Radiological evaluation of response to treatment: Application to metastatic renal cancers receiving anti-angiogenic treatment

S. Ammari a, R. Thiam a,b, C.A. Cuenod a,b, S. Oudard c, A. Hernigou a, C. Grataloup a, N. Siauve a,b, J. Medioni c, L.S. Fournier a,b,*

Abstract Targeted therapies have considerably improved the prognosis of patients with metastatic renal cancer (mRCC) but there are no reliable response assessment criteria reflecting the clinical benefits, because there is no regression in size, or it is delayed. Such criteria would help early identification of non-responders, who would then benefit from a change of treatment, and would avoid their being subjected to unnecessary side effects related to the treatment. We will review the imaging techniques currently available for evaluating tumour response in mRCC patients, including the response evaluation criteria in solid tumours (RECIST), the Choi criteria, the modified Choi criteria, and the CT size and attenuation criteria (SACT). We will also discuss functional imaging techniques, which are based on the physiological characteristics of the tumours, such as perfusion CT, magnetic resonance imaging or ultrasound (DCE-CT, DCE-MRI, DCE-US), diffusion MRI, BOLD MRI and new positron emission tomography (PET) tracers. It is not possible at present to propose a unanimously acknowledged criterion for evaluating tumour response to targeted therapy. However, there is a real need for this according to oncologists and the pharmaceutical industry, and radiologists need to be involved in reflecting on the subject.

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Renal tumours represent 2% of all malignant tumours in adults, and are the 13th most common cancer worldwide, with 208,000 new cases and 102,000 deaths per year [1]. The incidence of renal cancer and its mortality rate have been constantly rising throughout the world by 2–3% per decade [2,3].

The large majority of kidney cancers are renal cell carcinomas (RCC), histologically classified as clear cell (60–80%), papillary (10–15%) and chromophobic (5–10%) cancers. When the condition remains localised, RCC can be treated by surgery and thus be cured. In contrast, in the 20–30% of metastatic (mRCC) patients, either synchronously or some time after the surgery, the prognosis was until recently poor, with median overall survival of 8 to 10 months and a survival rate at 5 years of less than 10% [2].

This poor prognosis was explained by the limited therapeutic options for patients with metastatic renal cancer, since mRCC is resistant to conventional cytotoxic chemotherapy [4]. mRCC patients were usually treated with immunotherapy, as certain RCC tumours are capable of provoking an immune response. The anti-tumour effects most consistently observed were with interferon-α and/or interleukin-2. A few patients could thus obtain long-term complete remission. Interferon-α, the most frequently administered cytokine, led to an objective response of 7.5% and median overall survival (OS) of 13 months [4].

During the last 7 to 8 years, the introduction of therapies targeted against tumour vessels (anti-angiogenesis), including VEGF and mTOR inhibitors, has radically changed the therapeutic arsenal for mRCC and considerably improved the prospects for patients with this disease. In December 2005, the Food and Drug Administration approved the first targeted agent, sorafenib, for treating patients with cytokine-refractory mRCC. Following this, five other targeted agents have been approved for treating mRCC, including sunitinib, temsirolimus, everolimus, bevacizumab in combination with interferon-α, and more recently, pazopanib. These products have now replaced immunotherapy in the majority of patients with mRCC (Table 1) and produce significantly better progression-free survival in these patients [4], with median overall survival, depending on the studies, seeming to reach 2 to 3 years if all the therapeutic options that we have at present are added together.

In parallel with the progress in the therapeutic area, research has been conducted to accurately assess the therapeutic response to these new agents. Response to therapeutic drugs is usually assessed by evaluating the response of solid tumours using the Response Evaluation Criteria In Solid Tumours [5], or RECIST, which, since their introduction in 2000, have gradually become the standard method for evaluating treatments for solid (non-haematological) tumours. The RECIST response depends on change in the sum of the single dimension measurements of target tumour lesions for a given imaging procedure.

Although RECIST are clinically relevant for conventional chemotherapy, this does not seem to be the case for the new generation of anti-cancer agents, because targeted agents frequently induce stabilisation of the disease rather than regression [6,7] and lead to tumour necrosis [8–10]. These targeted agents produce a net clinical benefit but a low

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Method of administration</th>
<th>Progression-free survival (PFS in months)</th>
<th>Overall survival (OS in months)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Monoclonal treatments</td>
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<tr>
<td>Bevacizumab (Avastin®)</td>
<td>VEGF (Vascular Endothelial Growth Factor)</td>
<td>Intravenous</td>
<td>10.2</td>
<td>23.3</td>
<td>Escudier et al., 2007, 2010 [6,74]</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Intravenous</td>
<td>8.5</td>
<td>18.3</td>
<td>Rini et al., 2008, 2010 [75,76]</td>
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<tr>
<td>Tyrosine kinase inhibitors</td>
<td></td>
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<tr>
<td>Sunitinib (Sutent®)</td>
<td>VEGFR 1.2.3 and PDGFR and c-Kit; FLT3; RET</td>
<td>Oral</td>
<td>11</td>
<td>26</td>
<td>Motzer et al., 2007, 2009 [11,22]</td>
</tr>
<tr>
<td>Sorafenib (NEXAVAR®)</td>
<td>VEGFR 1.2.3 and PDGFR and c-Kit; FLT3; RET</td>
<td>Oral</td>
<td>5.5</td>
<td>17.8</td>
<td>Escudier et al., 2007, 2009 [48,77]</td>
</tr>
<tr>
<td>Pazopanib (Votrient®)</td>
<td>VEGFR 1.2.3 and PDGFR and c-Kit</td>
<td>Oral</td>
<td>9.2</td>
<td>Not available</td>
<td>Sternberg et al., 2010 [78]</td>
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<tr>
<td>mTOR inhibitors</td>
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<tr>
<td>Temsirolimus (Torisel®)</td>
<td>mTOR</td>
<td>Intravenous</td>
<td>5.5</td>
<td>10.9</td>
<td>Hudes et al., 2007 [7]</td>
</tr>
<tr>
<td>Everolimus (Afinitor®)</td>
<td>mTOR</td>
<td>Oral</td>
<td>4.9</td>
<td>14.8</td>
<td>Motzer et al., 2010, 2008 [79,80]</td>
</tr>
</tbody>
</table>
response rate according to RECIST in the treatment of renal cancer, whether the agent used is sunitinib [11], sorafenib [12] or bevacizumab + interferon [12]. Increase in the size of the tumour has also been described associated with necrosis, mimicking disease progression. Several teams have consequently developed new criteria based on size, on changes in attenuation (density) in computed tomography (CT) [10,13], in perfusion CT (DCE-CT) [14], magnetic resonance imaging (DCE-MRI) [15] or ultrasound (DCE-US) [16,17], or new tracers in positron emission tomography (PET) [18]. With these criteria, non-responders could be identified early; they would then benefit from a rapid change in therapy, which would avoid their continuing with costly but ineffective treatment causing side effects.

In this update, we will review the imaging techniques currently available and the criteria proposed for evaluating tumour response in patients with mRCC.

**Methods of evaluating the efficacy of new targeted therapies**

For CT, various criteria will be discussed, including RECIST, modified RECIST, the Choi criteria, the modified Choi criteria, and the Size and Attenuation in CT (SACT) criteria.

The use of functional imaging techniques will also be discussed, such as perfusion CT, MRI or ultrasound (dynamic contrast-enhanced acquisition or, respectively, DCE-CT, DCE-MRI, DCE-US), diffusion or BOLD MRI, and PET.

**Criteria based on size**

**RECIST 1.0**

The reference treatment evaluation method is based on measurement of the size of the lesions. In 2000, in order to simplify and standardise clinical trial assessment criteria, the European, American and Canadian cancer research organisations set out the Response Evaluation Criteria In Solid Tumours (RECIST) [5]. These criteria only apply to solid tumours and are based on measuring the longest diameter of a patient’s tumour lesions.

The principle is to make an exhaustive list of the lesions, whether they are primary or secondary, before beginning the treatment. They will then be monitored in later examinations to determine whether they are responding to treatment or not.

Two types of lesion are defined in the initial examination:
- **Target lesions** (Fig. 1): defined as lesions where the longest diameter is greater or equal to 10 mm and where the borders are sufficiently well defined for their measurement to be considered as reliable. The total sum of the greatest diameters (SGD) of all the target lesions selected is calculated and serves as a reference. A maximum of 10 lesions are selected per patient, and five per organ;
- **Non-target lesions** (Fig. 2): defined as the exhaustive list of all remaining lesions, not selected as targets because they were too small (<10 mm) or because their measurement was considered to be unreliable since their borders were difficult to define (bone lesions, leptomeningeal lesions, ascites, pleural effusion or pericarditis, carcinomatous lymphangitis, etc.), plus measurable lesions greater than 10 mm which were not selected as targets because there were more than five of them per organ, or they totalled more than 10.

During patient follow-up examinations, response to treatment is determined by changes in each category of lesions as follows:
- **Target lesion response** (Fig. 1) is evaluated from the percentage modification of the sum of their greatest diameters:
  - CR (complete response): disappearance of all the target lesions,
  - PR (partial response): reduction greater or equal to 30% relative to the pretreatment sum,
  - PD (progressive disease): increase greater or equal to 20% relative to the smallest sum measured during follow-up,
  - SD (stable disease): neither CR, nor PR, nor PD (% change relative to the smallest sum measured during follow-up);
- the response of the non-target lesions is assessed subjectively by the observer:
  - CR: complete disappearance of all the non-target lesions and normalisation of tumour markers,
  - PD: ‘unequivocal progression’ of non-target lesions (left to the observer’s judgement),
  - SD: neither CR, nor PD, i.e. the persistence of one or more non-target lesions and/or concentrations of tumour markers above normal;
- the appearance of a new lesion or lesions:
  - no: no new lesion,
  - yes: appearance of a new lesion or lesions;
- the overall response is a combination of the preceding answers: complete response, partial response, stable disease or progressive disease (Table 2).

**RECIST 1.1**

The RECIST were updated at the beginning of 2009 [19] based on an analysis of the literature and simulations from a database including more than 6500 patients and more than 18,000 lesions. The new version is known as version 1.1 (the former becoming 1.0) (Table 3).

The main modifications are as follows:
- the maximum number of target lesions selected changed from 10 to five per patient and from five to two per organ;
- the particular features of lymph nodes were taken into account and their shortest axis must be measured (not the longest axis as for other lesions). A lymph node may be chosen as a target lesion if its small axis measures greater or equal to 15 mm, and as a non-target lesion if its short axis is greater or equal to 10 mm and less than 15 mm. With a short axis less than 10 mm, it is normal. Thus, the sum of the greatest diameters in a patient with a complete response may not be zero, if certain of his targets were lymph nodes and they each measured less than 10 mm;
- target lesions will have progressed if the sum of the greatest diameters has increased by greater or equal to 20% relative to the reference sum, and if this increase is greater or equal to 5 mm in absolute terms;
- several examples are given to clarify ‘unequivocal progression’ of non-target lesions. In particular, the
Figure 1. RECIST target lesions before and after treatment. Three lesions can be considered as measurable and were therefore chosen as target lesions in this patient. a: 30 mm lung lesion; b: left external iliac adenomegaly measuring 21 mm in the short axis; c: peritoneal carcinomatosis of the greater omentum measuring 65 mm in contact with the greater curvature of the stomach. The sum of the greatest pretreatment diameters for this patient was assessed as $30 + 21 + 65 = 116$ mm. After treatment, all lesions had decreased in size (respectively d, e, f). The post-treatment sum of the greatest diameters for this patient was assessed as $16 + 10 + 39 + 65 = 65$ mm. There is a 44% reduction in the target lesions, which constitutes a partial response. Image d also shows a decrease in the other pulmonary lesions, defined as non-target lesions.
progression of a single lesion is insufficient to declare progression;
• the presence of new lesions must be unequivocal to declare the patient as progressing. This new version offers a guide for using PET to determine the metastatic nature, or otherwise, of new lesions.

Modified RECIST
Many studies have applied RECIST to evaluate response to targeted therapies in mRCC [20–22]. However, achieving an objective response (a 30% decrease in the sum of the size of target lesions) can take several months [11,22]. Indeed, the expected effect of targeted agents in mRCC is stability rather than significant tumour regression. Consequently, using statistical analysis, Thiam et al. [23] sought to determine a threshold for evaluating size that would best reflect benefit from treatment in terms of progression-free survival (PFS) (Table 3).

Taking PFS as the criterion of clinical benefit, thresholds of variation in the sum of the greatest diameters from −45% to +10% were tested on 334 patients treated with sunitinib for mRCC. A reduction of at least 10% in the sum of the greatest diameters proved to be the threshold which best distinguished responders \((n=256)\) with median PFS of 11.1 months, from non-responders \((n=78)\) with median PFS of 5.6 months. During the first cycle of treatment, 73% of patients were detected as responders according to the −10% threshold, while only 19% of patients had a response according to RECIST criteria (threshold of −30%).

The usefulness of this response threshold at −10% was confirmed in two studies on independent populations [24,25]. The main limitation to use this threshold is that,

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Evaluation of overall response according to the RECIST with all possible response combinations.</th>
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<tbody>
<tr>
<td>Lesion category</td>
<td>Responses</td>
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<tr>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Target lesions</td>
<td>CR</td>
</tr>
<tr>
<td>Non-target lesions</td>
<td>CR</td>
</tr>
<tr>
<td>New lesions</td>
<td>No</td>
</tr>
<tr>
<td>Overall response</td>
<td>CR</td>
</tr>
</tbody>
</table>

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.
in patients with small lesions, a 10% change in size may be within the margin of error of the measurement.

**Criteria combining size measurements and CT attenuation**

Significant changes in CT tumour attenuation have been observed with targeted therapies. The CT enhancement, or the attenuation after contrast agent injection, is related to the amount of blood reaching the tumour, and thus indirectly to tumour angiogenesis [26,27]. In metastatic RCC, the highest pretreatment attenuation values have been associated with a higher response rate with sunitinib or sorafenib [28], allowing the individual response of each metastatic lesion to be predicted [25,29]. These changes in lesion attenuation induced by the treatment are possibly associated with the therapeutic response because they reflect the necrosis induced by inhibition of the tumour vessels [30]. Conversely, increase in attenuation could be associated with disease progression.

To date, three different response evaluation criteria that take into account changes in attenuation have been studied in patients with mRCC: the Choi criteria, the modified Choi
criteria and the size and attenuation in CT criteria (SACT) (Table 3).

Choi criteria
Benjamin et al. [31] and Choi et al. [32] developed evaluation criteria in order to detect the efficacy of imatinib in patients with gastrointestinal stromal tumours (GIST). Imatinib is known to induce considerable tumour necrosis, which can be accompanied by a paradoxical increase in tumour size, thus simulating progression. The Choi criteria therefore combine changes in tumour attenuation expressed in Hounsfield units (HU) with size to determine tumour response.

According to Choi et al., a PR is defined as a decrease greater or equal to 10% in a tumour size measurement or a reduction greater or equal to 15% in the attenuation of target lesions measured using contrast-enhanced CT (Fig. 3), while PD is defined as an increase in size greater or equal to 10% that does not meet the PR criteria through a change in attenuation. In GIST patients treated with imatinib, the Choi criteria showed significantly better correlation with the survival rate than RECIST.

It was naturally considered that the Choi criteria might be useful for identifying, at an early stage of treatment, the patients with mRCC who are responding or, conversely, in whom there is progression.

One study evaluated the Choi criteria in 55 patients with mRCC treated with sunitinib [33]. During treatment, the median attenuation of the tumours decreased from 66 to 47 HU. According to the Choi criteria, 36 patients (65%) had a PR, six patients (11%) had a SD, and 13 patients (24%) had PD at the first evaluation after the start of treatment. Nineteen of the 36 patients with a PR presented it based only on the criterion of a decrease in attenuation greater or equal to 15%. Patients with a PR according to the Choi criteria had longer PFS and OS than those who were considered to be non-responders. At the first evaluation, the Choi criteria had therefore a clearly better predictive value for PFS and OS than the RECIST.

On the other hand, the definition of progression according to Choi was debated in this study. Indeed, some patients considered as progressing had prolonged PFS (3–10 months). Consequently, van der Veldt et al. concluded that the Choi criteria do not change the clinical management of patients with mRCC treated with sunitinib.

Modified Choi criteria
Nathan et al. [34] used modified Choi criteria, according to which there needs to be a reduction both in terms of the size and attenuation of target lesions, to define an objective response. With these criteria, a PR is therefore defined as a reduction in tumour size greater or equal to 10% PLUS

Figure 3. Target lesions according to Choi. Three lesions in this patient selected as target lesions according to RECIST can be considered as measurable according to Choi criteria. a: liver lesion of 134 HU; b: enlarged lymph node of the root of the mesentery of 122 HU; c: tissue lesion of the site of nephrectomy of 139 HU. The pretreatment mean of the attenuation of this patient is measured as \((134 + 122 + 139)/3 = 132\) HU.
a reduction in the attenuation of target lesions greater or equal to 15% measured by contrast-enhanced CT.

In this study, 32 patients with mRCC and treated with sunitinib or cediranib were evaluated. Ten had to be excluded from the analysis because no contrast agent was injected (due to renal impairment): this is a limitation to any criteria that use density. In the end, only 20 patients could be evaluated, with five, nine, and 13 patients showing a partial response (PR) according respectively to the RECIST, Choi and modified Choi criteria. The group concluded that the modified Choi criteria provided a better median assessment of progression-free survival time, but this study is of limited value due to its statistical weakness with a population of only 20 patients.

Size and attenuation in CT (SACT) criteria

According to the SACT criteria [35], a positive response is defined as:
- a reduction in size greater or equal to 20%;
- OR a reduction in mean attenuation greater or equal to 40 HU in at least one target lesion (excluding the lungs);
- OR a reduction in size of the tumour greater or equal to 10% and a reduction in mean attenuation greater or equal to 20 HU in half of the target lesions (excluding the lungs);

Patients are classified as non-responders when there is an increase in tumour size greater or equal to 20% or development of new lesions. In all other cases, they are stable.

In the SACT criteria, mean attenuation is measured by taking mean volumetric attenuation measurements (HU) for each target lesion using a 3D software (Oncocare, Siemens Healthcare). Volumetric measurements are calculated after semi-automatic contouring of the borders of the lesions using multiplanar images (in three orthogonal planes) for 3D restitution of the target lesions, to be saved and examined by a second observer.

Pulmonary lesions cannot be measured because of errors due to partial volume averaging between the soft tissues and the air. This is a potential limitation to the use of the SACT criteria in patients with mRCC, where the lungs are a frequent metastatic site.

The study by Dennis Smith et al. [35] examined 53 patients with metastatic clear cell cancer receiving sunitinib or sorafenib as first-line treatment. The size and attenuation in CT criteria (SACT) were evaluated and compared with the standards of the response evaluation criteria for solid tumours (RECIST) and with the modified Choi criteria, comparing progression-free survival of responders vs. non-responders according to each criteria. The authors showed that the most useful response criterion was reduction by more than 40% in the attenuation of at least one lesion. By defining clinical benefit as absence of progression for 250 days (8–9 months), the test was able to detect 75% of responders and 100% of non-responders. Thus, if none of the patient’s lesions had reduced in attenuation, they progressed “rapidly” (in < 250 days). RECIST and the modified Choi criteria only detected 16% of responders and 100% of non-responders and 93% of responders and 44% of non-responders, respectively.

There are several limitations to the current use of criteria based on attenuation in patients with mRCC treated with targeted agents. The time between the injection of the intravenous contrast agent and the acquisition must be observed. In addition, the injection of contrast agents may not be possible in a number of mRCC patients, who are often nephrectomised, since the administration of iodinated contrast agents is contraindicated in patients with renal failure. Finally, in the case of SACT, image analysis software needs to be used for measuring attenuations of a previously contoured volume, but is not universally available on all imaging workstations.

Perfusion based criteria (dynamic imaging of the microcirculation)

Dynamic contrast-enhanced (DCE) imaging techniques allowing analysis of tumour vascularisation have been under development for several years. They aim at specifically evaluating tumour vessels so as to detect the direct biological effect of anti-angiogenic treatments, rather than their indirect, late effects on the size of tumours [36].

The principle of dynamic imaging is monitoring the biodistribution of a contrast agent that acts as a tracer. After intravenous injection, the tracer is carried by the circulation into the tissues and, depending on its size, diffuses through the endothelial barrier resulting in its distribution in the interstitial space. Imaging follows the distribution of the tracer by measuring the changes in enhancement of vessels and tissues over time [37,38]. Acquisition is a repeated series of images centred on a specific lesion, in order to follow modifications over time in the concentration of the contrast agent in the tissue. The contrast agent is injected intravenously during acquisition. The data are then transmitted to a workstation so that regions of interest (ROI) can be defined in order to obtain signal variation curves over time. Image analysis software apply mathematical models yielding more or less complex microvascular parameters, or purely descriptive parameters (such as the area under the curve and percentage enhancement). This technique can be used with CT, MRI or ultrasound (Fig. 4).

Some teams have shown the advantages of perfusion imaging for assessing the response to anti-angiogenics in metastatic renal cancer, using CT, MRI or ultrasound.

Fournier et al. [14] studied the usefulness of perfusion parameters using CT in two phase III trials involving 51 patients with mRCC receiving anti-angiogenic treatments (sunitinib or sorafenib) vs. placebo or interferon alpha. The results showed higher baseline perfusion parameters in responders than in stable patients but this was not significantly predictive of survival. Secondly, there was a significant reduction in tissue blood flow (162.5 vs. 76.7 ml/min/100 ml, P = 0.0002) and tissue blood volume (9.1 vs. 3.9 ml/100 ml, P < 0.0001) in patients receiving anti-angiogenic treatment as early as the first cycle of treatment. The study concluded that perfusion parameters could help predict the biological response to anti-angiogenic agents before the start of treatment and help detect an effect after only one cycle of treatment [14].

A disadvantage of perfusion CT is the radiation dose, because series of scans are repeated. Studies have therefore been conducted using MRI (with injection of contrast agent or spin labelling [ASL]) [39–44]. However, analysis of DCE-MRI data is complex, and the conversion from signal
intensity to concentration makes absolute quantification more difficult than with CT. In addition, since quantification is dependent on the acquisition parameters, it is difficult to obtain results that are reproducible between centres. Less restrictive parameters such as Ktrans have been used to quantify vascularisation in MRI [39–41]. The Ktrans transfer constant simultaneously reflects the blood flow (perfusion) and its passage into the extracellular space through the vascular endothelium (permeability). Ktrans is thus a parameter that depends on capillary flow, the endothelial surface area and capillary permeability. It is simpler to calculate and does not require hypotheses to be presented to distinguish between perfusion and permeability. It is a good biomarker for the activity of any treatment, but precautions must be taken when using it, particularly to always ensure the same acquisition conditions [39]. In conditions where exchanges are limited by blood flow (perfusion > permeability), Ktrans approaches to permeability; in conditions where exchanges are limited by permeability (permeability > perfusion), Ktrans approaches to blood flow [45,46].

In a phase II study in 17 patients with mRCC receiving sorafenib, a 60% reduction in Ktrans was shown [42]. The percentage reduction in Ktrans and the change in tumour size in CT scans were significantly correlated with PFS. In addition, tumours with a high Ktrans before treatment were also significantly associated with better progression-free survival.

Ultrasound can also be used for monitoring anti-angiogenic treatments [16,47]. A number of clinical trials with targeted agents have included DCE-US and have shown that the parameters obtained can be correlated with tumour response [16,48]. DCE-US was studied in patients with mRCC being treated with sunitinib [49] or sorafenib [16,48]. In 38 patients treated with sunitinib for mRCC, significantly different values were found between parameters at baseline and 15 days after the start of treatment, which correlated with PFS [49]. An increase in time to peak intensity greater than 29% and a decrease in the washout slope greater than 76% were associated with increased PFS and OS [49]. This technique is of interest due to its ease of use, and the possibility of repeating measurements without adverse effects.

Positron emission tomography (PET)

Evaluation of [18F] FDG PET/CT

PET using [18F] fluoro-2-deoxy-D-glucose ([18F] FDG) is the functional imaging tool most commonly used in oncology [50,51]. The use of [18F] FDG is based on the fact that malignant tumour cells have a high rate of glucose metabolism, and are therefore just as avid for its analogue, [18F] FDG, which cannot be metabolised and thus remains trapped in the cells.

However, the use of [18F] FDG PET in patients with mRCC is limited, because RCCs and their metastases have a low rate of glucose metabolism [51–55]. A negative [18F] FDG result does not exclude the presence of RCC. The use of [18F] FDG PET is only accepted as an addition to confirm
equivocal progression in the rare cases where the tumour accumulates FDG, as has been proposed in RECIST version 1.1.

Other tracers for PET have been developed, such as [11C]acetate, which accumulates in tumour cells due to very active membrane lipid metabolism [56, 57]. [11C]acetate is incorporated into the tricarboxylic acid cycle by acetyl coenzyme A, and then into cell membrane phospholipids. A recent study showed a reduction in the absorption of [11C]acetate after only 2 weeks of treatment with sunitinib [58].

Evaluation of [18F]-FMISO PET/CT

Hypoxia of malignant tumours can affect the results of anticancer treatments because it can produce resistance to chemotherapy and radiotherapy. [18F]-fluoromisonidazole ([18F]-FMISO) is the agent most frequently used to assess tumour hypoxia in vivo with PET. It is a nitroimidazole derivative and, like all the molecules in this group, is selectively trapped in hypoxic cells. This tracer freely penetrates into normal and hypoxic cells by diffusion, and within the cells, it can be reduced by a number of enzymes. In normoxic cells, nitroreduction is not O2-dependent and is rapidly reversible. In hypoxic cells, this reduction leads to the formation of hydroxylamine followed by fragmentation of the tracer, producing chains which bind to the intracellular proteins. This binding is closely dependent on the oxygen concentration [59]. Labelled with 18F, FMISO allows tumour hypoxia to be imaged by PET.

It has been shown in vitro that (1) the rate of [18F]-FMISO binding in hypoxic cells could be 28 times higher than in normoxic cells, (2) [18F]-FMISO did not accumulate when the O2 pressure in the interstitial tissue was greater than 10 mm Hg [60].

[18F]-FMISO is currently only available in France for preclinical applications.

Hugonnet et al. [18] evaluated initial tumour hypoxia in mRCC and the changes after treatment with sunitinib using PET imaging with [18F]-FMISO. They demonstrated that sunitinib at first reduced tumour hypoxia probably by normalising the tumour’s vascular supply. However, this study did not produce statistically significant results demonstrating that tumour hypoxia, initially or after 1 month of treatment, could be linked to a greater risk of progression or death in patients treated with sunitinib for mRCC.

Other functional MRI techniques: diffusion-weighted MRI (DW-MRI) and blood oxygenation level-dependent MRI (BOLD MRI)

Diffusion-weighted MRI

The principle of diffusion-weighted MRI is exploration of the microscopic movement of water. Two intense, symmetrical gradients are applied, causing dephasing then rephasing of spins in the voxel [61]. Moving water molecules will leave the voxel and be incompletely rephased, resulting in a signal loss [62]. According to the Intra Voxel Incoherent Motion concept (IVIM), initially set out by Denis Le Bihan, molecules can move in two ways: Brownian diffusion resulting from random thermal molecular movements, and movement within the capillary network of microvessels due to the pseudo-random orientation of capillaries at the voxel scale, reflecting perfusion [63].

Diffusion is characterised by the b factor, reflecting the strength of the gradient. The higher b factor is, the more the sequence is diffusion-weighted. The b factor depends on the characteristics of the diffusion gradients (amplitude, length of time applied, time between the two gradients, distance apart) [64]. To correctly determine the signal loss respectively due to Brownian diffusion and perfusion, several b values must be applied and the signal subjected to mathematical analysis to separate the two components (diffusion and perfusion).

When using low b values, signal loss is mainly due to perfusion [63]. It could then be possible to estimate tumour perfusion without injecting a contrast agent, and consequently assess the effect of anti-angiogenic treatments on tumour vascularisation.

When using high b values, signal loss is mainly due to Brownian diffusion. Intracellular water molecules have much more limited movement than water molecules in the extracellular space, particularly because of the existence of cell membranes and the cytoskeleton. A very cellular tissue, such as tumour tissue, will thus have a low diffusion coefficient (the molecules diffusing little) [65].

In RCC, DW-MRI has been evaluated mainly for characterising primary tumours [66, 67]. Experience with DW-MRI for monitoring mRCCs during treatment is limited [68]. The only study that evaluated diffusion-weighted MRI in monitoring metastatic renal cancer during anti-angiogenic treatment is the study by Desar et al. [69] on a series of 10 patients receiving sunitinib. Diffusion-weighted MRI was performed before, and at D3 and D10 after beginning treatment. The diffusion-weighted sequence was performed with three b values (50, 300, and 600 s/mm2), but generating a single ADC value. In this study, the ADC had increased significantly by the third day, which was thought to be linked to the development of necrosis and cellular oedema, followed by a decrease by the 10th day that could be explained by the decrease in blood flow due to dehydration and cell death.

Few data are available concerning the effect of anti-angiogenic treatments on perfusion or diffusion in the tumours [70]. In addition, there is no consensus in the literature concerning the choice of b values [71].

BOLD MRI

Blood Oxygenation Level-Dependent MRI (BOLD MRI), also called intrinsic susceptibility imaging, is a technique which is sensitive to tissue oxygenation. Haemoglobin in its deoxygenated form has paramagnetic properties, i.e. it modifies the local magnetic field in a tissue. In practice, this means that there is a signal loss proportional to the amount of deoxyhaemoglobin in the red blood cells of the vessels of a tissue, provided that a suitable sequence is performed known as a gradient echo sequence. However, it follows that the signal loss is also influenced by other factors such as the amount of red blood cells in the tissue, itself related to the number of vessels (the blood volume), and the velocity of blood circulation (blood flow) [72]. This imaging thus reflects the overall state of oxygenation of a tissue, combining all of these parameters. It therefore
seems logical to take an interest in this technique for evaluating anti-angiogenic treatments. In preclinical studies in animals [73], it has been shown that the R2* value of tumours decreases dose-dependently with anti-vascular treatment in pro lactinoma and fibrosarcoma models. There have not yet been any studies analysing the usefulness of BOLD MRI in the response to anti-angiogenic treatment in humans.

Conclusion

There are many techniques available in clinical practice for evaluating response to treatment, providing an alternative to purely morphological imaging. However, studies in humans are still at the preliminary stage, and the medical community needs to start to consider how to evaluate their usefulness in daily practice.

The use of CT has the advantage of being the technique used in regular follow-up for monitoring patients. Size criteria are the easiest to use in practice, possibly by modifying the threshold from which point the patient is considered to be a responder. This is what oncologists do in practice, since they are satisfied that absence of progression shows that their treatment is effective. As far as the usefulness of attenuation measurements is concerned, this could be improved by functional perfusion acquisitions, providing additional information on the physiological effect of anti-angiogenic agents. This technique might be useful where dose adjustment is necessary, when side effects are poorly tolerated. Indeed, it would allow testing the continuing effect of the treatment on tumour vascularisation, despite the reduction in dose.

MRI allows a ‘one stop shop’ strategy to be used in a single examination which could include morphological, dynamic, diffusion and BOLD techniques. MRI is limited by its higher cost and lower availability. In addition, the acquisition technique greatly influences signal, and it is more difficult to compare between one machine and another and from one protocol to another. It remains a cognitive tool essential for understanding the phenomena underlying the action of anti-angiogenic agents.

Ultrasound does not allow whole body evaluation of a metastatic disease. However, as far as the quantification of vascularisation by dynamic imaging is concerned, its advantages are its safety, its low cost and its ease of access.

It is therefore possible to propose a unanimously acknowledged criterion for evaluating tumour response to targeted therapies. Systematic validation of this criterion would be necessary for it to provide a basis for therapeutic decisions, by evaluating reproducibility, repeatability, and inter-individual and inter-machine variability. It would then have to be validated on large independent multicentre populations, and ultimately, the benefit of use of this criterion for the patient’s survival or quality of life would have to be demonstrated. Such studies are very costly and complex to implement. However, oncologists are expressing a real need for this for guiding their choice of therapy, as is the pharmaceutical industry, and radiologists must take an active part in developing and validating new tools.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


Radiological evaluation of response to anti-angiogenic treatments


