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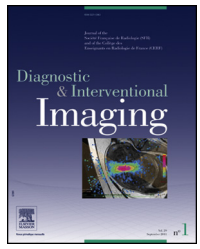

REVIEW / *Genito-urinary imaging*

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

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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-angiogenics), 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 Targeted therapies for renal cancer with the actual agents (molecular targets and method of administration).

Drug	Target	Method of administration	Progression-free survival (PFS in months)	Overall survival (OS in months)	Reference
Monoclonal treatments					
Bevacizumab (Avastin®)	VEGF (Vascular Endothelial Growth Factor)	Intravenous	10.2	23.3	Escudier et al., 2007, 2010 [6,74]
Bevacizumab	VEGF	Intravenous	8.5	18.3	Rini et al., 2008, 2010 [75,76]
Tyrosine kinase inhibitors (TKI)					
Sunitinib (Sutent®)	VEGFR 1.2.3 and PDGFR and c-Kit; FLT3; RET	Oral	11	26	Motzer et al., 2007, 2009 [11,22]
Sorafenib (NEXAVAR®)	VEGFR 1.2.3 and PDGFR and c-Kit; FLT3; RET; RAF	Oral	5.5	17.8	Escudier et al., 2007, 2009 [48,77]
Pazopanib (Votrient®)	VEGFR 1.2.3 and PDGFR and c-Kit	Oral	9.2	Not available	Stermberg et al., 2010 [78]
mTOR inhibitors					
Temsirolimus (Torisel®)	mTOR	Intravenous	5.5	10.9	Hudes et al., 2007 [7]
Everolimus (Afinitor®)	mTOR	Oral	4.9	14.8	Motzer et al., 2010, 2008 [79,80]