Chapter

Current Imaging Techniques in Renal Cell Carcinoma

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Abstract

Renal cancers are one of the 10 most commonly seen cancers in both sexes. The incidence of renal cancers is high in Western developed countries and lower in Eastern and developing countries. The overall incidence of malignancy has been increasing in recent times. Ultrasound (USG) is very commonly used imaging technique; however recent advances like contrast enhanced ultrasound helps to differentiate various cystic renal masses. Availability of newer imaging techniques such as Computed tomography scan (CT scan) and Magnetic resonance imaging (MRI) and their various applications may play a role in better and early diagnosis of such lesions. Due to its highly metastatic nature, accurate staging is more important to facilitate proper treatment. Fluoro-deoxyglucose positron emission tomography (FDG PET) is widely applied in detection, staging/restaging and surveillance of such lesions. In this chapter, we will try to cover the recent advances in various modalities for detection of renal cancers, particularly renal cell carcinoma (RCC).

Keywords: renal cancer, renal cell carcinoma, ultrasound, CT scan, MRI, PET scan, contrast enhanced ultrasound

1. Introduction

Renal cell carcinoma is the most common renal malignancy. The steady increase in incidental diagnosis of small renal cancers in last several decades can partly be dedicated to frequent abdominal imaging [1]. The risk benefit ratio has to be considered while resecting a renal mass for the presumption of cancer which can turn out to be of benign or indolent nature. Per cutaneous renal biopsy can be the gold standard for such pre surgical diagnosis; however it yields non diagnostic rate of 10–15% and the intra tumoral heterogeneity hampers its widespread use [1]. Hence, accurate pre surgical characterization of renal cancers is very needful to avoid over treatment and to facilitate the proper line of treatment to the surgeon.

Ultrasound is the most basic and commonly used imaging technique for diagnosis of renal cancers. It is non invasive, cost effective, readily available and widely used technique with advantages of real time imaging and without need of ionizing radiation. The basic disadvantage of USG is its operator dependency. Though USG is sufficient to differentiate simple or minimally complex cystic masses as benign lesions, it is not reliable to differentiate more complex cystic and solid lesions [1]. Newer advances in USG like contrast enhanced Ultrasound, ultrasound molecular imaging,

elastography and micro doppler techniques are nowadays being investigated for better accuracy of ultrasound and to expand its role in tumor characterization.

Contrast enhanced CT scan (CECT) is considered the gold standard for the assessment of solid renal masses. CT scan offers the best imaging technique to properly diagnose and stage renal cell carcinoma along with post treatment surveillance. Post contrast mass enhancement and heterogeneous nature of renal masses also help to differentiate various subtypes of renal cell carcinoma but with less success. Apparent diffusion coefficient (ADC) distribution parameters for renal whole tumor are useful in discriminating oncocytoma from RCC [2]. Another pre processing method called Laplace of Gaussian (LoG) can be used to reduce the image noise while highlighting the degree of heterogeneity within the tumor and entropy can be used to quantify tumor heterogeneity. Both of these methods can be applied to conventional CT scan and can help substantially to predict the Fuhrman Grade of RCC [3].

Multi parametric MRI (mpMRI) is routinely used in clinical practice for renal mass evaluation nowadays. Common subtypes of RCC and other commonly seen benign epithelial renal masses can be non-invasively differentiated with the help of mpMRI. Recent advancement in algorithm for interpretation of mpMRI known as clear cell likelihood score (ccLS) can predict clear cell histology in cT1a mass. However it does not allow for prediction of high grade histology [4]. Another application is MR texture analysis (MRTA) which can generate several parameters showing excellent diagnostic value in differentiation of RCC from lipid poor angiomyolipoma (AML) and oncocytoma [5]. Contrast enhanced MRI (CEMRI) provides superior soft tissue resolution and delineates primary extent of tumor and venous tumor thrombus involvement. It is also useful for patients with iodine contrast allergies or in patients with impaired renal function. CEMRI can help in differentiation of tumor subtypes depending upon enhancement mode and apparent diffusion coefficient (ADC) values [6].

PET/CT scan simultaneously evaluates the lesion anatomy and provides metabolic information. It is widely used for pre operative staging and post operative restaging. Diagnostic results of primary RCC with FDG PET scan varies depending upon the tumor pathology and nuclear differentiation. FDG PET/CT detects venous tumor thrombus and can distinguish it from venous bland thrombus almost comparable to CEMRI. However PET/CT is more useful for distant organ metastasis [6]. Newer radio tracers like Prostate Specific Membrane Antigen (PSMA) also offer valid imaging option for RCC. Undefined renal mass evaluation and therapy response assessment can also be done with PSMA PET scan. PSMA based Radio ligand therapy is also a future development option. Recent advances like PET/MRI provide combined anatomic and metabolic information. It has very promising results in detection of RCC. However, detailed studies are in progress for its application.

2. Role of different imaging modalities in diagnosis of RCC

Role of Imaging in evaluation of RCC is for characterization of renal lesions. Various imaging modalities are being used for detailed evaluation of RCC in pre operative as well as post operative periods and also for guiding the proper treatment method along with for surveillance of RCC.

The first step in the process is to determine whether the lesion is cystic or solid. Cystic lesions are classified depending upon their imaging appearance using Bosniak classification system (**Table 1**). USG can easily describe these findings; however more complex and higher grade cysts need to be evaluated with further investigations. Solid

Category	Characteristics	Presentation
I	• Benign, simple cyst with well defined thin smooth wall (≤2 mm). • No evidence of septa, calcification or solid nodules. • Attenuation of contents equivalent to simple fluid (−9 to 20 HU) on unenhanced CT scan. • The wall may enhance on contrast studies.	
II	• Thin & smooth walls. • Few internal septa which can enhance. • May show wall calcification foci. • Homogeneous mass with −9 to 20 HU density on unenhanced CT scan. • Homogeneous hyper attenuating (≥70 HU) masses on unenhanced CT scan. • Homogeneous low attenuation masses that are too small to characterize.	
IIF	• Minimally thick (3 mm) smooth enhancing wall or septa or many (≥ 4 in number) thin (≤2 mm) enhancing septa. • Septal calcification focus	
III	• cystic masses with thick(≥4 mm width) irregular septa or smooth walls • septa with measurable enhancement	
IV	• clearly malignant cystic mass with criteria of category III • Also contains enhancing soft tissue components (≥4 mm) independent of wall or septa.	

Table 1.
Bosniak categorization criteria of renal masses with graphical presentation [7].

lesions can be accurately diagnosed as benign or malignant on the basis of CT or MRI findings. Once the lesion is diagnosed as solid or complex cystic lesion and the probability of RCC is made, further imaging plays an important role. In this section, we will cover the basic imaging features of RCC with various advances in each modality.

2.1 Ultrasound

Ultrasound (USG) is the basic investigation used to differentiate various renal cysts/masses. It is non invasive, readily available, cost effective imaging technique which offers real time imaging without risk of ionizing radiation. However major drawback of USG is its operator dependency. Conventional USG is capable to classify indeterminate renal masses with simple or minimally complex features as benign. However it is not reliable to classify more complex cystic or solid masses. The renal masses are characterized depending upon their walls and contents on USG and their various enhancement patterns on CT scan. Widely used classification method is Bosniak classification which includes various parameters like, cyst wall, internal septa (thickness and number) and their enhancement patterns, wall or septal calcifications, internal nodules and their enhancement (**Table 1**) [7]. Considerable proportion of renal masses may display equivocal features on Conventional CT scan and MRI which makes them difficult to be distinguished as benign or malignant [8]. Hence, various

advancements are available or being studied for the non invasive use of USG in characterization of renal masses as follows.

2.1.1 Contrast enhanced ultrasound

Contrast enhanced ultrasound (CEUS) is newer technology addressing some of the drawbacks of non enhanced gray scale imaging and traditional color doppler ultrasound for evaluation of vascularization within the normal soft tissue or any focal lesion. Most commonly used contrast medium for CEUS is intravenously injectable micro bubbles. They are microspheres measuring about the size of red blood cells with biodegradable lipid or protein shell and a gas core. They are usually filled with per fluorocarbon like per flourobutane gas as it is heavier than air (for stability purpose). Other components like polyethylene glycol, proteins can also be added to the outer shell for improved stability.

Due to micron size of these bubbles (1–4 micrometer) they stay confined to the vessel and they can also pass through tiny capillaries. It enables high reflection and sound scatter in blood and they resonate non-linearly when insonnated by ultrasound waves. The unique signals gained from these micro bubbles are separated from the background which allows detection of blood flow within the tissue (**Figure 1**). The micro bubbles remain within the circulation for only few minutes and rapidly get cleared via reticulo-endothelial system and through lungs. Major advantage of ultrasound contrast agents over CT or MRI contrast agents is their use in renal insufficiency. First pass (bolus) dose of micro bubbles within the region of interest is done to assess levels of vascularity in real time with use of techniques like time intensity curve analysis, maximum intensity projection analysis or re-perfusion analysis. Contrast micro bubbles allow for better focal lesion detection and help to differentiate benign from malignant lesions. It also allows to measure tumor size accurately [8]. While lack of radiation, lower cost and high safety of contrast media are major advantages of CEUS, operator dependency and few other technical limitations are disadvantages of it which can limit its reproducibility.

Simple renal cyst shows no evidence of enhancement due to its clear contents and no vascularity within it. However, confusion due to equivocal findings for lower degree complex cysts can also be cleared with CEUS as many times a more complex cyst may not show enhancing contents on contrast scan and thus it can be stamped as

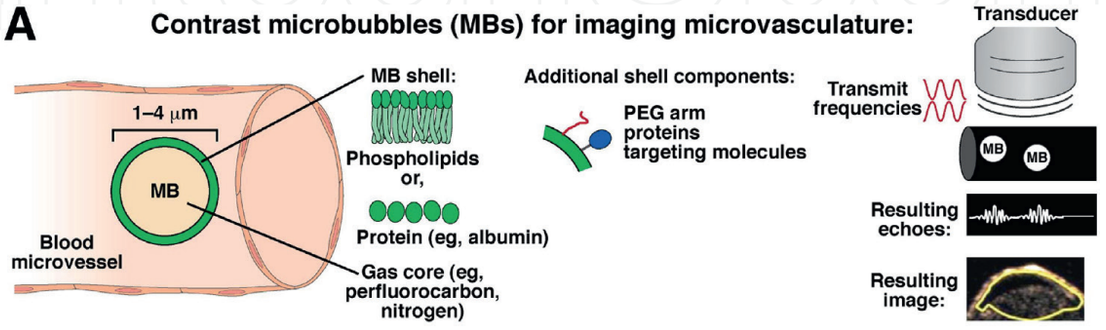

Figure 1.
Non targeted and molecularly targeted CEUS with micro bubbles. The gas core with shell of lipid or protein is basic formation of micro bubble (on left side). Pulse inversion technique is used for detection of micro bubbles. Two inverse phase (red colored) pulses are transmitted through the tissue and echoes are reflected back from micro bubbles or from tissue. The echo reflected from micro bubble represents white wave and from tissue represents flat line [8].

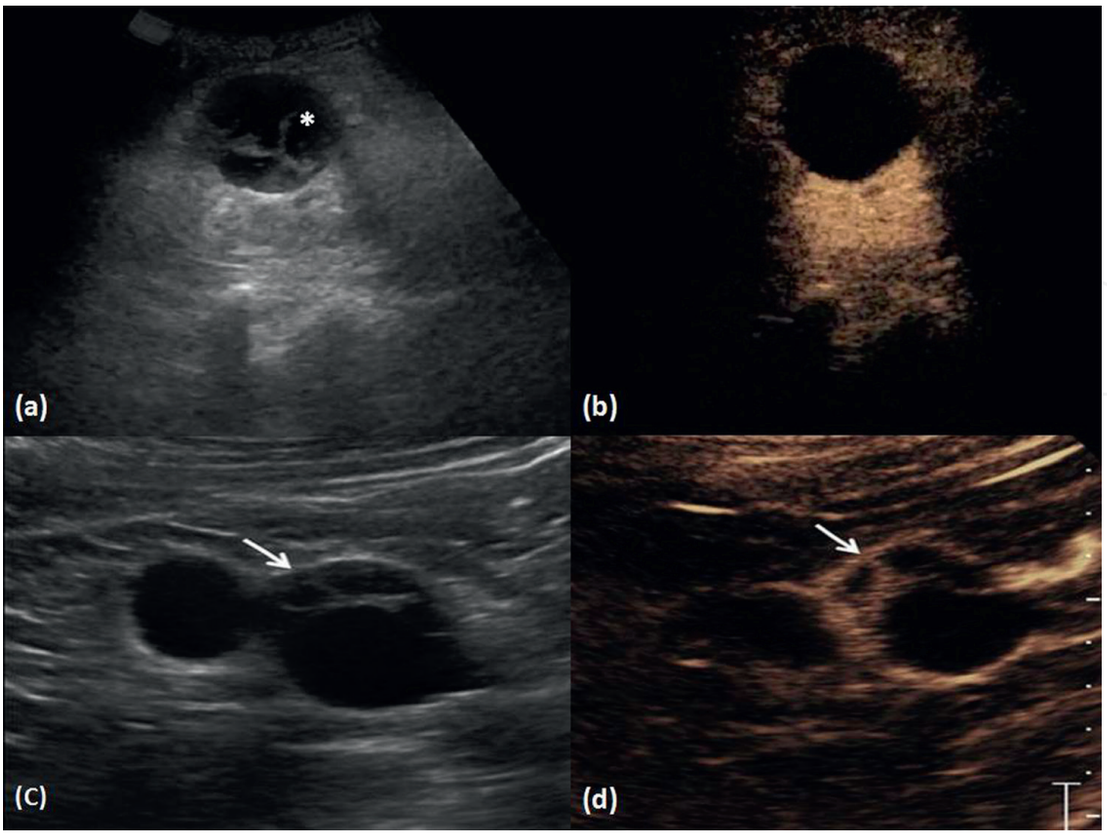

Figure 2.
(a) Gray scale imaging of renal cyst with internal thick septa (*). (b) on CEUS, the septa are not visible and the cyst remains clear. Final diagnosis is simple cyst. (c) Gray scale imaging of renal cyst with internal septa(white arrow) (d) on CEUS the internal septa enhance suggesting the cyst to be complex in nature [9].

benign lesion (**Figure 2**). Difference of perfusion within the lesion and surrounding renal cortex helps to characterize solid lesions also [1].

CEUS shows great value in evaluation of septations and mural nodules within the renal cysts due to their distinct enhancement. Equivocal results in Bosniak Category IIF and III cysts can be avoided with the use of CEUS. According to some studies CEUS has comparable results in classification of benign versus malignant renal masses as in CECT or CEMRI. According to Furrer et al., reported pooled sensitivity and specificity for CEUS, CECT and CEMRI in evaluation of renal masses to be 96%, 90% and 96% and 78%, 77% and 75% respectively [10]. Other researchers also compared CEUS with CECT and CEUS to CEMRI in solid renal lesions and reported almost similar results [11, 12]. However, lesions with fat within were excluded from these studies. Fat poor angiomyolipoma (AML) and oncocytoma have non differing imaging features on USG hence, they cannot be properly distinguished from RCC through CEUS. Quantitative features of CEUS i.e. analysis of time intensity curves help in distinction of various subtypes of RCC and from typical AML from RCC. However, there is considerable overlap in imaging features of these masses [1].

The enhancement of tumor less than that of surrounding renal parenchyma indicates it to be indolent or benign. However some benign lesions like oncocytoma also show hyper enhancement making it difficult to differentiate it from RCC on CEUS. However, RCC exhibits delayed contrast washout compared to adjacent renal parenchyma [13]. Marked enhancement and delayed washout of contrast medium are findings associated with clear cell RCC (ccRCC) (**Figure 3**). However these features

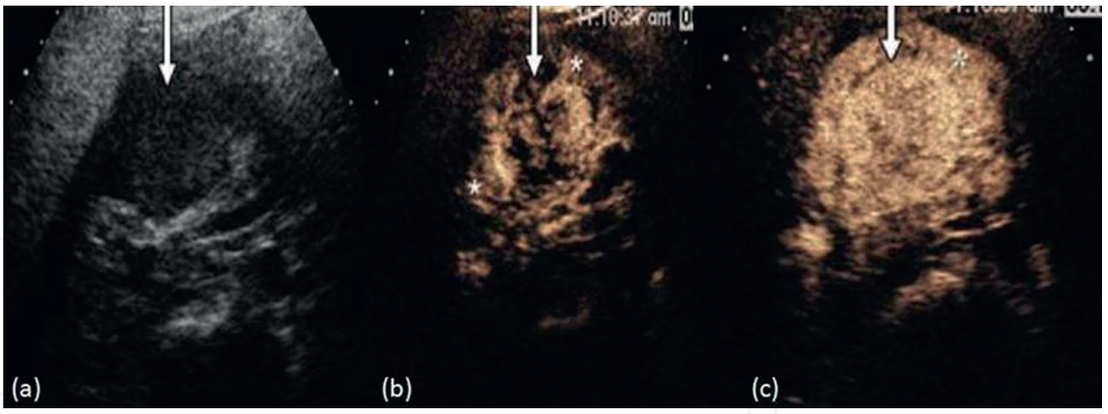

Figure 3.
(a) Gray scale imaging of renal mass showing hypo echoiec mass lesion at mid pole of right kidney (b) 16 seconds after contrast injection, heterogeneous enhancement (white arrow) which is higher than the adjacent renal parenchyma (*). (c) 19 seconds after contrast injection it shows uniform enhancement [13].

alone were not enough for the diagnosis and so, a combination of tumor heterogeneity with delayed contrast washout had specificity of 82% and positive predictive value of 85% for conventional ccRCC. At the same time hypo enhancing ccRCC are a challenge for diagnosis. Also, CEUS can reliably detect enhancing tumor thrombus within the renal vein.

2.1.2 Ultrasound molecular imaging

Molecular imaging is a highly innovative approach which involves targeting and real time, in vivo evaluation of physiological processes. As an extension of CEUS, molecular targeted micro bubbles are developed. Ideally response to ongoing systemic treatment is determined by changes in the volume of the tumor. Molecular imaging allows evaluation of changes in tumor physiology earlier than the tumor volume changes. This can help in earlier evaluation of tumor progression and response to treatment which aids in timely therapeutic decision making. Molecular imaging can characterize features like angiogenesis more potentially helping in treatment option choices. Many researchers have studied molecular imaging in mice models. They found the response to therapy detection was better for molecular imaging than with the volume measurements [14]. Molecular imaging has the potential for serial monitoring and assessment of disease response to systemic therapy, still it is in very early phases of development and much research is needed [1].

2.1.3 Elastography

Ultrasound elastography measures the tissue stiffness (which is present in diffuse parenchymal diseases) and the resultant tissue architectural changes. Strain elastography is a qualitative or semi qualitative evaluation of tissue elasticity using external compression and decompression cycles from the transducer. Shear wave elastography (SWE) is a quantitative assessment of tissue elasticity by measuring propagation speed of shear waves through the tissue. It does not require external compression and relies on a high amplitude push pulse known as acoustic radiation force impulse (ARFI). So it is less operator dependant. Strain elastography helps to aid in the discrimination of benign from malignant lesions, RCC from AML and RCC from transitional cell carcinoma (TCC). SWE also has potential value in differentiating

various sub types of RCC, pseudo tumor and AML. However it cannot differentiate ccRCC from AML. Few studies have been done for its utility; however the value is limited in validation and application in renal mass characterization is limited at present. Omur et al. stated that mean strain index values are significantly higher in malignant lesions compared with benign solid renal lesions [15].

2.1.4 Micro Doppler techniques

Simple renal cysts show no evidence of internal vascularity due to clear contents as opposed to solid lesion. In such reasons, the pattern of vascularity may help in mass discrimination (malignancy versus pseudo tumor). Novel micro Doppler studies improve the detection of slow flow within the small diameter vessels which increases the ability to detect subtle vascularity within the lesion [16]. Conventional Doppler has threshold limits lower than such novel techniques. Advantages of such techniques are exclusion of the need of IV contrast medium. However the results have not been compared to that of CEUS. Further investigations and studies are needed for its implications.

2.2 CT scan

CT scan is the primary imaging technique for the diagnosis, staging, treatment planning and surveillance of RCC. Contrast enhanced CT scan is performed after intravenous injection of contrast medium. And then various phases are taken according to

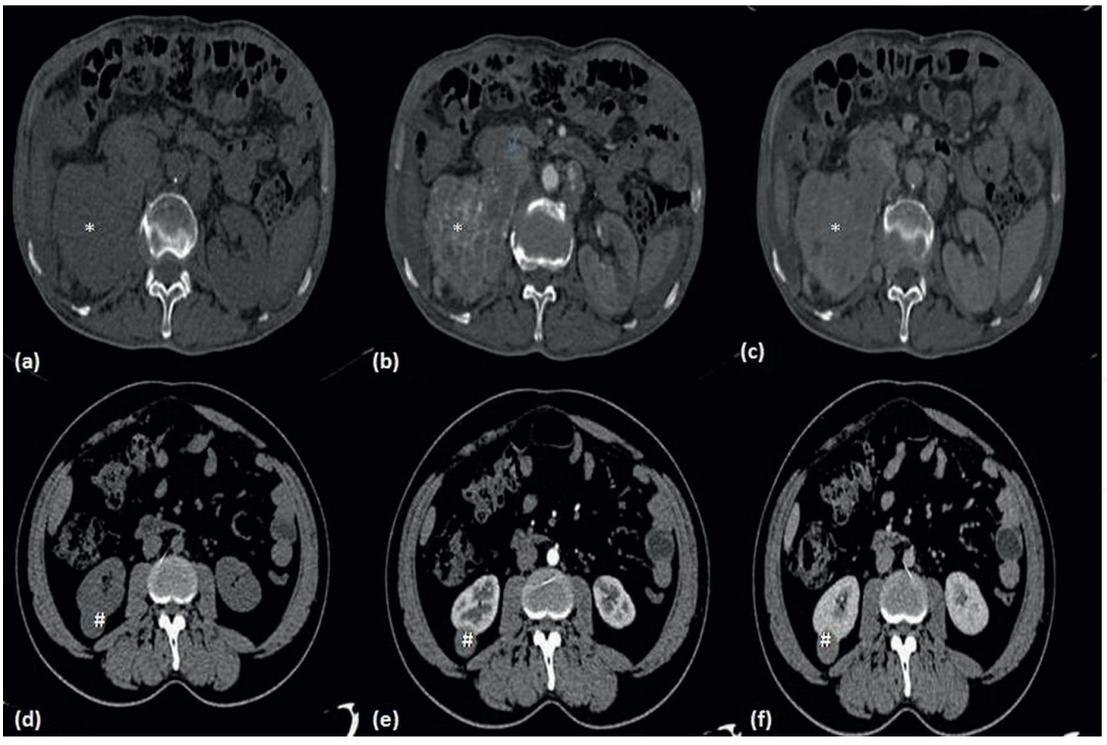

Figure 4.
(a-c) Axial CT imaging of right renal mass- clear cell carcinoma, showing enhancement pattern on various phases. (a) Non enhanced phase shows hypodense lesion in right kidney(*) (b) similar lesion enhances heterogeneously on arterial phase(*). Thrombus within renal vein and IVC is also noted (arrow). (c) Similar lesion shows contrast wash out on venous phase(*). (d-f) Axial CT imaging of right renal mass- papillary cell carcinoma, showing enhancement pattern on various phases. (d) Non enhanced phase shows hypodense lesion in right kidney(#). (e) Arterial phase shows minimal enhancement of the lesion(#). (f) Similar lesion shows increased enhancement on venous phase(#).

the time interval i.e. nephrographic phase, cortico medullary phase and delayed phase. Various sub types of RCC exhibit various patterns of enhancement in different phases of CECT scan; hence they can be differentiated accordingly. Clear cell RCC (most common subtype) is hyper vascular with heterogeneous texture and it enhances in nephrographic phase and the contrast washes out in corticomedullary phase; Papillary RCC is hypovascular so it enhances over the period of time with the phases (**Figure 4**); Oncocytoma shows almost similar pattern of enhancement however the central non enhancing scar is the characteristic feature of oncocytoma. Chromophobe RCC has intermediate vascularity and is usually well circumscribed. Another important finding in RCC to sought for is tumor thrombus involvement of renal vein and IVC. Venous extension of tumor in RCC is best seen in corticomedullary phase of CECT scan.

2.2.1 CT perfusion

CT perfusion allows visualization and quantification of blood perfusion in tissue. After iodine based contrast agent injection, low dose contrast enhanced CT scan images are achieved at multiple time intervals and the contrast passes through vessels and tissue. It allows quantitative analysis of blood flow, blood volume and mean transit time. The role of CT perfusion is well known for analysis of stroke; however, its role in abdominal solid tumor imaging like RCC is still in primary stages. Due to increased vascularity in RCC, it is easily visualized with CT perfusion (**Figure 5**). Most RCC treatments affect angiogenesis and targeted therapies have a greater effect on metastatic sites than on the primary tumor site. Targeted treatment reduces tumor vascularity, decreases proliferation and increases apoptosis and immune cell infiltration as

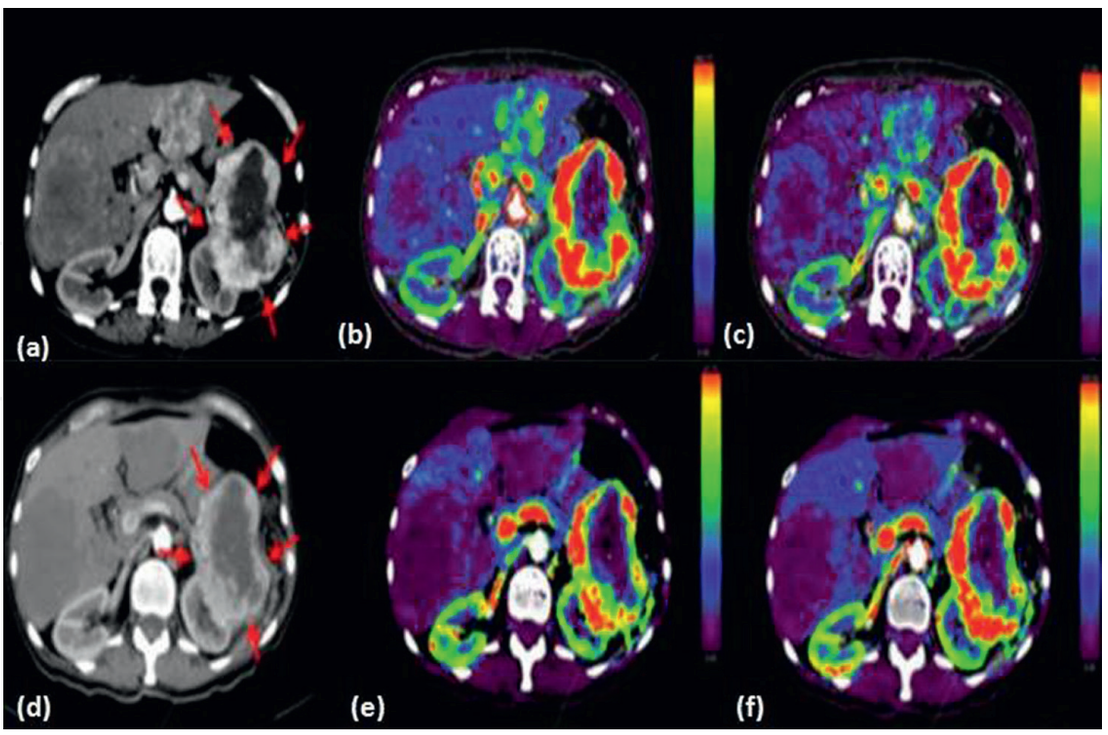

Figure 5.
(a-f) Axial images of contrast enhanced CT scan and perfusion of left renal mass. (a-c): Images of left renal mass before starting treatment (red arrows). Blood flow was 116 (±84.12) ml/100 ml/min and blood volume is 13.79 (± 7.79) ml/100 ml. (d-f) Similar patient at 8 days of starting treatment. The blood flow showed mild reduction to 100.13 (± 77.96) ml/100 ml/min and blood volume to 10.38 (±9.6) ml/100 ml [17].

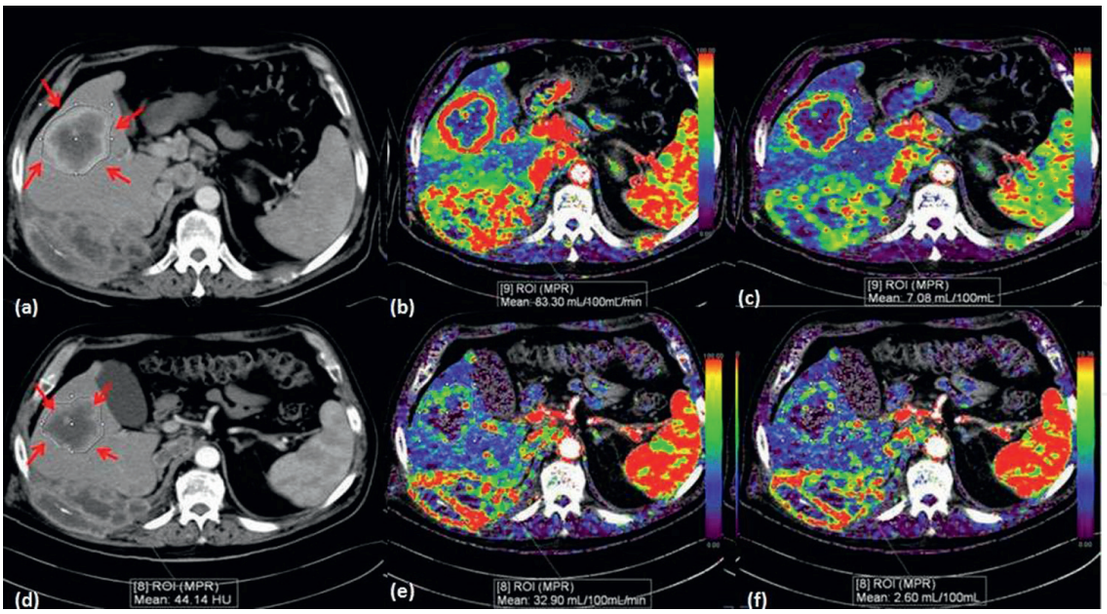

Figure 6.
(a-c): Axial imaging of contrast enhanced and perfusion CT scan of metastatic lesion in right lobe of liver before starting treatment (red arrows). Primary lesion is RCC. Blood flow was 83.3 (±70.48) ml/100 ml/min and blood volume is 7.08 (± 7.23) ml/100 ml. (d-f) Similar patient at 8 days of starting treatment. The blood flow reduced significantly to 32.90 (± 28.88) ml/100 ml/min and blood volume to 2.60 (±3.35) ml/100 ml [17].

early as 1 week after treatment initiation [17]. Treatment response determined through various bio markers can be assessed as early as 12 weeks after initiation of treatment. However, with the help of CT perfusion, this time can be reduced to as early as 1 to 2 weeks. Albeit, the majority of data have been published which have this latent time period of 5 to 10 weeks after initiation of treatment; more research is needed for the reduced time interval in such studies. In a highly metastatic tumor like advanced RCC; the main goal of systemic treatment is cessation of progression of tumor which can prevent the specific morbidity due to pain or hemorrhage. Alice et al. found larger reduction in blood volume in metastatic lesions than in primary lesions. They also stated that early perfusion changes in the metastatic lesions can determine the response of particular therapy (**Figure 6**) [17].

2.2.2 Dual energy CT scan (DECT)

DECT is newer type of CT scanner having two sets of x ray tubes with two different levels of energy which pass through the patient body. Interaction of these two energy x ray beam with the body tissue helps in material identification and quantification [18]. These two datasets at high and low energy helps in additional characterization of kidneys and urinary tract. DECT is also used to evaluate iodine and calcium concentrations and helps to differentiate pathological processes and evaluate internal structure of the lesion [19]. Minimal enhancing hypodense renal tumors can be differentiated from a cyst through iodine quantification which is a biomarker for tumor vascularity. Improved visibility of the lesion reduces the frequency of repeated follow up imaging. It also helps in assessment of tumor response in context of tumor vascularity and necrosis. DECT is capable of reducing the radiation dose by applying virtual non contrast images which eliminates the need for pre contrast imaging.

Papillary RCC has low vascularity and shows homogeneous and low enhancement compared to adjacent renal parenchyma on CT scan making it difficult to differentiate

from more benign lesions like cyst. Iodine specific DECT allows color coded display of iodine inside the renal lesion facilitating differentiation of a non enhancing cyst from enhancing solid lesion easily. Sensitivity of iodine signal compensates for the poor enhancement of lesions such as papillary RCC and allows its accurate characterization [20]. DECT is also useful in evaluation of patients with polycystic kidney diseases (PCKD) with renal mass lesions. PCKD patients also have to undergo multiple follow up for extended period of time; in such cases DECT helps by offering reduced radiation dose. In post treatment (thermal ablation) renal lesions and in residual renal tumors; enhancement assessment (i.e a sign of viability) is difficult on conventional CT scan owing to changes due to ablation and perinephric bleeding. DECT with iodine mapping proves a valuable tool. Park et al. stated the diagnostic performance of DECT for predicting tumor progression in patients treated with Radio frequency ablation with sensitivity 100% and specificity 91.5% [21]. Normalizing iodine ratio with aorta reduces the variability due to different acquisition protocols. Also, iodine ratio was proposed to be an independent predictor for differentiating ccRCC from non ccRCC lesions (**Figure 7**) [22]. Given its better results in differentiating ccRCC from other subtypes, DECT may emerge as a novel technique for choosing patients for surveillance noninvasively.

2.2.3 CT texture analysis (CTTA)

Heterogeneity is the key feature of renal cell carcinoma. CT texture analysis is emerging tool to quantify tissue for heterogeneity in renal cell carcinoma which cannot be perceived through naked eye. It is a technology for automatically extracting quantitative parameters from the images of CT scan. It can extract plenty of features from each image and thus can provide more detailed information than conventional imaging [23]. It can differentiate fat poor AML from RCC [24]. It provides valuable information for grading, staging and predicting the prognosis of tumor. Conventional and contrast enhanced CT scan along with CTTA can non-invasively classify grades of RCC. However, detailed research is needed for better application of such technology.

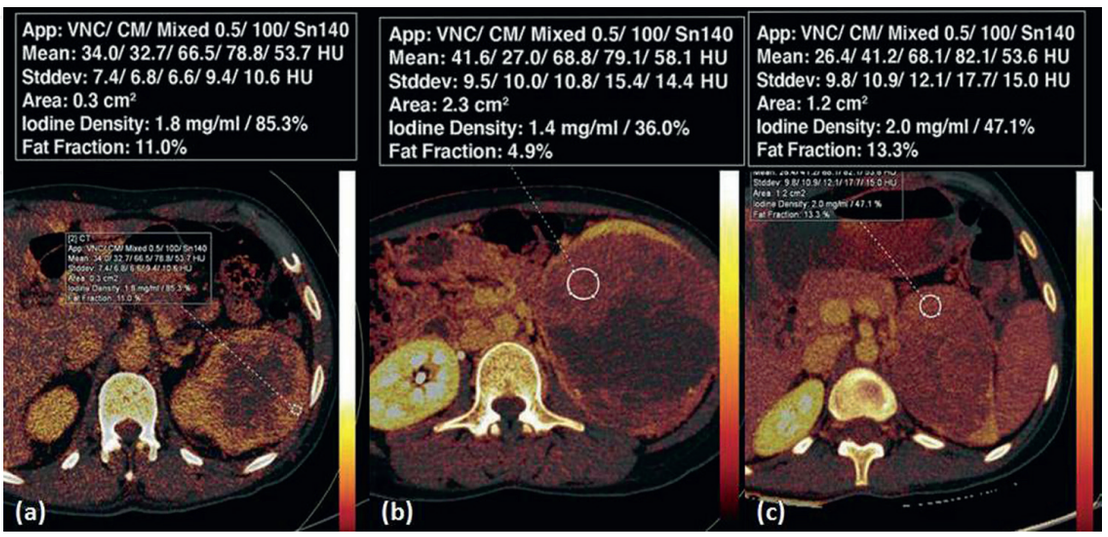

Figure 7.
Axial section of dual energy CT scan (DECT) image showing ccRCC, papillary RCC and Chromophobe RCC in left kidneys of three different patients. Iodine ratio (appears as iodine density in images) is 85.3% in ccRCC, 36% in papillary RCC and 47.1% in Chromophobe RCC. Circles denotes the region of interest in tumors [21].

CTTA avoids the subjective influence of image processing and reduces the errors. Conventional Imaging techniques assess the tumor in context of its size, shape and contrast enhancement which can only define the outline and cannot provide the grade of lesion. Subtle changes within the pixel intensity of the lesion occurring due to tumor heterogeneity in low and high grade RCC are picked up easily in CTTA. CTTA performs comprehensive evaluation of lesions and avoids sampling error.

2.2.4 Fast Fourier transform (FFT) analysis

FFT analysis helps to differentiate various solid non fat containing enhancing renal tumor on CT scan. It uses a quantitative parameter such as tumor attenuation which is extracted from multiphase CT scan. Such features also help in differentiating various renal tumor subtypes. Various parameters gained in FFT analysis are FFT magnitude (measuring diversity of measurements) and complexity index (CI). Entropy of FFP magnitude, entropy of FFP phase and complexity index is calculated for the final result and depending upon them inference is made. On applying FFT analysis to segmented tumor images, the magnitude spectrum of malignant tumors show increased intensity of frequencies whereas it is comparatively lower in benign lesions owing to the level of heterogeneity [25]. The FFT magnitude, FFT phase and CI entropy measurement is able to indentify grade I and IV tumors from the rest of them. However heterogeneity of ccRCC is higher papillary RCC in all grades.

CI index is helpful in differentiating ccRCC from oncocytoma in excretory phase where the CI is higher for ccRCC. Similarly lipid poor AML (lpAML) can be differentiated from oncocytoma with the help of entropy of FFG magnitude which is higher in lpAML than oncocytoma in excretory phase (**Figure 8**). lpAML shows rapid enhancement on corticomedullary phase with washout in excretory phase. Usually, the difference between lpAML and oncocytoma is most prominent in nephrographic and excretory phases. However, no significant differentiation between FFT metrics is noted between Chromophobe RCC and papillary RCC [25].

All the quantitative metrics can provide assessment of tumor heterogeneity to improve the diagnostic confidence. They are not useful alone, a combination of imaging features are a must. FFT metrics have a lower value in benign lesions and it can identify the differences between lpAML and oncocytoma from ccRCC. Additionally 3D analysis can also be possible which can help in regions to be targeted for biopsy.

2.3 MRI

Superior soft tissue contrast of MRI has a sensitivity and specificity in detecting and characterizing RCC comparable to contrast enhanced CT scan. It avoids the risk of ionizing radiation and helps to detect very small enhancing regions within complex cystic lesions. However it is less accessible, costly and takes a longer time for scanning. Along with CT thorax, MRI can be used for pre operative staging of RCC due to its yield of rich morphological and functional information. Renal MRI protocol includes non contrast enhanced T1 and T2 weighted sequences, chemical shift imaging for detection of fat and dynamic contrast enhanced 3D gradient echo sequences for tumoral contrast enhancement. Dynamic imaging can obtain corticomedullary, nephrographic and excretory phases. Coronal 3D fast gradient echo sequence with fat suppression after dynamic series facilitates imaging of renal venous anatomy and inferior vena cava (IVC) for evaluation of thrombus. Subtle enhancement within

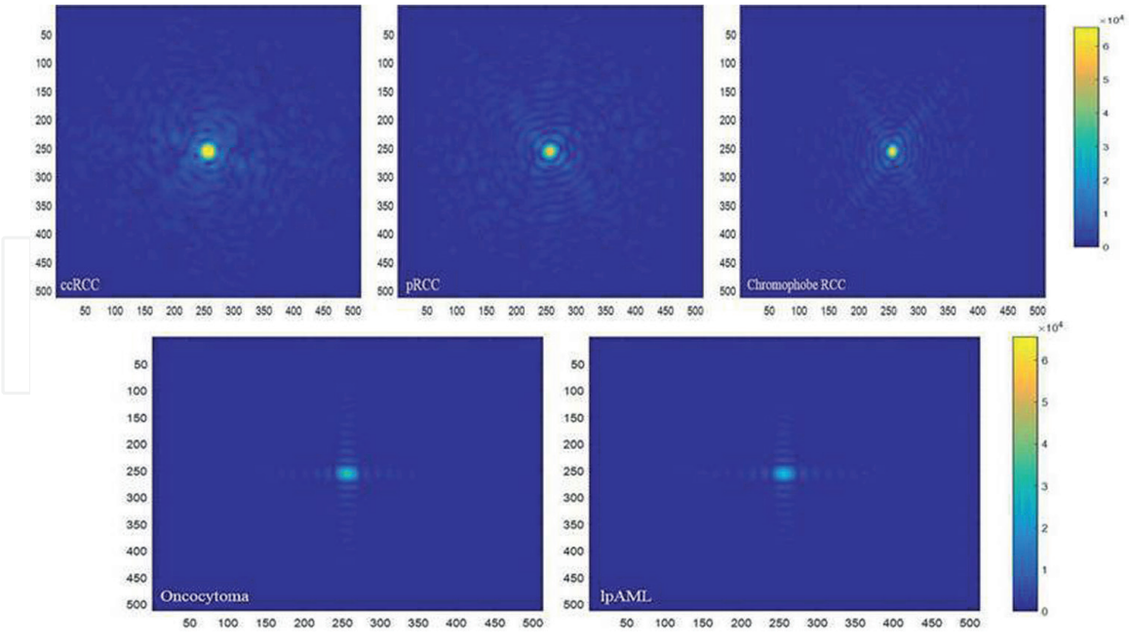

Figure 8.
Magnitude spectrum of malignant renal masses (upper row) and benign renal masses (lower row). High frequency in malignant tumors and lower in benign tumors is noted [25].

the mass lesion can be obtained with 3D gradient echo sequence due to its ability to subtract post and pre contrast images.

Various MRI features in different sequences can help to differentiate various RCC subtypes. Microscopic fat within the AML can be easily demonstrated by India ink artifacts surrounding the macroscopic fat in the mass on in and out of phase images [19]. T2 weighted sequence and post contrast sequence helps to characterize the complexity of cystic or necrotic RCC. ccRCC is seen as iso or hypo intense mass lesion as compared to its adjacent renal parenchyma on pre contrast T1 weighted sequences and appears as heterogeneously hyperintense on T2 weighted sequences. ccRCC show intense heterogeneous enhancement on cortico medullary phase MRI unlike other RCC subtypes. ccRCC also appears as hypointense on T2 weighted sequences on excretory phases with rapid wash out of contrast medium. Papillary RCC is homogeneously low signal intensity on T2 weighted sequences due to intra tumoral hemosiderin and shows low enhancement on contrast enhanced dynamic sequences. ccRCC showed more intensity changes than papillary RCC on corticomedullary and nephrographic phase images (**Figure 9**). However, it has been stated that signal intensity changes on corticomedullary phases are most reliable parameter for differentiating ccRCC and papillary RCC [27]. Various quantitative techniques e.g. arterial spin labeling (ASL), diffusion weighted imaging (DWI) and intra voxel incoherent motion (IVIM) have the ability to assess vascularity within the tumor and can be useful for differentiating between various RCC subgroups and in post treatment surveillance.

2.3.1 MR perfusion

MR perfusion is a technique measuring vascularity (perfusion) of the tissue after the injection of contrast agent. Where multi parametric MRI can assess enhancement of the tissue, MR perfusion gives quantitative parameters. Signal intensity curves are generated and placed against time and post processing is done to achieve perfusion

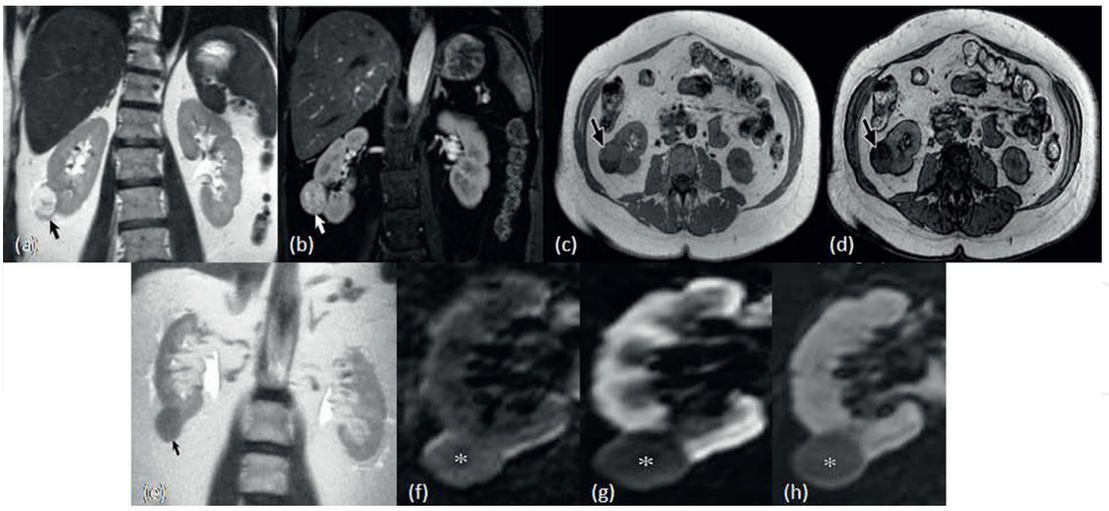

Figure 9.
(a-d) MRI images showing ccRCC. (a) Coronal non fat saturated T2 weighted single shot fast spin echo images showing high signal intensity renal mass arising from right kidney lower pole (black arrow). (b) Coronal contrast enhanced corticomedullary fat saturated T1 weighted gradient recalled echo MR image showing high contrast enhancement within the lesion (white arrow). (c) Axial in phase and (d) axial out of phase non fat saturated T1 weighted gradient recalled echo MR images. Signal dropout is seen on image (d) in comparison to image (c) denoting presence of intra voxel fat. (e-h) MRI images showing papillary RCC. (e) Coronal non fat saturated T2 weighted single shot fast spin echo MR image showing low signal intensity lesion at lower pole of right kidney (black arrow). Coronal T1 weighted fat saturated spoiled gradient recalled echo MR images in pre contrast (f), corticomedullary phase(g) and nephrographic phase (h) of similar lesion (*). Low contrast enhancement is seen in corticomedullary (g) and nephrographic phases (h) [26].

parameters. Tissue perfusion can also be achieved without contrast agent in arterial spin labeling technique (ASL). In ASL, red blood cells (RBCs) are used as endogenous contrast agent that is labeled non invasively with MR gradient and radio frequency and then perfusion within the tissue is calculated with the help of inflow of labeled RBCs. The use of endogenous contrast eliminates the erroneous calculation due to vascular permeability and it can also be done in patients with contraindications to MR contrast agents. However it has low sensitivity in hypo vascular tumors. Tumor grading in RCC can also be done with MR perfusion. Higher grade RCC shows higher perfusion values. In anti cholinergic drug therapy administered for metastatic RCC; changes in vascularity are achieved before the changes in the size of tumor and thus early response assessment can be done [28].

2.3.2 Diffusion weighted MRI

Diffusion weighted (DWI) is a functional imaging which uses random motion of water particles. (Brownian motion). The extent of vascularity within the tissue as well as presence of an intact cell membrane is the features which determine the impedance of diffusion of water molecule. That is quantified by apparent diffusion coefficient (ADC) maps. If the diffusion of water molecule is restricted, ADC value is less e.g. in tumor cells with dysfunctional cell membranes. DWI can detect cellular changes in the tissue before traditional imaging. Zhang H et al. reported the significant difference of ADC with pooled weighted sensitivity 88% and specificity of 72% in a study assessing DWI's ability to differentiate benign from malignant masses [29]. ADC values for ccRCC and oncocytoma are higher compared to papillary RCC due to their high vascularity. However no significant ADC value difference is seen between ccRCC and oncocytoma (**Figure 10**). Conventional ADC value derived from single slice ROI

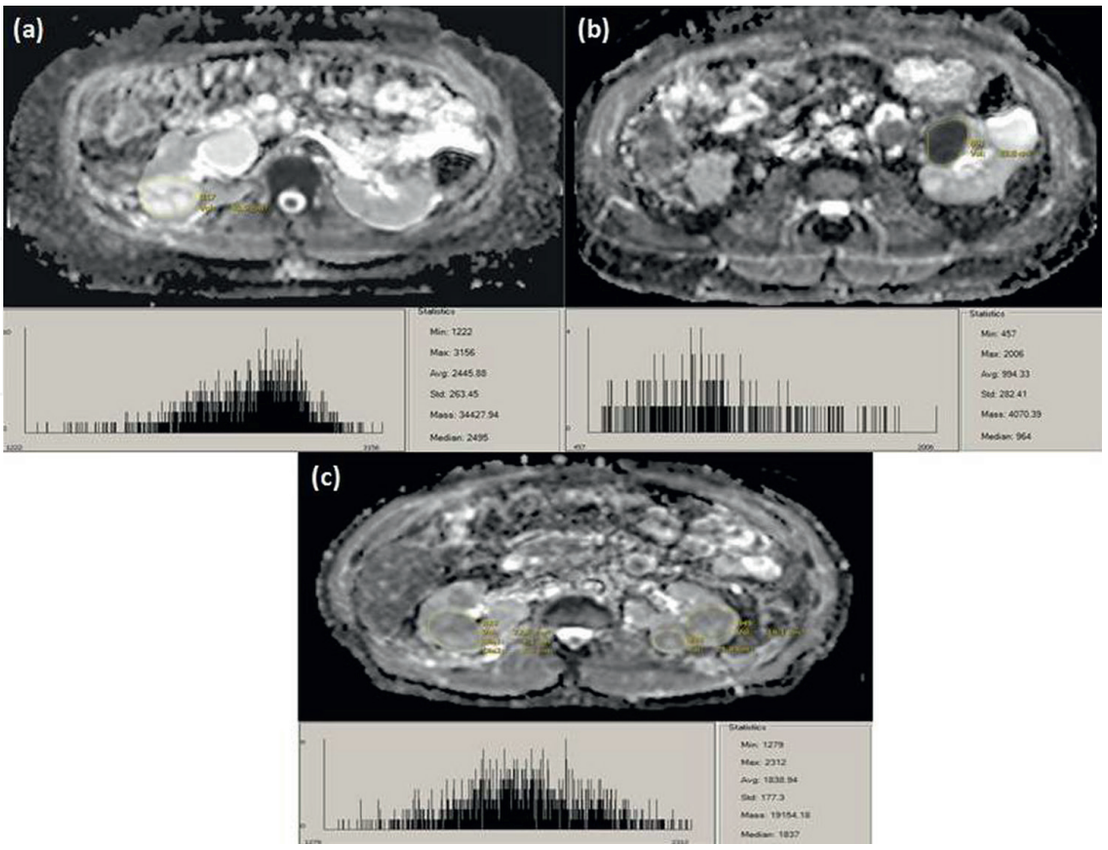

Figure 10.
ADC map and histogram of (a) ccRCC (b) papillary RCC and (c) oncocytoma lesions [30].

is less accurate than near technique where whole lesion analysis is done. Whole lesion analysis helps to evaluate tumor structure and histology more accurately. Distribution of ADC values on histogram helps the radiologist to identify the heterogeneous features of the lesion which are more common to ccRCC or oncocytoma as compared to papillary RCC [30]. Mean ADC values derived from small region of interest (ROI) within the tumor have been studied for differentiation of renal tumors. IVIM and diffusion kurtosis are newer quantitative parameters helping in differentiating renal benign from malignant masses and also help in grading of RCC. IVIM is bi exponential parameter including true as well as pseudo diffusion. It calculates various parameters like diffusivity (D), pseudo diffusion coefficient (D*) and perfusion index (F). A significant variation is noted in diffusion kurtosis parameters between various RCC subtypes and grades [28].

2.3.3 Bold

BOLD is non invasive quick MRI sequence evaluating deoxyhemoglobin level in the kidney. The oxygen tension in kidneys varies with the blood flow as well as with the need for the filtration. Cortex of the kidney is perfused well and is high in oxygen levels whereas medullary region is relatively less perfused and shows low oxygen tension. As a result there is higher production of deoxyhemoglobin. Deoxyhemoglobin has a para magnetic effects and causes rapid photon dephasing. Decreased T2 relaxation time is achieved due to higher amount of deoxyhemoglobin [28]. BOLD MRI has established role in brain imaging. Various renal lesions would show altered perfusion

in the kidney so BOLD MRI can be a helping tool for differentiating benign from malignant renal lesions. However, still renal application of BOLD MRI has to undergo a lot of research.

2.3.4 Proton spectroscopy

Proton spectroscopy (H1MRS) is a newer technology studying various chemical metabolic agents in determining various pathologies. It studies chemical compositions and metabolic processes *in vivo*. The changes in Larmor frequency within the magnetic field is due to differing chemical composition, which is called "chemical shift". As of now the established role of Proton spectroscopy is in imaging of central nervous system, breast and prostatic regions [28]. However Kim et al. studied five patients with biopsy proven RCC and found the difference of lipid and choline as per the tumor grade (**Figure 11**) [31]. However, MR spectroscopy has various limitations also i.e. complexity of acquisition, processing and data interpretation. It has low sensitivity and poor spatial resolution. Hence it can only be used as complementary technique for basic MRI.

2.4 Single photon emission computed tomography (SPECT)

SPECT is used in various clinical settings including living kidney donation, surveillance of renal function during chemotherapy or in patients for endo radiotherapy. An agent ^{99m}Tc-Sestamibi is an established tracer used for cardiac applications which is highly specific for mitochondria. Due to increased amount of mitochondria in the renal oncocytoma lesions, role of ^{99m}Tc-Sestamibi can be rationalized for differentiating various renal masses. ^{99m}Tc-Sestamibi SPECT/CT has sensitivity and specificity

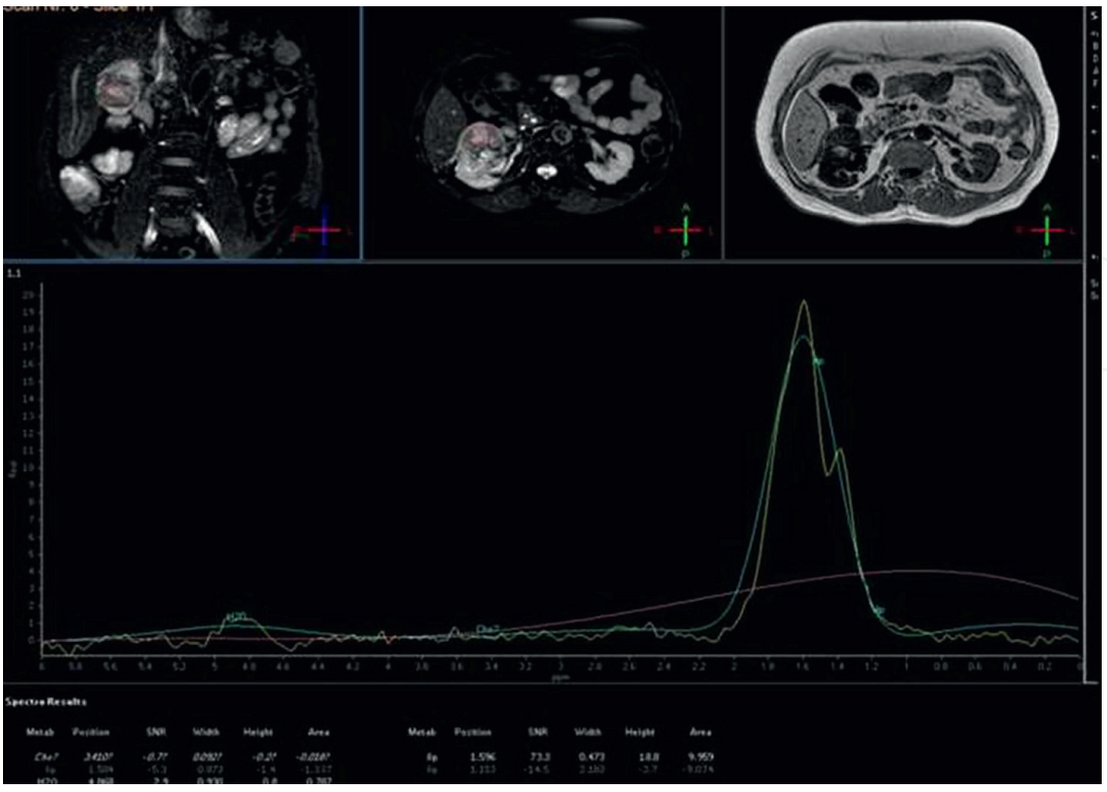

Figure 11.
MR spectroscopy of low grade RCC showing increased lipid lactate peak [28].

of more than 87% to differentiate between renal oncocytoma and oncocytoma/ Chromophobe masses versus RCC. However due to multiple advantages of PET scan, it has overruled the use of SPECT in renal lesions [32].

2.5 Positron emission tomography (PET) scan

Improved absolute quantification, improved spatiotemporal resolution and simultaneous acquisition for attenuation correction and anatomic co-registration are major advantages of PET scan over SPECT [32]. PET scan using fluoro deoxyglucose (FDG) is a functional imaging detecting various malignancies through observation of glucose uptake and rate of glycolysis in neoplastic tissue. It is useful in restaging of RCC and to detect metastatic lesions. However, it is less satisfactory in detection of primary diseases. The major excretion route for FDG is kidneys and thus an unfavorable back ground activity is seen which hinders the results making it less preferable for detection of primary renal lesions. Papillary RCC shows high avidity for FDG. ccRCC variant shows limited FDG uptake and so, non FDG molecular agents need to be evaluated for their use in other subtypes of RCC [19]. Higher FDG intake in to tumor thrombus compared to bland thrombus indicates another use of FDG in patients with RCC. Wang HY et al. reported overall sensitivity and specificity of FDG PET as 79% and 90% in identification of extrarenal lesions respectively [33]. Alongi et al. stated the sensitivity of FDG imaging to be 74% and specificity 80% and also stated that FDG positive cases resulted in significantly lower (69%) five year survival rates compared to FDG negative cases (19%) [34]. FDG PET can detect larger lesions compared to smaller ones and also can detect higher grade masses more easily than low grade masses. Various other PET scan agents are also identified and some of them are superior to FDG in various aspects.

^{18}F labeled anti-1-amino-3-[^{18}F]-flurocyclobutane-1-carboxylic acid (anti-^{18}F-FACBC) is useful in differentiating papillary RCC from ccRCC. PSMA targeting radio tracer agent ^{18}F-DCFPyL provides highly specific use in ccRCC. ^{68}Ga labeled PSMA PET shows higher sensitivity for detection of metastasis in RCC. ^{18}F-PSMA-1007 also has been applied to test its capability for surveillance in metastatic RCC.

^{18}F-Fluoromisonidazole (FMISO) PET is used for evaluation of tumors which are hypoxic and show poor response to targeted therapy. ^{18}F-Fluorothymidine (FLT) PET can differentiate inflammation from tumors more accurately than ^{18}F-FDG. ^{11}C acetate PET can be used in primary renal lesions. ^{18}F-fluoroethylcholine PET is used for evaluation of metastatic RCC. ^{68} Ga-PSMA PET is very effectively being used in patients with Carcinoma Prostate, it is most widely investigated tracer for RCC also [35]. However, the role of PET scan in detection of primary renal lesions is not significant. Hence, advanced modalities like PET CT and PET MRI are being studied for their role in RCC.

2.5.1 PET/CT scan

Physiological excretion of ^{18}FDG via the kidneys makes it difficult to evaluate renal lesions with the background of high FDG activity. However FDG PET can reveal various differences in metabolic activity based on histological subtypes of RCC. To acquire advantages of both these imaging technologies, hybrid advance imaging combining PET scan with CT scan has been evolved. The physiological advantages of PET scan are combined with anatomical images of CT scan and the superimposed image can correlate the high activity regions with the anatomical site making diagnosis

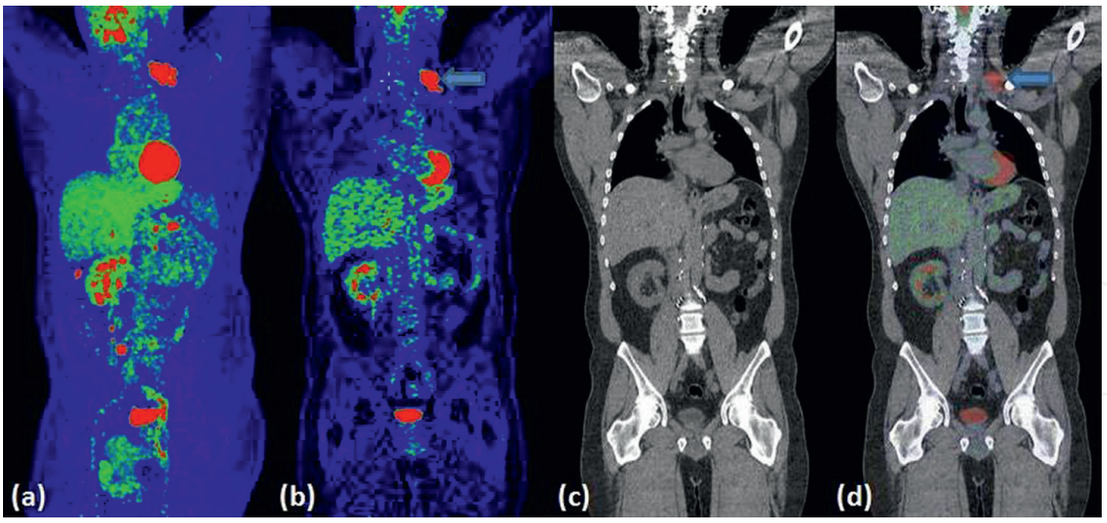

Figure 12.
(a) FDG PET MIP image of patient with RCC (b) coronal PET image (c) coronal CT scan image and (d) PET/CT scan fusion image of similar patient. Left supra clavicular regional metastatic lymph nodes are clearly visualized in PET/CT scan (blue arrow) which was not seen on CT scan (c) [19].

more accurate. Hybrid PET CT scanners eliminate the disadvantage of two separate scanners for PET and CT scans and combine both the modalities in single scanner (**Figure 12**). That results in improved anatomical demarcation along with improved diagnosis of post operative scar tissue, surgical clips and relations with surrounding organs [35]. Many authors have proposed that a predictor called standardized uptake value (SUV) in PET scan is a significant predictor for Fuhrman's grading of RCC [35]. A SUV value cutoff of 3.0 can differentiate between low and high grade ccRCC with sensitivity 89% and specificity 87%. ccRCC shows higher SUV than chromophobe RCC. However, Chromophobe RCC is very difficult to differentiate from oncocytoma lesions even with hybrid PET CT scan.

Quantitative measurement like SUV in FDG PET/CT can play a role in prediction of the tumor progression by objective estimation of biological behavior of tumor. Namura et al. evaluated the impact of SUVmax on survival in advanced RCC patients. They concluded high SUVmax to correlate with poor prognosis [36]. High grade tumor show intense tracer uptake and a higher SUV. SUVmax exceeding 10 was associated with the highest rate of mortality [37]. As high grade primary RCC with high SUVmax has high chances of occult metastasis. Thus FDG PET/CT helps to predict the extrarenal disease. Sensitivity and specificity of FDG PET was ranging from 63–75% and 90–100% respectively when compared to CECT scan in detection of extra renal pelvis [35]. PET/CT scan is less accurate to assess metastatic lesions measuring less than 5 mm in lungs and liver. However, for detection of metastatic lesions in bone and adrenal glands, FDG PET/CT scan is very sensitive. FDG PET/CT scan showed high predictive value in surveillance of targeted therapy.

2.5.2 Pet/MRI

PET/MRI combines the advantages of anatomical localization and attenuation correction map for quantification of PET images through concurrent acquisition. It uses the same reference frame which helps to overlay the *in vivo* independent structural, functional and metabolic features of the tumor. Most widely used method for assessment of therapy response is Response Evaluation Criteria in Solid Tumors

(RECIST v1.1). It is dependent on one dimension measurements on imaging for tumor diameter and RECIST v1.1 may not be able to detect early responses on imaging. Here, advanced technologies like PET/MRI can play a useful role. Various obstacles have been experienced in diagnosis made with PET/MRI like, different imaging sequences have to be transformed in to voxel wise correspondence for spatial heterogeneity, to eliminate or correct acquisition artifacts due to movement and image parameter drift and visual assessment of data. This issue can be overcome with computer extracted parameter from radiological images which is known as radiomics [38]. Radiomics captures the image texture through quantification of changes in signal intensity within the tumor which can be due to early treatment response. These features can be missed visually.

3. Summary

Multi modality imaging is advised for pre treatment diagnosis, discrimination of various subtypes and post treatment surveillance of RCC. Conventional imaging techniques at times falls short for proper diagnostic information. Advanced hybrid techniques are being evaluated a lot these days and they will provide a lot more information in future. Detailed study is being executed in various modalities which will be helpful for better characterization of renal cell carcinoma and its subtypes.

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