

REVIEW

Metastatic renal cell cancer

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Abstract

Targeted therapy is the treatment of choice in patients with metastatic renal cell cancer (mRCC) at most institutions although a combination of cytokine therapy and targeted therapy still is being investigated. Morphological size-based criteria (RECIST) has failed in monitoring the effect of targeted therapy in patients with mRCC, as successful therapy often does not result in a decrease in tumour size. Modifications of size-based criteria and criteria based on computed tomography (CT) contrast enhancement has been introduced. Different imaging modalities that rely on characteristics other than size such as dynamic contrast-enhanced (DCE) ultrasonography, DCE CT, DCE magnetic resonance imaging (MRI), diffusion-weighted MRI, positron emission tomography and texture analysis seem to contribute with prognostic information, even at baseline scans, and can predict tumour response early after initiating therapy. No new standard for the imaging follow-up of targeted therapy in mRCC has been established.

Keywords: *Targeted therapy; renal cell carcinoma; mRCC.*

Introduction

Renal cell carcinoma (RCC) accounts for 2% of all adult malignancies, and represents 90% of renal tumours, of which 75% are clear-cell carcinomas^[1,2]. Approximately 30% of patients present with metastatic disease at the time of diagnosis, and approximately 30% of patients with initially localized disease ultimately develop metastatic disease. Untreated, the 5-year survival rate for metastatic RCC (mRCC) is 2%, and the median survival is approximately 8 months^[2,3].

As a result of the increased use of diagnostic imaging performed for other indications, an increasing number of RCCs are found incidentally, so the size of the tumour and the stage at presentation are currently decreasing^[2,4].

RCC is remarkably resistant to conventional chemotherapy and radiotherapy. Before the era of targeted therapies, cytokine therapy consisting of interleukin-2 and interferon were standard therapies for mRCC. However, the development of targeted agents has changed the treatment of choice for patients with mRCC^[1,3].

Objective response assessment is important to describe the effect of anticancer treatment. For years, it was generally accepted that a decrease in tumour size based on morphological imaging correlated with treatment effect. However, targeted therapies frequently cause disease

stabilization rather than a substantial regression in tumour size, and early necrosis induced by targeted therapies may even simulate progressive disease^[5].

To reduce costs and drug-induced toxicities from the growing number of targeted agents, there is a need for imaging techniques that can predict tumour response or resistance, optimally in the pretreatment phase or as early as possible after initiating therapy.

Morphological imaging

Since 2000, the Response Evaluation Criteria in Solid Tumours (RECIST) has become the most commonly used international guideline for evaluation of treatment response in solid tumours^[6]. RECIST is a one-dimensional measurement of the sum of the longest diameters of target lesions. Often the initial response of targeted therapy in mRCC is associated with tumour stabilization and morphological changes rather than a shrinkage in tumour size (Fig. 1), and the best response according to RECIST may be postponed until several months after initial drug administration^[7]. Using RECIST in the follow-up of patients with mRCC receiving sunitinib, stable disease at first evaluation is not predictive for progressive disease or partial response at a later

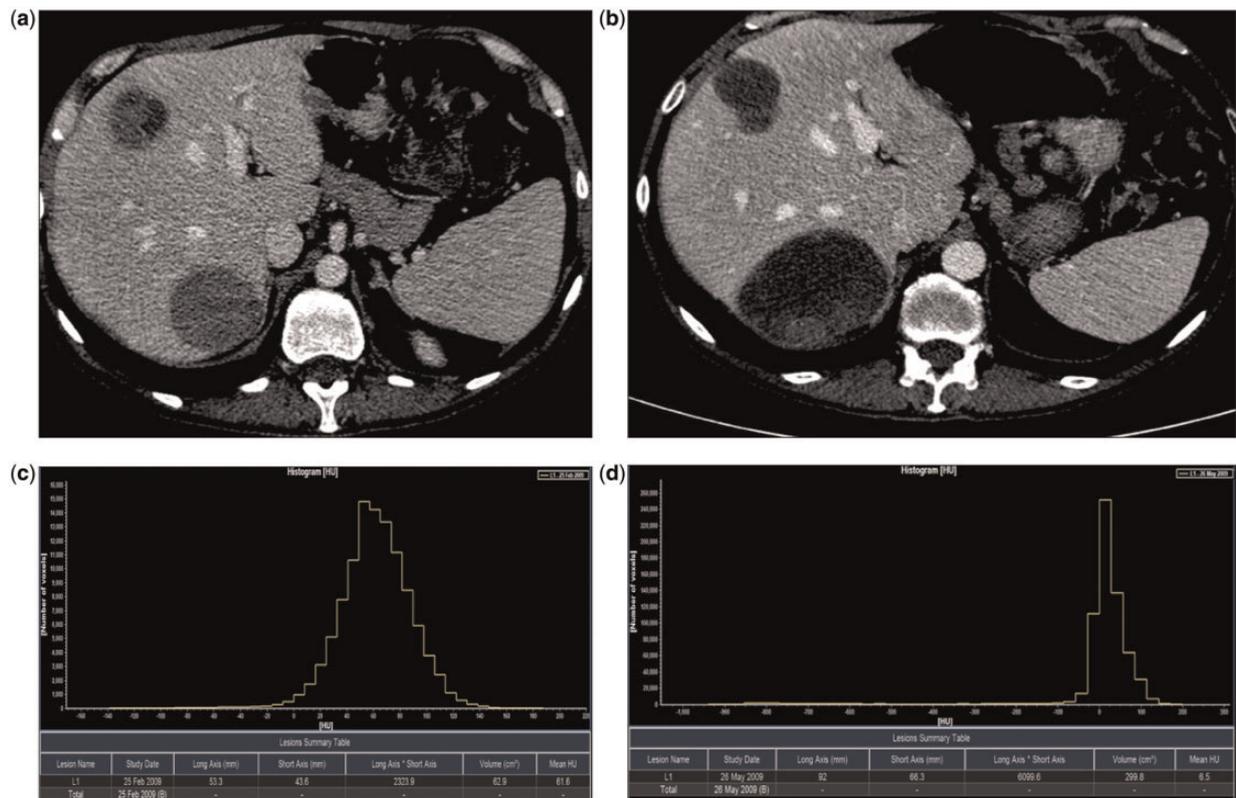


Figure 1 Liver metastases in a patient with renal cell cancer (a) before and (b) after sunitinib therapy. Semi-automatic lesion segmentation can be performed and quantitative data derived, (c) before and (d) after. The diameters, volume, mean attenuation of the whole lesion and histograms showing the distribution of voxels with a certain attenuation value can be displayed. In the liver lesion shown, it is obvious that the diameters and the volume of the lesion increased. The mean attenuation of the lesion decreased and the histogram changed dramatically. Instead of size measurements and mean attenuation, alterations in the histogram may be a more sensitive method for assessing treatment effect.

evaluation^[8]. In another study on patients with mRCC treated with sunitinib using progression-free survival as the end point, Thiam et al.^[9] reported that a threshold of at least 10% decrease in the sum of the longest diameters was more accurate in predicting partial response than the threshold of 30% as defined in RECIST. Krabejewski et al.^[10] verified in a recent retrospective study that a 10% reduction in the sum of the longest diameters on the first follow-up computed tomography (CT) scan is a predictor of a positive outcome in patients with mRCC receiving targeted therapy. So it seems that when using lesion size for treatment assessment, a threshold of -10% instead of -30% is better at distinguishing responders from non-responders among patients with mRCC receiving targeted therapy.

RCC tumours are highly perfused, and tumour enhancement on contrast-enhanced CT is correlated with microvessel density (a pathologic marker representing tumour vascularity in RCC)^[11] and tumour angiogenesis^[12]. A decrease in tumour density is associated with response to therapy and the development of necrotic areas^[13]. Therefore, application of contrast-enhanced CT according to the Choi criteria^[14] seems attractive.

The Choi criteria prescribe partial response as more than 10% decrease in one-dimensional tumour size or a 15% decrease in tumour attenuation on contrast-enhanced CT. Progressive disease is defined as more than 10% increase in size while not meeting the partial response criteria for change in enhancement.

At first evaluation for patients with mRCC treated with targeted therapy, assessment using the Choi criteria has been shown to have better predictive value for progression-free survival (PFS) and overall survival (OS) than RECIST^[8,15]. However, it has also been shown that a 10% reduction in the sum of largest diameters is a better predictor than the Choi criteria^[10]. Using modified Choi criteria (a decrease in size >10% and a decrease in tumour attenuation >15%), Nathan et al.^[16] showed that such estimation is better correlated to time to progression than the Choi criteria. When contrast attenuation-based criteria are applied, standardization of the contrast phases is crucial. Enhancement is not only influenced by the contrast media phase, but also by cardiac output, distribution volume, injection rate, volume and concentration of the contrast medium and the acquisition parameters of the scanner. Different scanners may

give different results despite using the same acquisition parameter settings and the same contrast media policy.

In a retrospective study assessing tumour enhancement on arterial phase scans, Han et al.^[17] found that pretreatment tumour enhancement was associated with treatment outcomes after targeted therapy in patients with mRCC. It has also been demonstrated that an increase in contrast enhancement may be associated with progressive disease^[18].

Smith et al.^[18] introduced the size and attenuation CT (SACT) criteria, and found in a retrospective study of patients with mRCC receiving targeted therapy that these criteria gave better prognostic information than the Choi criteria or the RECIST criteria. In the SACT criteria, three-dimensional volumetric attenuation assessment was combined with tumour size. Due to the fact that central necrosis is often seen in responders, the same authors incorporated this in morphology, attenuation, size and structure (MASS) criteria^[19], and found that the assessment of mRCC target lesions on contrast-enhanced CT is more accurate using MASS criteria than SACT criteria, modified Choi criteria and RECIST criteria. Although promising, the MASS criteria need to be prospectively validated in larger patient populations.

Although semi-automatic tools make it easy to segment and measure the volume of a lesion and calculate the mean attenuation of a whole lesion (SACT criteria), there is as yet no evidence that three-dimensional measurements are better than two-dimensional measurements. However, as seen in Fig. 1, a histogram showing the distribution of voxels according to Hounsfield unit values can also be derived from three-dimensional measurements. Such histograms show that the tumour does have heterogeneous attenuations and that the histogram and the heterogeneity may change due to treatment. Using CT texture analysis, Goh et al.^[20] showed that lesion values of entropy decreased and lesion values of uniformity increased after two cycles of tyrosine kinase inhibitors in mRCC. Furthermore, it was shown that baseline entropy and uniformity correlated with time to progression, suggesting that baseline heterogeneity may additionally present predictive information.

The lung is the most common site for metastases from RCC. Monitoring the effect of treatment of such lesions is a challenge for the aforementioned criteria (Fig. 2), and therefore some criteria definitions omit lung metastases. Lung metastasis in mRCC quite often cavitate and contain air.

Functional imaging approach

RCC and its metastases are highly vascular, and targeted therapies use several cellular pathways to interfere with angiogenesis and tumour vasculature. Therefore, imaging

modalities that can assess the vascularity and the changes in vascularity of such tumours are of great interest^[11,12].

Dynamic contrast-enhanced CT

Dynamic contrast-enhanced (DCE) CT measures the temporal changes in tissue enhancement after administration of iodinated contrast media. The contrast enhancement is linearly proportional to the iodine concentration. The method can estimate parameters of first-pass perfusion as well as permeability. A positive correlation between microvessel density and the DCE CT measures of relative blood flow and relative blood volume has been shown^[17,21,22], and it was found that tumour blood flow and tumour blood volume decreased in mRCC metastases after one cycle of treatment with targeted drugs^[23]. In our experience, functional parameters such as blood flow and blood volume are superior to measurements of diameter, volume and contrast enhancement (Fig. 3) when early response evaluation is considered using PFS or OS as end points. Ng et al.^[24] demonstrated that tumour blood flow at baseline was inversely correlated to PFS in patients with mRCC receiving interferon treatment. However, Fournier et al.^[23] found that DCE CT baseline figures may predict the response of targeted therapy in mRCC. This discrepancy may rely on different treatment regimens. In our experience, a high baseline blood flow or blood volume is predictive of favourable outcome when PFS or OS are end points. Just as in contrast-enhanced CT, standardization of protocols is necessary when DCE CT is considered^[25] before the discipline can be introduced into daily routine, because the results obtained depend on the acquisition parameters and the contrast media policy. However, DCE CT can easily be combined with contrast-enhanced CT of the thorax, abdomen and pelvis, which is the traditional discipline in the routine imaging procedure.

Magnetic resonance imaging

DCE magnetic resonance imaging (MRI) can also be applied to measure the temporal changes in enhancement after administration of gadolinium-based contrast media. The technique is more complicated than DCE CT, and the relationship between contrast concentration and signal intensity is more complex and non-linear. However, the contrast medium kinetic is similar to iodinated contrast media in CT. Traditionally, parameters such as K_{trans} are used in DCE MRI, and not first-pass parameters as in CT. K_{trans} reflects several aspects of the biological response of the tumour to targeted therapy. Flaherty et al.^[26] has shown that K_{trans} decreased significantly after sorafenib treatment in patients with mRCC, and that high K_{trans} values before treatment were associated with improved PFS. Hahn et al.^[27] also showed a correlation between high baseline K_{trans} values and improved PFS. As with DCE CT, DCE MRI techniques also need standardization before they can be applied in

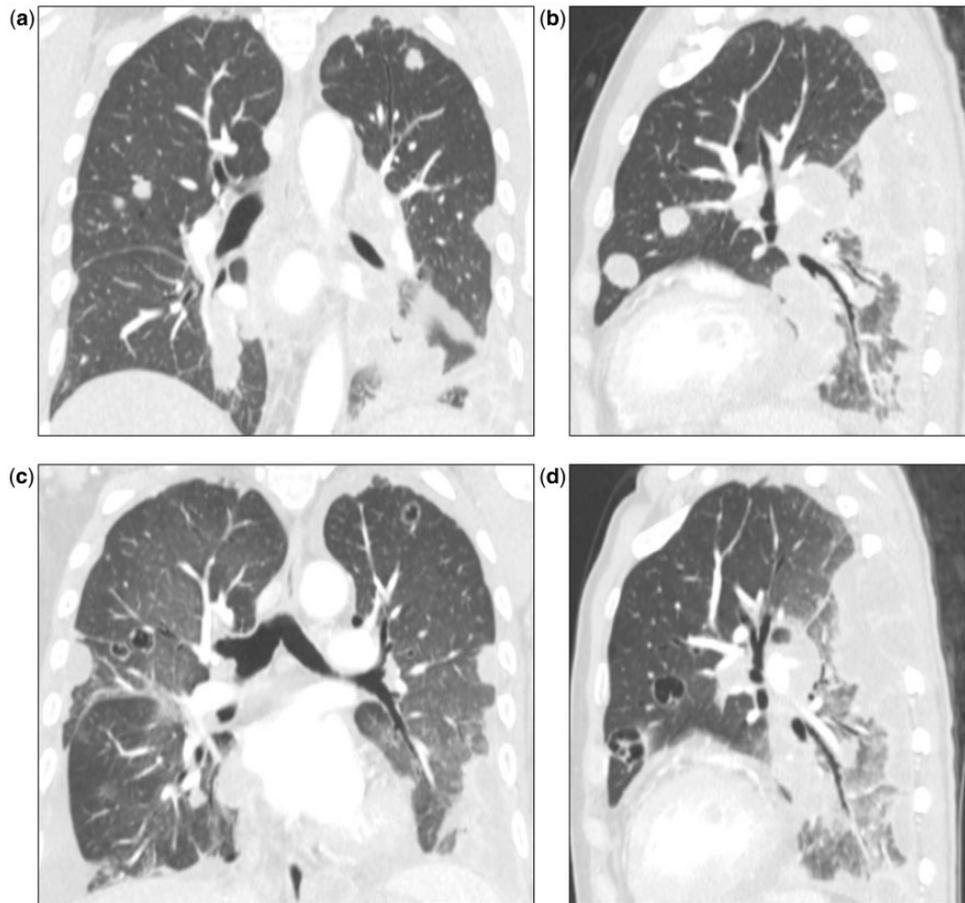


Figure 2 Lung metastases in a patient with renal cell carcinoma (a, b) before and (c, d) after targeted therapy. The most common site for metastases from RCC is the lung. Monitoring the effect of treatment on such lesions is a challenge, and some treatment evaluation criteria even omit lung metastases as target lesions.

daily routine, as the parameters obtained depend on acquisition protocols as well as on consensus of the kinetic model to be used.

Diffusion-weighted (DW) MRI is based on the water diffusion properties of tissues. The technique does not need administration of contrast media. In general, single-shot echo planar imaging sequences based on gradient-echo techniques are used. The strength and duration of the applied diffusion sensitizing gradients is indicated by their b -value. The apparent diffusion coefficient (ADC) can then be calculated. Tissues with high cellularity or decreased interstitial spaces show restricted diffusion that results in low ADC values compared with tissues with low cellularity or increased interstitial space. DW MRI has been shown to be helpful in the characterization of renal tumours^[28]. DW MRI may have the potential to monitor the effect of targeted therapy in mRCC. In a pilot study of 10 patients with mRCC, Desai et al.^[29] showed that, compared with baseline, the ADC values increased 3 days after sunitinib treatment followed by a decrease to baseline levels at day 10. Further studies and larger patient groups are needed to evaluate if the early changes observed by

DW MRI can be clinically useful for evaluating the treatment effect of targeted therapy in mRCC.

DCE ultrasonography

DCE ultrasonography is able to visualize tumour vascularization. Most often a bolus injection of microbubbles is used. The microbubbles serve as a blood pool agent, and time–intensity curve analysis can be applied. Time to peak intensity and area under the curve, which correlate with blood flow and blood volume, can be quantified. In patients with mRCC treated with sunitinib, Laussau et al.^[30] showed that DCE ultrasonography parameters at baseline and on day 15 were significantly different between responders and non-responders. DCE ultrasonography does have a major drawback as the discipline cannot evaluate lesions localized to the lung, the most common site of metastases in RCC.

Positron emission tomography

In positron emission tomography (PET), radiopharmaceuticals are administered. These tracers contain

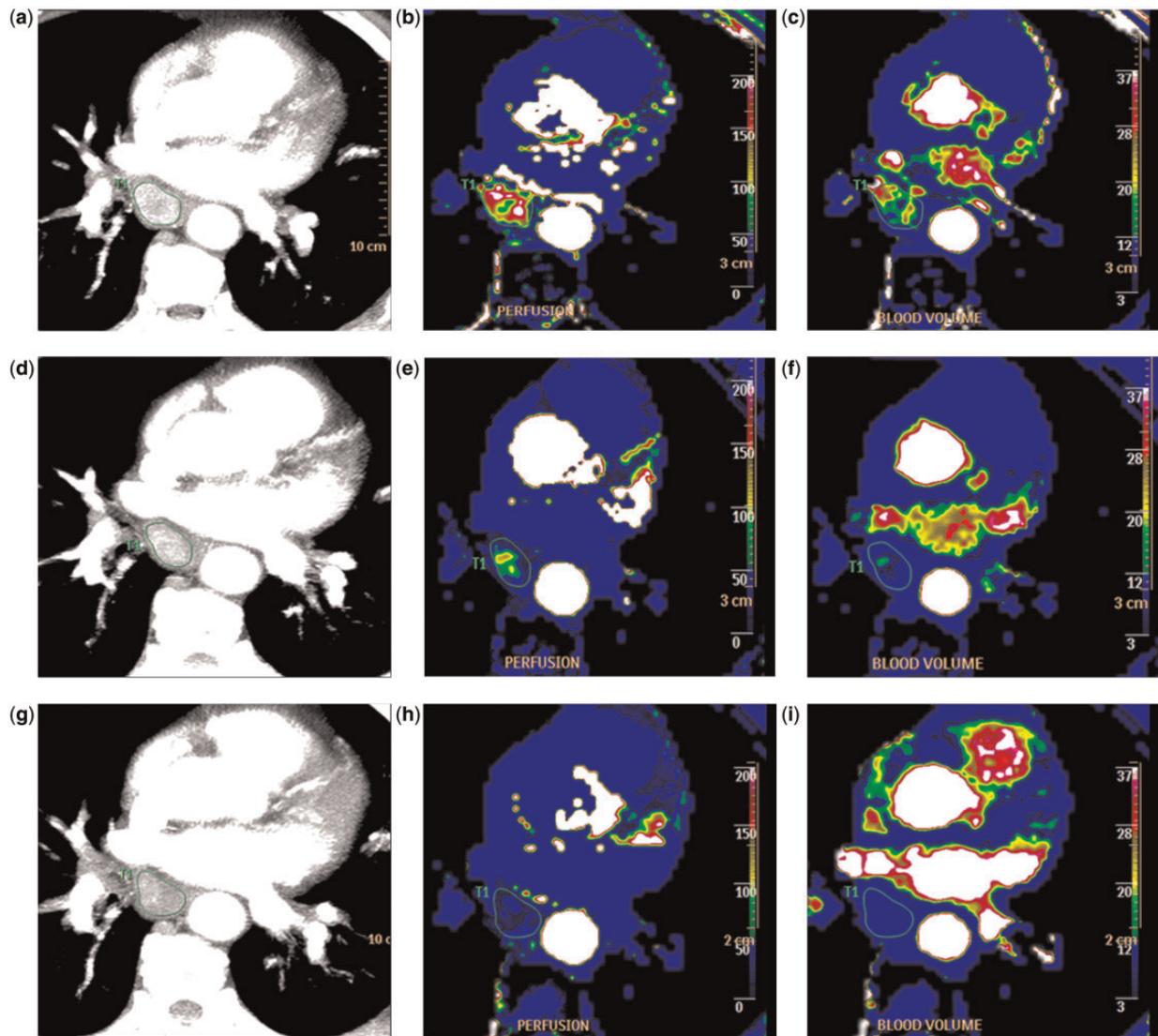


Figure 3 A metastatic lymph node in the mediastinum was a target lesion in this patient with mRCC. In the first column, maximum intensity projection illustrations are presented, the next column illustrates perfusion maps and the third column shows blood volume estimations. The upper row represents baseline, the second row at week 5 and the third row at week 10 after targeted therapy. Visually, the diameter and the volume of the lesion remain unchanged, whereas the enhancement decreased over time. The perfusion and the blood volume also decreased (the green and red colours) within the lesion. Perfusion and blood volume seem to be predictive parameters much earlier than morphological criteria in response evaluation of targeted therapy in mRCC. Quantitative measurements can also be applied.

positrons that decay by the release of photons to produce tomographic images in the PET scanner. The most commonly used radiotracer in oncology is [^{18}F]fluorodeoxyglucose (FDG), an analogue of glucose. Malignant tumour cells metabolize glucose and its analogue FDG. FDG is phosphorylated and trapped in the cell. FDG is excreted by the kidney, which may mask pathologic uptake. In a prospective study, Aide et al.^[31] found a high rate of false-negative results when localized RCC was considered (Fig. 4). However, it was found that FDG-PET was efficient for the detection of distant metastasis. In another prospective study^[32], the sensitivity of FDG-PET for the detection

of distant metastasis from RCC was more modest, mostly due to the small size of the metastasis. In a prospective study of 14 patients with mRCC treated with sunitinib, it was found that PFS correlated with the baseline standardized uptake value^[33], and when mRCC shows increased uptake of FDG, PET may play a role in the response evaluation of targeted therapy.

Radiotracers such as [^{11}C]acetate, which are not excreted in the urine, may prove useful for imaging RCC. Immuno-PET, which involves radiolabelling of monoclonal antibodies with positron emitters that bind to an antigen on tumour cells^[34], may change imaging in RCC.

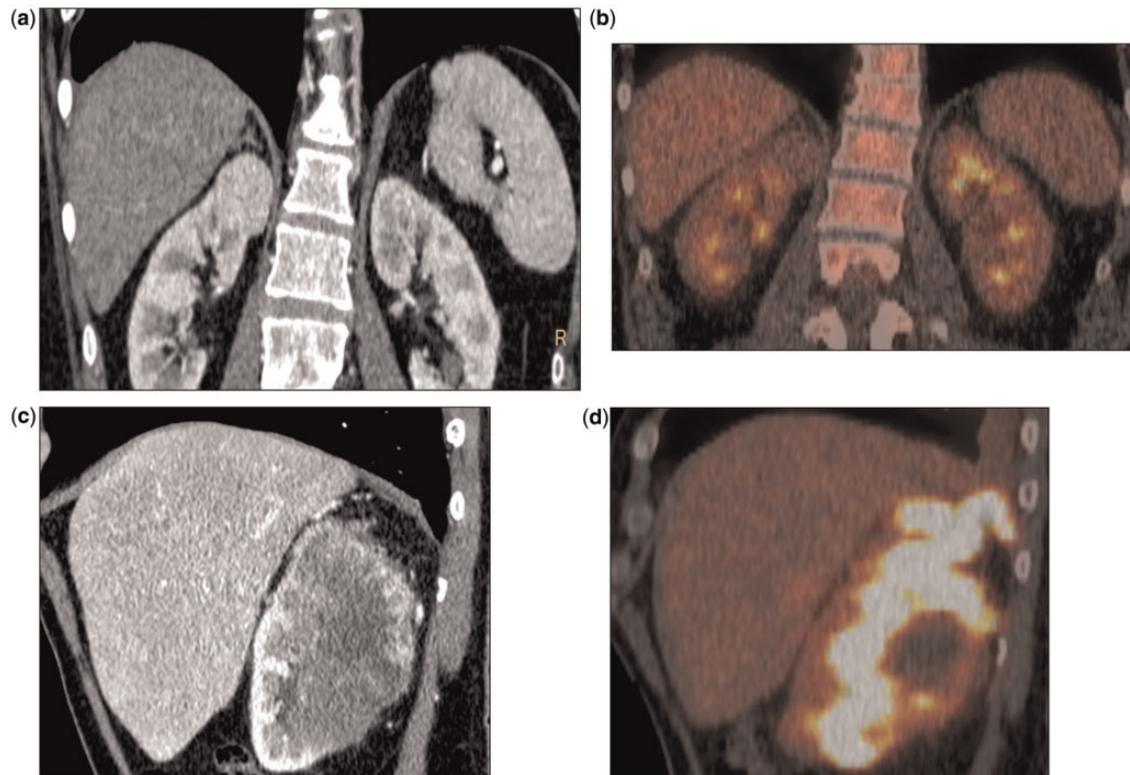


Figure 4 FDG-PET in the evaluation of RCC is hampered by the fact that FDG is excreted by the kidney and may mask FDG uptake in pathologic tissue. Other factors are also involved^[31]. In (a) a modest contrast enhancement on contrast-enhanced CT of the RCC at the upper pole of the kidney is seen. The corresponding PET/CT (b) showed no pathologic uptake of FDG in the tumour. In (c) a large RCC with inhomogeneous contrast enhancement on contrast-enhanced CT is demonstrated. In the corresponding PET/CT (d), a pronounced uptake of FDG in a large part of the tumour is depicted.

Key points

Historically, patients with mRCC have had a poor prognosis. However, targeted therapies have improved PFS and OS compared with earlier treatment strategies. Traditional imaging evaluation only assesses the morphological tumour changes. Treatment with targeted therapy must often be continued for several months before tumour reduction is seen. No early predictor of successful treatment in patients with mRCC treated with targeted therapies has been established. As targeted therapy causes changes other than tumour size reduction, new follow-up criteria are warranted. In this context, functional imaging surrogate parameters seem to be an improvement and may have potential to enhance traditional imaging evaluation.

Conflict of interest

The authors have no conflicts of interest to declare.

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