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Imaging of Renal Cell Carcinoma: State of the Art and Recent Advances

Key Words

Renal carcinoma · Ultrasonography · Magnetic resonance imaging · Computed tomography · Positron emission tomography

Abstract

Background and Aim: Renal cell carcinoma (RCC) is the 13th most common cancer worldwide and accounts for 4% of all adult malignancies. Herein the state of the art and recent advances in cross-sectional radiological imaging applied to RCC are reviewed, including ultrasonography, computed tomography, magnetic resonance imaging, and positron emission tomography. **Methods:** Literature search of peer-reviewed papers published by October 2010. **Results:** In front of more conventional and widespread imaging tools, such as ultrasonography and computed tomography, an array of newer and attractive radiological modalities are under investigation and show promise to improve our ability to noninvasively detect renal tumors and its recurrences, accurately assess the extent of the disease, and reliably evaluate treatment response, particularly in the era of antiangiogenetic therapy. **Conclusions:** Recent major advances in radiological imaging techniques have considerably improved our ability to diagnose, stage and follow-up RCC. Further studies are needed to evaluate the potential of most recent and still investigational imaging tools.

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Introduction

Renal cell carcinoma (RCC) is the 13th most common cancer worldwide and accounts for 4% of all adult malignancies in the USA [1]. About 30% of patients present with metastatic disease (mRCC) at diagnosis, and about 30% of all other patients will develop metastases subsequently. The mortality is as high as about 25%, the highest among urological tumors.

The implementation of modern cross-sectional imaging modalities in clinical practice has drastically changed the diagnosis, treatment, and surveillance of RCC. In particular, the modern imaging techniques caused an impressive increase in the number of small, incidentally discovered renal tumors allowing early detection and treatment and, consequently, improving long-term survival for RCC [2–4].

Major goals expected from imaging techniques consist of a correct differential diagnosis between benign and malignant renal lesions, an early diagnosis, and precise depiction of the extent of the disease that can be directly related to the prognosis by means of the TNM classification and staging system (table 1) [5]. In addition, an emerging purpose of cross-sectional imaging is represented by the assessment of clinical response to targeted therapy of advanced RCC.

Table 1. TNM classification system of RCC [UICC, 2002]

Description	
<i>Classification</i>	
T classification	
T1	confined to kidney, T1a <4 cm, T1b <7 cm
T2	confined to kidney, >7 cm
T3	confined to Gerota's fascia
T3a	extending to ipsilateral adrenal or perirenal/peripelvic fat
T3b	extending to renal vein or IVC below diaphragm
T3c	extending to IVC above diaphragm
T4	extending beyond Gerota's fascia
Tx	primary tumour cannot be assessed
N classification	
N0	no regional lymph node metastasis
N1	metastasis in a single regional lymph node
N2	metastasis in more than one regional lymph node
Nx	regional lymph nodes cannot be assessed
M classification	
M0	no distant metastasis
M1	distant metastasis
Mx	distant metastasis cannot be assessed
<i>TNM stages</i>	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1, T2, T3 N1 M0
Stage IV	T4 N0, N1 M0
	any T N2 M0
	any T any N M1

In this article, we aimed to review the state of the art and recent advances in cross-sectional radiological imaging applied to RCC, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET).

Ultrasonography

Diagnosis of Primary Tumor

Grey-Scale and Doppler US. Nowadays, US examination is often the first imaging technique used to evaluate patients with suspected RCC and allowing its initial diagnosis. Because of its widespread diffusion, US has determined a huge increase in incidental and early detection of RCC [4]. The US study of the size, attenuation features, and vascular distribution of a renal mass may reportedly suggest the pathologic nature of the lesion and may add useful diagnostic information to that of

other imaging techniques. Furthermore, Doppler US allows for noninvasive assessment of vascular flow signals from tumor neovascularity. Thus, vascular flow detected by color Doppler US was reported to be strongly suggestive of conventional clear cell histology [6]. Kitamura et al. [7] reported that color Doppler US had a diagnostic accuracy similar to dynamic CT in most patients with renal solid tumors and that the color flow pattern was different among RCC subtypes. These observations suggest the use of color Doppler US as an additional tool in patients whose tumor is poorly attenuated or in those with contraindications for contrast medium and radiation [7]. The use of US has been also centered on the differentiation between RCC and angiomyolipoma, although there is an overlap in the appearance of these two tumors [8–10]. Combined grey-scale and color and/or power Doppler US findings have been shown to be highly sensitive for distinguishing atypical cysts from solid lesions [11]. Concerning the ability to detect small renal tumors, the US accuracy remains lower when compared to CT despite the recent technical improvement of grey-scale imaging. Jamis-Dow et al. [12], in their study of 205 masses (92% <3 cm) with pathological correlation, showed that US depicted less and bigger renal masses than CT; the sensitivity of US for tumors that are ≤3 cm in diameter was only 67%. Color/power Doppler US appears to improve the diagnostic performance for small tumors [13]. US shows further deficiencies in the field of RCC imaging such as identification of complex cystic lesions requiring surgery, venous tumor thrombus extension and metastatic lesions [14]. These shortcomings are partly due to the well-known inherent limitations of US imaging such as reliance on operator experience and on patient's constitution.

Tissue Harmonic and Contrast-Enhanced US. Among US techniques under investigation, tissue harmonic imaging (usually by using the second harmonic) offers several advantages such as improved axial and lateral resolution, less reverberation and side-lobe artefacts and increased contrast resolution. Tissue harmonic imaging is now routinely available on modern ultrasound machines and has been found to be useful for a more precise depiction of renal cystic lesions [15]. More recently, the sonographic imaging of intratumoral macrovasculature and microvasculature has achieved more detail by using the contrast-enhanced US (CEUS) [16, 17]. CEUS is a rapidly evolving technique using US-specific intravenous contrast agents in the form of 'microbubble' [18]. Microbubbles are not subjected to extravascular diffusion and enable detection of blood vessels with a diameter as small as

Fig. 1. Complicated benign cystic renal mass (stable at 12-month follow-up) in a 66-year-old woman. **a** Oblique US image obtained in the contrast-specific mode before contrast agent administration shows a large cystic renal mass. Thin endocystic septae (arrows) are almost completely suppressed by the software. **b** Oblique contrast-enhanced US image obtained in the contrast-specific mode during the nephrographic phase with the same technical param-

eters used in **a**. The endocystic septae appear strongly hyperechoic due to the presence of microbubbles (arrows). Expanding endocystic nodules are not seen. This cyst was classified as a Bosniak II lesion. **c** Transverse contrast-enhanced CT image of the right kidney obtained during the nephrographic phase shows a large renal cyst (c) with perceived thin enhancing septae (arrows) (Bosniak category II lesion). From Ascenti et al. [24], with permission.

40 μ m [19]. The safety and the stability of microbubbles have been increased, together with the contrast resolution and contrast-to-tissue ratio in the image of more recent CEUS equipments [20]. Dynamic CEUS (DCE-US) is a functional imaging technique that, combining Doppler US and a microbubble contrast agent, allows detecting microvessels and quantitatively assessing solid tumor perfusion [21]. Ascenti et al. [17, 22] observed that contrast agent did not increase the diagnostic accuracy of power Doppler in the differential diagnosis of hyperechoic renal lesions; conversely, it can be advantageous for the characterization of suspected pseudotumors and complex cysts. Accordingly, Mazziotti et al. [23] reported a complete concordance of CEUS with CT and MRI in the characterization of all 24 pseudotumors considered dubious at conventional and power Doppler US. A complete concordance between CEUS and CT in the differentiation of surgical and nonsurgical complex cysts was reported in another study [24] (fig. 1). Conversely, Clevert et al. [25] reported a tendency for CEUS to upgrade the classification of cysts when compared with CT, and suggested its use as additional examination to CT in uncertain cases. Pulse inversion harmonic imaging (PIHI), coded harmonic imaging (CHA) and agent detection imaging (ADI) are other techniques of

grey-scale harmonic CEUS developed by various US equipment manufacturers [26, 27]. In particular, ADI is a microbubble-specific harmonic CEUS modality designed for the optimal detection of signals from the contrast agent with using high mechanical index technique. ADI has been reported to be able to detect intratumoral anechoic areas typical of RCC better than conventional US [28].

Staging

Results of published studies on staging accuracy of US examination are conflicting, likely depending on patients population, study design, technological differences in the imaging machinery and, finally, radiologist's experience. Early publications reported a staging accuracy of US inferior to that of spiral CT [29]. Conversely, other authors concluded that duplex Doppler US was at least as accurate as CT scanning in the staging of RCC [30, 31].

Second-harmonic CEUS with a second-generation contrast agent has been reported as effective in improving the sonographic visualization of tumoral pseudocapsule (85.7% sensitivity vs. 21% of US) [32]. The presence of an intact pseudocapsule is a specific sign of lack of perinephric fat invasion and represents key information in some centers to plan nephron-sparing surgery [33]. Jiang

et al. [34] claimed that CEUS features of RCC are very dependent on the size of the tumor, thus the frequency of pseudocapsule sign was significantly higher in tumors of 2.1–5 cm than in those of <2 cm and >5 cm. ADI has also been reported to be able to detect the presence of a tumor pseudocapsule in 82% of cases compared to 18% of grey-scale US [28].

Tumor Thrombus Detection

RCC has the propensity to invade and propagate along major venous structures and US examination is also used for the evaluation of the extent of a tumor thrombus in the inferior vena cava (IVC). Many authors reported that the overall accuracy of Doppler US was higher than, or at least similar to CT scan or MRI in detecting tumor extension into renal veins and IVC [30, 31, 35–37]. However, the sensitivity of this diagnostic tool seems depending on the position of the thrombus. While the sensitivity can reach the 100% if the tumor thrombus involves the intrahepatic portion of the IVC, it drops to 68% if the thrombus lies below the level of the insertion of the hepatic veins [38]. Depending on the patient's constitution, it has been reported that the IVC is not completely visualized in 43.5% of the cases [38].

Intraoperative US

US is also applied as imaging guidance during surgery and minimally invasive diagnostic and therapeutic procedures. US remains the only available intraoperative technique helping surgeon to ensure nephron-sparing surgery. Intraoperative US was able to identify 24 lesions deep in the renal parenchyma (18 cystic and 6 solid) in 17 patients treated with partial nephrectomy by Walther et al. [39]. Choyke et al. [40] performed intraoperative US with high-frequency transducers (7 MHz) and color Doppler after all visible renal lesions have been removed and identified additional tumors in 25% of patients with hereditary RCC.

Intraoperative real-time transesophageal US monitoring of the cranial extent of a thrombus into the suprahepatic IVC and the right atrium has been proved to be minimally invasive and to provide reliable dynamic information that assists to place a venous clamp, to remove completely the thrombus, and to decrease the risk of its migration [41–43].

US-Guided Minimally Invasive Procedures

Since its first description [44], a few reports have emphasized the utility of US-guided biopsy of renal masses [45–48]. Unlike CT, US allows real-time visualization of

the needle as it enters the mass so that it can be directed to solid components in the lesion allowing a better core specimen [47].

Targeting and monitoring the treatment of small renal tumors with radiofrequency ablation (RFA) or extracorporeal high-intensity focused ultrasound (HIFU) is another emerging field of application of real-time US [49–52]. Although most centers utilize some combination of CT, MRI and US to accurately place the probe for RFA, Lyrdal et al. [50] reported the feasibility of RFA of small renal tumors using US guidance only. Hoeffel et al. [51], using CT or MRI as the reference standard, reported that CEUS had a high specificity for the early diagnosis of residual tumor after renal RFA.

Antiangiogenetic Therapy Assessment

With the advent of antiangiogenetic therapy in clinical practice as the most effective treatment for mRCC patients [53], the number of targeted agents is growing fast thus making it urgently necessary to find surrogate markers of tumor response [54]. Molecular imaging methods targeting at highly specific markers of angiogenesis are under development for measurement of tumor vascularity and angiogenesis [55]. Thus, changes in blood flow may precede morphologic tumor shrinkage during vascular-targeted therapy, and their noninvasive appraisal may serve as a means of monitoring early tumor response.

While molecular methods will require years of testing before validation in humans, there is a renewed interest in the capability of DCE-US to assess tumor response during the antiangiogenetic therapy. DCE-US has been investigated in some studies on mRCC patients treated with tyrosine kinase inhibitors [56–58]. Lamuraglia et al. [57] found that, in 30 mRCC patients treated with sorafenib or placebo, the combination of a decrease in contrast uptake exceeding 10% and stability or a decrease in tumor volume allowed to discriminate good from poor responders at 3 weeks. Lassau et al. [58] observed that, in 38 mRCC patients treated with sunitinib, the ratio between DCE-US values at baseline and day 15 correlated with response in 5 of 7 functional parameters. Robust correlations were found between some functional US parameters and survival outcomes in these studies [57, 58]. Hopefully, the results of an ongoing large French national study will define the role of DCE-US in monitoring antiangiogenetic therapy [59].

Fig. 2. Stage T1N0M0 RCC in the left kidney of a 51-year-old man. **a** Contrast-enhanced axial CT image obtained during the corticomedullary phase shows a 5.1-cm heterogeneously enhancing mass in the left kidney that was confirmed as RCC T1N0M0 at pathology after partial nephrectomy. **b** Coronal CT image of the same tumor.

Computed Tomography

Diagnosis of Primary Tumor

CT represents the gold standard of cross-sectional imaging for the diagnosis, staging and surveillance of RCC, especially after the modern development in CT scanner technology, first of all the introduction of the helical scanners in the early 1990s (fig. 2) [14, 60, 61]. Recently, multi-detector-row CT (MDCT) scanners have been developed that use multiple rows of detectors with a widened beam shape able to obtain a true volume scan and ultra-thin sections (<0.5 mm) with minimal time for motion artefact. Currently, 16-row MDCT are commonly available, but MDCT technology is progressing rapidly, with 4–40-detector-row scanners being replaced by 64–128-row scanners, and 256-row being in development [62].

In patients with RCC, MDCT allows the possibility to scan in multiple phases of enhancement and to obtain high-resolution multiplanar and three-dimensional (3D) images of the affected kidney with superb anatomic details thanks to near-isotropic voxels, thin-slice collimation and high speed of acquisition [60, 63, 64]. Today, the triphasic (unenhanced, corticomedullary or arterial phase, and nephrographic phase) MDCT and the 3D reconstructions provide the surgeon with comprehensive and reliable information of utmost importance for an accurate preoperative planning, especially in case of nephron-sparing surgery [5, 65–68]. 3D-MDCT has radically reduced the need for diagnostic catheter angiography that remains indicated for specific therapeutic purposes [69].

A major task of CT is the detection of small renal masses. Narrow slice thickness decreases partial-volume effects, allowing the detection of smaller lesions and characterization of solid and cystic structures [62].

In particular, nephrographic-phase scans have been reported to enable greater detection and better characterization of small renal masses than corticomedullary-phase scans [70]. Another relevant task of CT is also to find imaging features able to reliably differentiate between different subtypes of RCC. In the published studies, some characteristics such as enhancement pattern, presence or absence of calcification and cystic degeneration, tumor-spreading pattern and vascularity are overlapping among the subtypes of RCC, although a combination of them may help predicting a specific tumor subtype [71–79]. The degree of enhancement has been reported to be a unique CT finding for the differentiation of conventional clear cell RCC from nonconventional subtypes [71–73]. Jinzaki et al. [74] reported that clear cell RCC showed a peak attenuation value in the cortical nephrographic phase of >100 HU, whereas for other subtypes the values were <100 HU. The possibility to reliably distinguish papillary RCC from conventional RCC has been claimed [75, 76]. Reportedly, papillary RCC could be actually ruled out with a tumor-to-parenchyma enhancement ratio $\geq 25\%$ [75]. It remains very difficult to distinguish between RCC and oncocytoma [73–75], although 4-phase MDCT appears of help in this regard [80]. A homogeneous enhancement and prolonged enhancement pattern have been observed to be statistically significant predictors for differentiating angiomyolipoma with minimal fat from RCC [79]. The sensitivity of MDCT to distinguish between simple cyst and a hypovascular RCC, such as a papillary tumor, is affected by the shortcoming of the so-called ‘pseudoenhancement’ that is an increase in attenuation greater than 10 HU, the commonly accepted upper limit for simple cysts [81].

Of note, CT remains also a useful imaging technique to guide a core biopsy of undefined renal lesions. This procedure has been more accepted in the recent literature [82].

Staging

Although most studies claimed a staging accuracy of up to 90% with CT [83, 84], results on the ability of CT to reliably assess local tumor stage and perinephric fat invasion are conflicting. Catalano et al. [83] demonstrated complete consistency of tumor size estimates with surgical pathology in 40 MDCT examinations of RCC patients; the detection of perinephric fat invasion on 1-mm primary reconstructions achieved 95% accuracy. In a prospective series of 82 RCCs with histopathologic correlation, Hallscheidt et al. [85] observed that MDCT offers similar accuracy in tumor staging as MRI. Several other studies reported a low sensitivity of CT in detecting fat invasion or pseudocapsules, with better results obtained using MRI [86–89]. Türkvtan et al. [89] reported in their review of MDCT in 57 RCC patients that 86% of them with tumor confined within the renal capsule were correctly staged, but one T1 and four T2 tumors were overstaged because the imaging evidence of perinephric spread was ascribed on pathology to previous inflammation, organizing perinephric hematoma, and perinephric fat necrosis. The comparison of the accuracy of CT with that of modern CEUS in the depiction of pseudocapsules deserves further investigation.

Ipsilateral adrenal involvement from RCC is found in up to 10% of patients. The detection of a normal adrenal gland at MDCT in patients with RCC has been associated with 100% negative predictive value for metastasis [90, 91].

The prediction of lymph nodes metastasis remains a limitation of CT because it is based essentially on node size criterion [5, 89]. CT has a false-negative rate of about 10%, and false-positive rate still ranges from 3 to 43% [5].

Good to excellent agreement between MDCT and surgical pathology has been reported for M staging [89]. Contrast-enhanced MDCT is more accurate than chest radiography to detect pulmonary metastasis early and is very sensitive for abdominal metastasis or retroperitoneal recurrences [90].

Tumor Thrombus Detection

In the past MRI has been always considered the best technique for staging venous tumor involvement of RCC [64, 92, 93]. However, recent advances in MDCT technology, with its multiplanar reconstruction capability and

appropriate timing of the contrast-enhanced acquisitions, have increased accuracy in the delineation of the superior extent of the tumor thrombus to the equivalent of MRI, with the advantages of widespread availability, shorter examination time, and lower cost [14, 85, 94–96]. Türkvtan et al. [89] observed that 16-row MDCT correctly identified and localized the extension of the tumor thrombus in 10/10 patients, although in one patient invasion of the IVC wall was not detected. IVC wall invasion remains hard to be accurately diagnosed with all types of cross-sectional imaging.

Antiangiogenic Therapy Assessment

Based on RECIST criteria, change of tumor size at CT represents the standard criterion to assess response to systemic therapy against RCC [97]. However, MDCT still has some limitations in tumor size measure such as reproducibility in tumors that are irregular or with diffuse invasion; furthermore, the reduction in size of primary RCC after vascular-targeted therapy is usually small and slow [5, 54, 98].

Recently, in order to improve response assessment in patients with mRCC treated with tyrosine kinase inhibitors, the volumetric mean tumor attenuation of target lesions at contrast-enhanced MDCT has been proposed as an alternative potential response criterion [99]. Han et al. [100] also observed in these patients that higher pretreatment values of tumor enhancement on contrast-enhanced MDCT is a predictor of better response to antiangiogenic therapy with either sunitinib or sorafenib. On the other hand, an increase in contrast enhancement during the treatment may be associated with disease progression [99].

Dynamic contrast-enhanced CT (DCE-CT) is a functional perfusion CT that using perfusion software and focusing on a selected area of interest can provide estimations of some tissue perfusion parameters. This technique has so far been evaluated in other solid tumors treated with antiangiogenic drugs and also deserves evaluation in mRCC patients [54, 101].

Magnetic Resonance Imaging

Diagnosis of Primary Tumor

No need for contrast medium or use of less nephrotoxic contrast material, delivering no radiation to the patient, high inherent contrast among different soft tissues and imaging from any of the three orthogonal anatomical planes remain the most important advantages of MRI.

MRI is still the imaging modality of choice in case of contrast allergy, functional renal impairment and pregnancy.

Compared to CT, in spite of the possibility of single-breath-hold fast spin-echo imaging sequences ('fast MRI') and new moving tabletop technology, MRI still requires longer examination times and has higher cost, lower availability and inferior capacity to detect lung metastasis and to provide whole-body images [5]. MRI images have better contrast resolution but decreased spatial resolution than CT. As for CT, in evaluating renal masses current MRI technique needs administration of contrast medium such as gadolinium that has been associated with nephrogenic systemic fibrosis in patients with reduced renal function.

MRI of the kidney is now used routinely with a torso phased-array surface coil. The much higher signal-to-noise ratio of a phased-array coil allows the acquisition of thinner sections with higher in-plane spatial resolution and reduced imaging times [64]. The imaging time is significantly reduced with high field-strength MRI (≥ 1.0 T) and modern software and can be further lowered with 'parallel imaging' techniques, a major advance in MR technology which uses the spatial information from a phased-array multicoil to reduce the number of signals needed for a given spatial resolution [102].

To find imaging features able to differentiate between different subtypes of RCC is a task of MRI as well. By using a chemical shift MRI technique, it is possible to identify clear cell RCC with a 42–82% sensitivity and 94–100% specificity by detecting the presence of intracytoplasmic vacuoles containing lipids [103–105]. It has been reported that on T_2 -weighted sequence papillary tumors exhibited low signal intensity with homogeneous pattern and delayed enhancement while clear cell RCC was hyperintense and heterogeneous [76, 106–110]. Pedrosa et al. [105] reported an overall sensitivity and specificity of MRI to predict the histologic subtype, using a feature analysis, of 92 and 83% for clear cell RCC, and 80 and 94% for papillary RCC, respectively. By using the 1.5 T 3D DCE-MRI protocol, Sun et al. [76] found that different patterns of enhancement allowed differentiation of the three most common RCC subtypes (clear cell, papillary and chromophobe) with high accuracy.

In patients with indeterminate renal masses or complex cystic lesions, especially when contrast-enhanced CT is equivocal, dynamic contrast-enhanced MRI (DCE-MRI) can be of help [61]. A 15% increase in signal intensity on post-contrast enhanced images is usually considered significant with 100% sensitivity and 94% specificity

in helping to distinguish between cysts and solid renal masses [64, 111]. However, due to better contrast resolution in MRI, cystic lesions can be upgraded using the Bosniak classification system. It is expected that the newer MRI techniques under development, such as arterial spin labeling (ASL) and diffusion-weighted imaging (DWI), would allow characterizing renal lesions by assessing the blood flow without using contrast media [112].

Staging

MRI shares with CT the major cause of RCC staging errors, the difficulty to correctly identify perinephric tumoral spread because of limitations of the imaging technique: inability to detect microscopic invasion of the perinephric fat, difficulty in distinguishing inflammatory changes from tumor infiltration, and insensitivity in differentiating small collateral blood vessels from tumor extension in the lymphatics [113]. However, MRI is considered the most effective imaging modality for showing the tumor pseudocapsule, with a reported 61–93% sensitivity [114–118]. Pseudocapsule appears on T_2 -weighted imaging as a rim of hypointensity interposed between hyperintense tumor and normal renal parenchyma [115, 116]. In case of hypointense tumors, such as some papillary tumors, the detection of the pseudocapsule may be less accurate. The accuracy of MRI for assessing perinephric fat has been reported to be 62–91%, depending on the sequences used [113, 118, 119].

Similarly to CT scan, the specificity for metastatic lymphadenopathy in RCC patient is low at MRI, with poor agreement for N-staging with pathology [113]. A low sensitivity due to an inability to show microscopic metastasis on MRI has been reported in many studies [120, 121]. The introduction of iron oxide-based superparamagnetic nanoparticles as novel contrast agents that are taken up specifically by lymph nodes is expected to increase the accuracy of MRI in nodal staging [122].

MRI has been shown to be highly sensitive and specific in diagnosing bone metastasis, more than bone scintigraphy [90]. MRI is also more sensitive than CT for the detection of small cerebral metastases that can be treated by surgery or focal radiation therapy [5]. Conversely, lung metastasis cannot be reliably excluded on MRI and requires evaluation with CT.

Tumor Thrombus Detection

MRI, with its multiplanar capability, is a reliable method for the preoperative assessment of venous tumor involvement. MRI has been shown to be superior to earlier generation CT for venous thrombus diagnosis and stag-

Fig. 3. Monitoring response to antiangiogenic therapy with arterial spin labeling (ASL) MRI. Coronal T₂-weighted (a) and perfusion images (b) in a patient with prior right nephrectomy for RCC and local recurrence in the nephrectomy bed (box). ASL MRI revealed high levels of perfusion within the mass, similar to those observed in the renal cortex on the left kidney (arrow). Coronal T₂-weighted (c) and perfusion images (d) of the same patient obtained 8 days after initiation of antiangiogenic therapy with sorafenib and bevacizumab revealed a minimal decrease in the size of the lesion but a marked decrease in tumor vascularity. From Pedrosa et al. [112], with permission.

ing and has replaced venacavography as the method of first choice, with reported accuracies of ranging between 65 and 100% [64, 92–94, 113, 123–125]. Actually, as noted above, modern MDCT technology can be considered comparable to MRI in accurately depicting venous thrombosis [14].

Antiangiogenic Therapy Assessment

The ability of MRI, either with (DCE-MRI) or without exogenous contrast media, to measure variables related to tumor vascularity and microvessel permeability has been investigated in order to assess the response to the antiangiogenic drugs [126–129]. The lack of ionizing radiation and the excellent sensitivity of MRI to detect small amounts of intravenous contrast are important compared with DCE-CT [112]. Studies showed an association of a high K^{trans} (volume transfer constant between the blood plasma and extravascular extracellular space) at baseline and a large decline in K^{trans} after treatment with a prolonged progression-free survival [126, 127].

Although DCE-MRI is very suited to evaluate tumor vascularity and improvements are expected with the de-

velopment of intravascular contrast agents, it is still restricted to clinical trials because of poor standardization, methodologic challenges, limited sensitivity and concerns related to potential harmful effects of MRI contrast agents.

Thus, novel MRI techniques for assessment of tumor vascularization and response to anticancer therapy are under investigation such as ASL, DWI, breath-hold proton spectroscopy (MRS), and blood oxygen level-dependent (BOLD) imaging [112]. ASL-MRI showed promise as an early predictor of clinical response to antiangiogenic therapies: patients with progressive disease within 4 months on treatment with a tyrosine kinase inhibitor ($n = 4$) had a nonsignificant increase in tumor blood flow at 1 month, whereas patients with stable disease or partial response at 4 months ($n = 6$) had a significant decrease in tumor blood flow at 1 month ($p = 0.02$) [130]. If validated, ASL-MRI may play an important role in determining the early effectiveness of new antiangiogenic drugs in RCC patients with the advantage of no use of contrast medium (fig. 3) [54, 112].

Positron Emission Tomography

Diagnosis of Primary Tumor

The pilot study by Wahl et al. [131] first demonstrated the feasibility and the potential utility of imaging renal cancers with 2-deoxy-2- ^{18}F -fluoro-D-glucose (FDG) and whole-body positron emission tomography (PET) scanning. However, FDG-PET showed insufficient accuracy in the characterization of renal masses, and in term of specificity and, especially, of sensitivity did not offer any advantage over standard imaging modality such as MDCT [132]. Among studies there is a broad range of reported accuracy rate of FDG-PET imaging for RCC, likely due to the differences in stage and grade of tumors evaluated and to the fact that FDG-PET may diagnose high-grade tumors more efficiently than low-grade disease [133–136]. Kang et al. [134] reported 60% sensitivity and 100% specificity of PET for primary RCC tumors, versus 91.7% sensitivity and 100% specificity of CT. Ramdave et al. [136] reported better results with a 94% accuracy of both FDG-PET and CT, but CT results were not blinded during interpretation of FDG-PET.

More recent radiotracers showed promise in diagnosing and characterising RCC. By using PET with a iodine-124-labelled antibody chimeric G250 (124I-cG250) reacting against carbonic anhydrase-IX ('immuno-PET'), Divgi et al. [137] reported 94% sensitivity and 100% specificity for clear cell RCC, suggesting the use of this antibody for distinguishing clear cell RCC from other tumor subtypes [14]. Other markers are under investigation, such as ^{18}F -fluoromisonidazole (FMISO), a noninvasive tumor marker of tissue hypoxia, and ^{18}F -fluorothymidine, a tracer that mirrors cellular proliferation [138, 139].

Staging

Whole-body FDG-PET scan has been reported to be an efficient tool for the detection of distant metastasis and local recurrence in RCC patients, especially when combined with MDCT (PET/CT) [132, 134]. However, while some authors reported promising results with high sensitivity rates and accuracy rates equal or even superior to those of conventional cross-sectional imaging [136, 140, 141], others did not confirm these findings [134, 142, 143].

Brouwers et al. [140] claimed that FDG-PET and CT performed equally well detecting 70 and 69% of the metastases, respectively, in a series of 20 patients with metastatic RCC after nephrectomy. Safaei et al. [141] reported 84% accuracy of FDG-PET for staging 36 patients with

advanced RCC; based on 25 biopsy-proved lesions, sensitivity and specificity were 82 and 88%, respectively.

Majhail et al. [142] reported only 63.6% (21/33) sensitivity of FDG-PET for the detection of distant metastases with 100% specificity and positive predictive value. Restaging a series of 25 RCC patients, Jadvar et al. [143] displayed that PET was discordant with CT in 7 patients (28%); interestingly, PET was falsely negative in 6 of these patients and did not demonstrate hypermetabolism in pulmonary (n = 4), mediastinal (n = 2), adrenal (n = 1) and lytic osseous (n = 2) metastatic lesions. In their largest series, Kang et al. [134] reported that FDG-PET was less sensitive than CT in the detection of retroperitoneal lymph nodes and/or renal bed recurrence (75 vs. 92.6%), lung metastases (75 vs. 91.1%) and bony metastases (77.3 vs. 93.8% of CT + bone scan); in total, PET detected 115/162 metastatic lesions (66.9%).

FDG-PET showed higher diagnostic sensitivity and accuracy (100 and 100%, respectively) to detect bone metastases in patients with RCC when compared with bone scan (77.5 and 59.6%, respectively) [144]. Nevertheless, correlation with cross-sectional imaging is recommended because of a significant rate of false-negative results for both techniques [5, 90].

FDG-PET/CT has the advantage to detect the metabolic activity of local recurrence of RCC that is not influenced by factors that jeopardize diagnosis of local recurrence with CT, such as migration of the adjacent normal organs into the renal fossa, postoperative scarring and artefacts from surgical clips [145]. In addition, FDG-PET/CT can examine the whole body in one procedure without the risk of renal functional damage or allergy to contrast agents. Park et al. [145] demonstrated that, for the surveillance of high-risk RCC, FDG-PET/CT had results as good as conventional methods and not influenced by the Fuhrman grade or the histological subtype. FDG-PET/CT had 89.5% sensitivity, 83.3% specificity, and 85.7% accuracy in detecting recurrence or metastasis.

Tumor Thrombus Assessment

Only sporadic reports reported data on the use of FDG-PET for the diagnosis of RCC tumor thrombosis [146, 147]. It has been reported that PET/CT may be helpful in the diagnosis of occult tumor thrombosis and its differentiation from venous thromboembolism (fig. 4) [148].

Antiangiogenetic Therapy Assessment

Lyrdal et al. [149] evaluated the early effects of sorafenib in 10 mRCC patients by using FDG-PET combined with CT. After 1–2 months, the mean glucose uptake in soft

Fig. 4. **a** Coronal FDG-PET images, coronal CT, and coronal PET/CT fusion images show abnormal FDG uptake in a right renal mass. **b** Transaxial PET, CT, and fusion images, as well as coronal PET-CT fusion image, show tumor extension into the right renal vein and inferior vena cava. From Schöder et al. [152], with permission.

lesions decreased to 71% (32–108%); in these lesions the sum of the diameters measured by CT decreased to 80% (57–94%) of the initial value according to RECIST criteria. FDG-PET has the advantage, compared with RECIST evaluation, to be not limited to soft lesions; thus, it was

possible to detect a decrease in glucose uptake to 82% (53–101%) in skeletal lesions as well [149]. Vercellino et al. [150] assessed 11 patients with mRCC who completed at least two cycles of sunitinib and found that early FDG-PET/CT findings, after one cycle of sunitinib, were con-

sistent with later CT results in 9 of 11 assessable patients; interestingly, of the other 2 patients that showed a metabolic partial response on PET and stable disease on CT, one achieved a partial response later on, suggesting that metabolic early changes are an indication of sunitinib activity [150]. Based on these preliminary findings to be confirmed in larger studies, patients with mRCC whose metastases present with uptake of FDG might be better monitored by FDG-PET/CT. Furthermore, the novel tracers for PET such as radioactive water ($H_2^{15}O$) and radiolabeled targeted agents ($[^{89}Zr]$ bevacizumab and $[^{18}F]$ Sunitinib) should be investigated for their role as surrogate markers of response to antiangiogenic treatments [54, 151].

Conclusions

Real-time and color Doppler US represent the most frequently used imaging tools for the initial diagnosis in patients with suspected RCC and offer valuable information on tumor vascularity and major venous vascular involvement. Although it shows promise, further improvements are necessary in order to support the widespread use of CEUS in clinical practice. Recent developments, such as harmonic imaging and ADI, may further increase the role of US in the evaluation of RCC patients.

The gold standard for characterization, staging and surveillance of RCC is still the CT. Recent technological advances such as three-phase helical MDCT and 3D rendering have already achieved a widespread use and represents powerful tool for preoperative planning in the era of minimally invasive treatments.

Although great progresses have been achieved in the MRI technique, at present this imaging modality is mainly used as a complementary problem-solving tool in selected cases of undefined renal lesions and suspected perinephric tumor spread or recurrence. Newer MRI techniques, such as ASL and DWI, have the potential to characterize renal lesions without using contrast media and deserve further investigation.

FDG-PET/CT is emerging as a useful tool in evaluating patients with suspected metastatic disease, but it has modest sensibility in the diagnosis and staging of RCC and, presently, can only complement conventional cross-sectional imaging modalities in equivocal cases. The newer radiotracers are expected to increase the accuracy of PET imaging in diagnosis and staging of RCC.

In the wake of targeted therapies for advanced RCC, functional imaging modalities show promise as surrogate biomarkers of response but larger prospective series are needed in order to validate early results and standardize the techniques.

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