of Radiological Features with Histological Features in Patients with Renal Cell Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Renal Cell Carcinoma (RCC) is a group of neoplastic lesions with unique cytogenetic characteristics and histopathological features. The majority of studies till date on RCC have been focusing on tissue histology to plan neoadjuvant treatment in clinical settings. An accurate forecast of the histopathological subtype has clinical implications in management and response to newer treatment strategies. It is pertinent to preoperatively distinguish a solid renal masses histologically but, there are currently no well-established imaging criteria to classify these tumours on the basis of radiographic evaluation.

Aim: To evaluate the differences in imaging characteristics of different histological subtypes of RCC by Power Doppler Ultrasound and Multi-Detector Computed Tomography (MDCT) scan.

Materials and Methods: This cross-sectional study was conducted in the Department of Urology, Gauhati Medical College and Hospital, Guwahati, Assam, India from March 2016 to December 2017. The study population consisted of 61 patients of RCC who were evaluated with MDCT and Doppler ultrasound prior to surgery and findings were correlated with histopathological forms of tumour. The Pearson Chi-square test and ANOVA test was used to statistically analyse the data.

Results: Histopathology revealed clear cell Renal Cell Carcinoma (ccRCC), chromophobe Renal Cell Carcinoma (chRCC) and papillary Renal Cell Carcinoma (pRCC) in 52, 4 and 5 patients, respectively. Heterogenous enhancement was found in 51 cases and among these 90.4% were ccRCC. Absolute attenuation values in Corticomedullary Phase (CMP) and Nephrographic Phase (NP) for clear cell and chromophobe subtype were higher than papillary subtype, i.e., 88.04±30.40 Hounsfield Unit (HU) and 72.41±20.17 HU for clear cell, 60.75±22.54 HU and 88±16.06 HU for chromophobe; 22.40±12.52 HU and 58.00±4.41 HU for papillary subtype, respectively. Papillary RCC (pRCC) showed a unique enhancement pattern, with a low peak enhancement (average peak of 55.40 HU) and greatest enhancement during the NP. In this study population ccRCC, ChRCC RCC and pRCC had mean Resistive Index (RI) of 0.63±0.06, 0.58±0.0 and 0.67±0.11, respectively.

Conclusion: Power doppler flow imaging is not useful in discriminating subtypes of RCC while multiphasic Computed Tomography (CT) imaging may be useful, particularly the phasic enhancement pattern to distinguish common RCC subtypes which may facilitate treatment planning and choosing appropriate tyrosine kinase inhibitors.

Keywords: Computed tomography scan, Histopathological subtypes, Malignant lesion, Mean attenuation value, Resistive index

INTRODUCTION

The Renal Cell Carcinomas (RCCs) are a family of neoplasms with unique molecular defects, cytogenetic characteristics, unique histopathological features and fluctuating neoplastic armaments. Most common classification of RCC includes ccRCC, pRCC, and chromophobe RCC (chRCC) and some small number of other unclassified tumours. RCC is the seventh most common malignancy for men and the ninth for women over world represents 2-3% of all malignances in adult [1].

Malignant tumour's usually boost of continuous neovascularisation which usually helps the uroradiologist to apply imaging parameters for precise confirmation of the mass in question. Accurate staging of RCC may be helpful for planning appropriate surgical modalities. A classification based on histopathology has clinical implications in the form of prognosis and response to various newer management schemes [2]. MDCT is widely used as the prime diagnostic modality for diagnosing and staging RCC at present with a diagnostic accuracy of 93% and sensitivity and specificity for staging up to 90% [2]. In progressive disease, a tailored management approach is deemed suitable since the efficiency of systemic treatment protocol may be influenced by the RCC subtype.

Previous studies have proposed that clear cell, papillary and chromophobe subtypes can be segregated non invasively on MDCT [3-5]. Power doppler flow imaging uses a method to detect the movement of Red Blood Cells (RBC) which is not influenced by the direction of the blood flow but it is incapable of determining direction of flow and velocity. Superb Microvascular Imaging (SMI) is a novel doppler diagnostic technique for determination of very slow blood flow state [6]. Many studies have been conducted, which combined an array of colour doppler and power doppler flow imaging pattern to predict the histological subtypes of solid renal masses [7-9]. For treatment planning and patient counselling it is decisive to preoperatively separate a solid renal tumour but, there are no well-established imaging criteria. Depending on vascularity and morphology of the RCC, it is expected that there will be diverse enhancing characteristics and Ultrasonography (USG) Doppler flow parameters of divergent histological RCC subtypes.

Till date, there have been no cross-sectional studies performed in the tertiary care institutes in North East India to the best of present author's knowledge, which compared the characteristic of power Doppler flow imaging and MDCT scans for the reliable identification of histological subtypes of RCC. Hence, present study was conducted with a primary aim to compare the capability of dynamic MDCT and USG Power Doppler characteristics in preoperatively subtyping

RCC and to connect their findings with histopathological features. The secondary objectives of the study was to formulate cut-off parameters for attenuation values in cases of MDCT and RI in case of Power Doppler to assess any correlation between these imaging features and various histopathological subtypes.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Urology, Gauhati Medical College and Hospital, Guwahati, Assam, India from March 2016 to December 2017. The ethical committee clearance was obtained prior to commencement of the study (IEC number MC/217/2016/40). Informed written consent was obtained from all the study subjects.

Inclusion criteria: All suspected cases of renal mass were included in this study.

Exclusion criteria: Cases presenting with associated Chronic Kidney Disease (CKD) with deranged renal function defined by the American College of Rheumatology (ACR) 2017 guidelines which indicate that an eGFR <30 mL/min/1.73 m^2 is associated with an increased risk of Contrast Induced Nephropathy (CIN) with intravenous injection. In this present study, the authors continued to regard CKD (eGFR <60 mL/min/1.73 m^2) as a risk factor for CIN or allergic to contrast agent were excluded [10].

Sample size calculation: The total number of cases was calculated based on a confidence interval scale of 95% with a z score of 1.96 and W/2 being the margin of error on each side of the sample mean and each data value had variance σ^2 [11]. The calculated value came out to be 56 patients. The formulae used for aforementioned calculation is $n=Z^2\ \sigma^2/W^2$.

A total of 61 consecutive patients who presented with renal mass either clinically or by imaging, were enrolled in the study.

Study Procedure

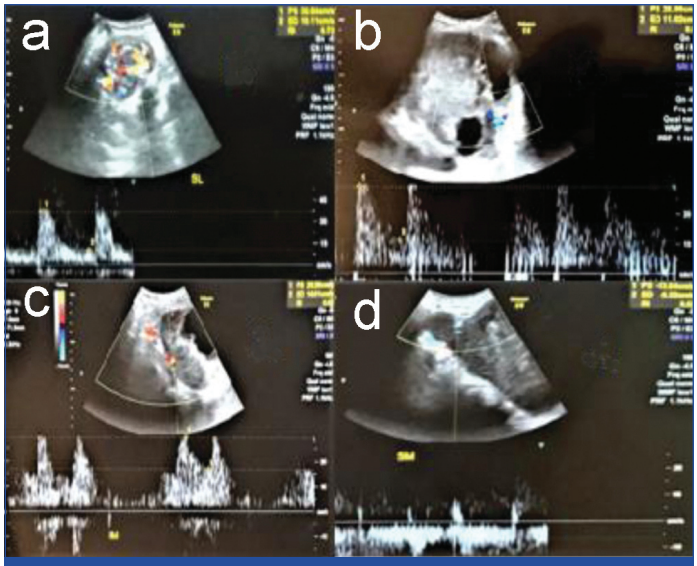
All the study subjects underwent dynamic helical MDCT scan and USG Doppler evaluation performed one week prior to surgery. Histopathology was planned according to American Joint Committee on Cancer (AJCC) 7th edition [12] and Fuhrmans grading [13]. The AJCC 7th edition consisted of T stage (primary tumour size), N stage (regional lymph node) and the M stage (metastasis). The Fuhrman grading system is based on assessment of the uniformity of nuclear size, nuclear shape and nucleolar prominence.

All relevant clinical, radiological data were noted preoperatively and histological characteristics depending on the biopsy were noted postoperatively. Doppler US examination was performed on Voluson™ E8 BT13 console 230 V. Power Doppler imaging of focal renal lesions was done to identify the signals which was not localised by colour doppler. The Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV) and the resistive index (RI=PSV-EDV/PSV) of the lesions were recorded. The baseline RI was calculated based on a previous study [14], in which the mean RI of the RCCs was 0.56±0.06 (range, 0.41 to 0.65) [Table/Fig-1].

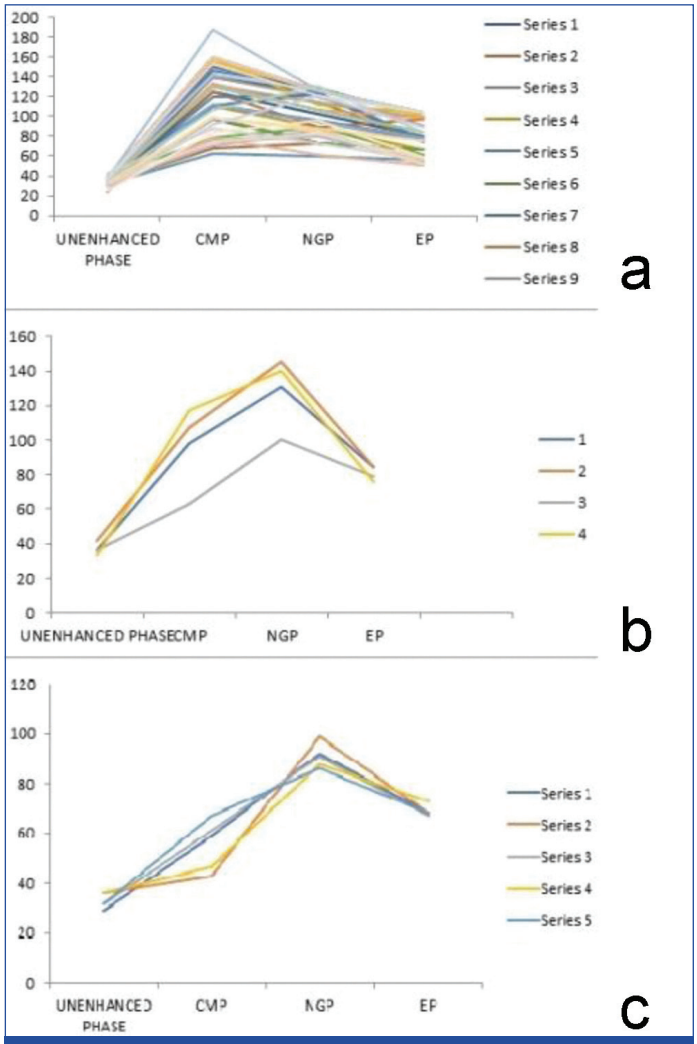
All MDCT examinations were performed on Philips 4541 101 28481 (Philips and Neusoft medical systems Co. Ltd., China). To evaluate the degree of enhancement of a tumour, the attenuation of four separate quadrants of interest (1 cm^2) were measured within the mass lesion and the mean of these four values were calculated. The location for measuring the attenuation value was chosen within the solid enhancing area. Absolute enhancement was defined as the difference in mean HU between the non contrast phase and any given contrast phase [Table/Fig-2] [15].

STATISTICAL ANALYSIS

The Pearson Chi-squared test ($\chi 2$) was used to compare categorical variables. The ANOVA test was used to compare quantitative variables. A p-value of less than 0.05 (5%) was considered statistically significant. For all statistical analysis SPSS software (version 21.0) was used.



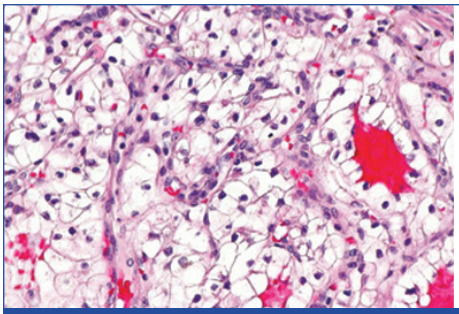
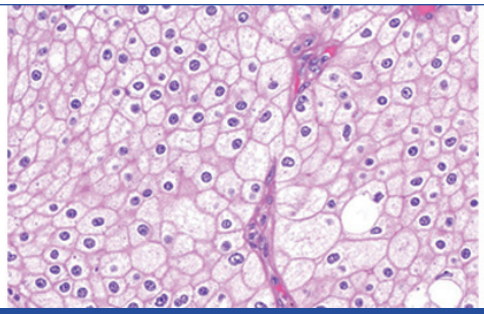
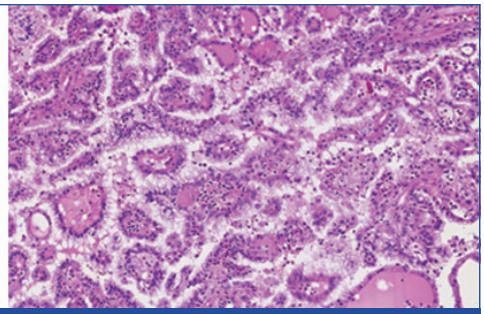
[Table/Fig-1]: Doppler ultrasound in clear cell carcinoma showing heterogenous mass in right kidney with a) RI 0.73 in superolateral quadrant; b) RI 0.62 in inferolateral quadrant; c) RI 0.43 in inferomedial quadrant; d) RI 0.63 in superomedial quadrant.



[Table/Fig-2]: Patterns of enhancement on multiphasic imaging of a) ccRCC; b) pRCC and c) chRCC.
*ccRCC: Clear cell RCC; Prcc: Papillary RCC; chRCC: Chromophobe RCC

RESULTS

In present study, out of 61 patients, 44 (72.1%) were males while 17 (27.9%) were females, with a male:female ratio of 2.58:1. Mean age in present study was 50±4.75 years. The histopathological examination with Haematoxylin and Eosin (H&E) stain of resected specimens revealed ccRCC in 52 (85.2%) patients [Table/Fig-3] while 4 (6.6%) patients had chRCC [Table/Fig-4] and rest 5 (8.2%) patients had pRCC [Table/Fig-5].

[Table/Fig-3]: Clear Renal Cell Carcinoma (ccRCC). (H&E 100X). **[Table/Fig-4]:** Chromophobe Renal Cell Carcinoma (chRCC) (H&E 100X). **[Table/Fig-5]:** Papillary Renal Cell Carcinoma (pRCC) (H&E 10X). (Images from left to right)

Majority of the lesions were found to have Fuhrman grade 2 with 27 (44.3%) subjects and grade 3 with 26 (42.6%) subjects [Table/Fig-6].

Parameters	Median (range) or No. (%)
Age	50±4.75 years
Male	44 (72.1)
Female	17 (27.9)
Side of tumour	
Left	33 (54.1)
Right	28 (45.9)
Histology	
Clear-cell	52 (85.2)
Papillary	4 (6.6)
Chromophobe	5 (8.2)
Fuhrman nuclear Grade	
1	4 (6.6)
2	27 (44.3)
3	26 (42.6)
4	4 (6.6)

[Table/Fig-6]: Patient and tumour characteristics of study population.

Out of 61 patients, only 7 (11.5%) patients had tumour size <4 cm, 15 patients had tumour size in the range of 4-7 cm while 18 (29.5%) had tumour size between 7-10 cm. A total of 21 (34.4%) had tumour size more than 10 cm. Maximum number of tumours were in T2 category (47.6%) while T3 had 18% cases. There is no significant difference in size of tumour among various subtypes in study population p-value of 0.410 [Table/Fig-7a]. A lymph node enlargement of >1 cm was recorded in 26 (42.6%) patients which was detectable on CECT scan only. No significant difference noted between types of RCC for the presence of enlarged lymph nodes detected in Contrast-enhanced Computed Tomography (CECT) scan (p=0.949) [Table/Fig-7b]. Metastasis was found in 11 (18%) patients. No significant difference seen among types of RCC regarding presence of systemic metastasis (p=0.624) [Table/Fig-7c].

Tumour size category	Frequency	Percent (%)	p-value
T1 (< 4 cm)	7	11.5	
T2 (4-7 cm)	15	24.6	
T3 (7-10 cm)	18	29.5	**0.41**
T4 (> 10 cm)	21	34.4	
Total	61	100.0	

[Table/Fig-7a]: Distribution of tumours according to their size category in the study population.
Chi-square test; level of significant p-value <0.05

Node enlargement	Frequency	Percent	Positive in HPE	p-value
No	35	57.4	0	
Yes	26	42.6	7 (27%)	0.949
Total	61	100.0		

[Table/Fig-7b]: Distribution of cases according to presence of lymph node enlargement in CT scan in the study population.
Chi-square test; level of significant p-value <0.05

Metastasis	Frequency	Percent (%)	p-value
No	50	82.0	
Yes	11	18.0	0.624
Total	61	100.0	

[Table/Fig-7c]: Distribution of cases according to presence of metastasis.
Chi-square test; level of significant p-value <0.05

In this study population, ccRCC, ChRCC and pRCC had mean RI of 0.63±0.06 (0.36-0.87), 0.58±0.0 (0.58-0.68) and 0.67±0.11 (0.46-0.87), respectively. No significant correlation was perceived between types of RCC with that of intratumoural RI measured by Power Doppler (Pearson's R coefficient=4.36, p<0.001) [Table/Fig-8].

RCC subtype	Minimum RI	Maximum RI	(Mean±SD) Resistive index	p-value
Clear cell (ccRCC)	0.36	0.87	0.63±0.06	
Chromophobe (ch RCC)	0.58	0.68	0.58±0.0	<0.001
Papillary (pRCC)	0.46	0.87	0.67±0.11	

[Table/Fig-8]: Mean colour doppler indices in various subtypes of RCC.
ANOVA test; level of significant p-value <0.05

A 10 (16.4%) patients had homogenous enhancement while 51 (83.6%) had heterogenous enhancement. On CT scan 26 (42.6%) patients had lymphadenopathy, while systemic metastasis, renal vein thrombosis, intratumoural necrosis and intratumoural calcification was observed in 11 (18%), 11 (18%), 45 (73%) and 18 (70.5%) cases, respectively [Table/Fig-9].

Characteristic	N (%)
Homogenous enhancement	10 (16.4)
Heterogenous enhancement	51 (83.6)
Lymphadenopathy	26 (42.6)
Systemic metastasis	11 (18)
Renal vein thrombosis,	11 (18)
Intratumoural Necrosis	45 (73)
Intratumoural calcification	18 (70.5)

[Table/Fig-9]: Tumour characteristic based on MDCT scan in the tumour population.

There was no significant difference observed regarding presence of enlarged lymph nodes detected in CT scan (p=0.949), presence of systemic metastasis (p=0.624), renal vein thrombosis (p=0.313), intratumoural necrosis (p=0.090) and presence of intratumoural calcification (p=0.110) among all three RCC subtypes [Table/Fig-10].

Data depicting mean attenuation values and absolute enhancement values are demonstrated in [Table/Fig-11,12], respectively. Significant difference was noted in mean attenuation values between clear and pRCC in CMP (p=0.001). A substantial divergence was also noted in absolute enhancement values amidst clear and pRCC in CMP (p=0.001).

RCC subtype	Lymphadenopathy	Systemic metastasis	Renal vein thrombosis	Intratumoural necrosis	Intratumoural calcification
Clear cell	22	10	11	41	18
Chromophobe	2	0	0	2	0
Papillary	2	1	0	2	0
p-value	0.94	0.624	0.313	0.090	0.110

[Table/Fig-10]: Tumour histopathology based on CECT scan in the tumour population.
ANOVA test; level of significant p-value <0.05

RCC subtype	Attenuation value Mean±SD (HU)			
	In UECT	In CMP	In NP	In EP
Clear cell	32.293±3.85	122.33±32.17	123.25±15.50	82.75±18.49
Chromophobe	35.25±1.50	96±22.0	123.25±15.50	82.75±18.49
Papillary	33±3.00	55.40±10.03	91±1.73	68.80±2.38
p-value	0.759	0.0001	0.332	0.415

[Table/Fig-11]: Mean attenuation value of 3 subtypes of RCC different phases.
ANOVA test; level of significant p-value <0.05
*UECT: Unenhanced computerised tomographical; CMP: Corticomedullary medullary phase; NP: Nephrographic phase; EP: Excretory phase

RCC subtype	Absolute attenuation value Mean±SD (HU)		
	In CMP	In NP	In EP
Clear cell	88.04±30.40	72.41±20.17	48.25±17.04
Chromophobe	60.75±22.54	88±16.06	47.50±3.31
Papillary	22.40±12.52	58.00±4.41	35.80±2.58
p-value	0.001	0.442	0.716

[Table/Fig-12]: Absolute enhancement value of 3 subtypes of RCC in different phases.
ANOVA test; level of significant p-value <0.05

Based on absolute enhancement values in different phases a rapid and high attenuation enhancement that instantly washes out in the delayed phase was noted in cases of ccRCC. While in cases of chRCC, no major change in enhancement values was observed in CMP and NP and washout was slow comparative to ccRCC. The highest peak HU observed in ccRCC was 188 HU. ccRCCs more often peaked in the CM phase. pRCCs showed a peculiar enhancement pattern, with a low peak enhancement (average peak of 55.40 HU) and greatest enhancement during the NG and delayed phases. For pRCC absolute enhancement in the CMP was <30 HU and NG phases it was >40 HU. Peak of enhancement was observed in NG phase [Table/Fig-2].

DISCUSSION

The RCC is the most prevalent adult renal tumour and 30-40% are incidentally detected [16]. Triphasic MDCT is the idealised approach for comprehensive evaluation of renal masses. The ccRCC accounts for almost 70% of RCCs with overall five years survival rate ranging from 55-60%, respectively. The share of pRCC is around 15-20% of RCCs with a high five years survival rate ranging from 80 to 90%. chRCC accounts for 6-11% of the cases and have the best prognosis overall of approximately 90% in five years. Collecting duct carcinoma is an isolated form of RCC consisting about 1% of the cases; with a worse overall prognosis of less than 5% when seen at a five years perspective [17]. With commencement of modern treatment schemes and adjuvant strategies like cytotoxic chemotherapy, radiofrequency, immunotherapy, antiangiogenic therapy, and cryoablation techniques, predicting the subtype of RCC is beneficial for deciding the treatment option as well as measuring response to current adjuvant therapies. Histopathological typing of RCC can be predicted by using multiphasic MDCT and Doppler USG as shown by previous studies [18]. The H&E stain used in the study identified various cell types and tissues. It provides relevant details about the shape, pattern and structure of cells in the provided sample [19].

In the present study, the mean actual enhancement in CMP was 122.33±32.17 HU for clear cell, 96±22.0 HU for chRCC and 55.40±10.03 HU for pRCC. In a larger patient cohort including ccRCC, pRCC authors commented on enhancement diversity of two types of tumours on postcontrast CT images. In the CMP, the authors showed that attenuation values of ccRCC (142.6±35.4 HU) were significantly higher than those of pRCC (81.8±24.4 HU) [17,18]. The result published by the aforementioned authors is in sync with the present study results. Another researcher explored the utility of a single phase CECT in the analysis of RCC subtypes in a group consisting of spectrum of ccRCC, pRCC and chRCC patients in which he obtained a significantly lower mean quantitative tumour percentage enhancement and tumour-to cortex enhancement values for pRCC compared to ccRCC and chRCC patients [20]. The present study echoed similar results with respect to tumour to cortex enhancement (114±8.4 HU, p=0.03) in the CMP for pRCC but did not find mean tumour enhancement to be significant while comparing pRCC and other various subtypes in CMP. The present and the previous authors failed to diversify pRCC patients from other's using these quantitative enhancement indices [21].

In the NP reported by a previous study, an extrusive distinction was also present among 2 subtype tumours, measuring (105.1±17.5 HU) for ccRCC and (67.3±14.4 HU) for pRCC, respectively (p<0.05). This result is in array with the angiographic findings that most ccRCC show hypervascularity in the arterial phase and most pRCC show hypovascularity. The strong enhancement of ccRCC is because of its alveolar architecture and rich vascular network [22]. In the present study, NP revealed mean attenuation value for ccRCC as >100 HU and for pRCC it was <100 HU. There are atleast two major categories of blood vessels with contrasting prognostic implications [23] within ccRCC. These are undifferentiated vessels and differentiated vessels with a higher undifferentiated vessel density attributing poorer prognosis and higher differentiated vessel density correlating with better prognosis. The study correlated enhancement patterns with micro-vessel density within tumour size.

According to another researcher, pRCC had comparatively low levels of peak enhancement and fluctuation in attenuation in different phases of MDCT scan [24]. The pattern of enhancement noted in pRCC seen in present study population is not in accordance to the pattern mentioned in the aforementioned study. In present study, we observed that for pRCCs absolute enhancement in the CMP was <30 HU and NG phases it was >40 HU but in previous study absolute enhancement in the CMP was <32 and in NG phase was <40 [24]. Another set of research analysis used two post contrast phases to differentiate between renal masses in which some studies used the CMP and NP [25] phases while other utilised CMP, NP and EP [26-28]. They reported that if mean attenuation value (MAV) in the CMP was ≥95 HU, it could predict ccRCC or ChRCC with high sensitivity and specificity and greater than 95% and 82%. The authors in the present analysis echoed the aforementioned results with MAV between CMP and NP phase ≥90 HU with a sensitivity and specificity of 90% and 79% (p<0.01) while the same was in the range of 60 HU while concerning ccRCC and chRCc (p=0.06). In the present study, similar pattern of enhancement was observed in cases of ccRCC. An increase in enhancement values during the CMP increase the chances of ccRCC while increasing HU in the NG phase decreased the likelihood of ccRCC. Present study revealed heterogenous

enhancement in 51 (83.6%) cases and among these 47 (90.4%) were ccRCC. These peculiar enhancement values on MDCT correlated well with pathological finding of intratumoural necrosis which is common in ccRCC [29]. Homogenous enhancement was seen in two cases of chRCC and two cases of pRCC. Only 5 (9.6%) of the ccRCC showed homogenous enhancement. Present study showed homogenous enhancement was found predominantly in non ccRCC.

Few previous studies which barred the CMP, commented that rapid washout in ccRCC diversify it from other renal masses while a different subset of authors did not observe this rapid washout in ccRCC [28-32]. This study results suggested that a high CMP attenuation in a lesion clearly suggested ccRCC than other malignant and benign subtypes. The NP and EP had a high cut-off point with high positive and negative predictive value in discriminating the 2 groups of ccRCCs and chRCCs from pRCC which was due to the fact that pRCC did not show significant washout in NP which explained the significance of incorporating CMP, NP and Excretory Phases (EP) in the present study.

Some authors have incorporated morphometric characteristics, homogeneity and growth pattern to suggest tumour histology [1,33-36]. The present study did not find tumour morphology or other factors useful in determining histology. This may be due to the relatively small sample size.

Surekha B et al., found a highly significant difference in regard to PSV and Doppler shift frequency between ccRCC and chRCC and they attributed it to hypervascularity seen in ccRCC. High PSV in ccRCC is due to increased flow and arterio-venous shunts being more in clear cell type [37]. High PSV was observed in ccRCC cases in this study too but, it did not have significant correlation with this sub type. In the present study, similar results were found on similar pattern of RI as mentioned in the aforementioned study. Though ccRCC has a high micro-vessel density and hyper vascularity in comparison to other types of RCC the intratumoural RI measurement in the present study population showed that there was no significant difference among all types of RCC (p>0.001).

Limitation(s)

No correlation of high-grade tumours was done with differing enhancement patterns possibly due to a single centre study. With multiple centres and larger cohort of patients enrolled in those centres, it may be possible to detect more subtle differences among low and high-grade variants of RCC.

CONCLUSION(S)

The present study concluded that MDCT scan was comparatively better than power doppler in the discrimination of ccRCC from pRCC and chRCC. With MDCT, the degree of enhancement is the most valuable parameter in differentiating among the subtypes of RCC and enhancement pattern may play a supplemental role although a definitive diagnosis cannot be achieved by radiographic data alone at present with limited data in hand. A specific algorithm based on mean attenuation values and pattern of enhancement can accurately predict between various subtypes of RCC. Future large scale multi-centric prospective studies are needed to determine whether adding MDCT protocol can improve preoperative tumour subtyping and aid in orderly management schedule.

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