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Review – Renal Disease

Assessing the Response to Targeted Therapies in Renal Cell Carcinoma: Technical Insights and Practical Considerations

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Abstract

Context: The introduction of targeted agents for the treatment of renal cell carcinoma (RCC) has resulted in new challenges for assessing response to therapy, and conventional response criteria using computed tomography (CT) are limited. It is widely recognised that targeted therapies may lead to significant necrosis without significant reduction in tumour size. In addition, the vascular effects of antiangiogenic therapy may occur long before there is any reduction in tumour size.
Objective: To perform a systematic review of conventional and novel imaging methods for the assessment of response to targeted agents in RCC and to discuss their use from a clinical perspective.
Evidence acquisition: Relevant databases covering the period January 2006 to April 2013 were searched for studies reporting on the use of anatomic and functional imaging techniques to predict response to targeted therapy in RCC. Inclusion criteria were randomised trials, nonrandomised controlled studies, retrospective case series, and cohort studies. Reviews, animal and preclinical studies, case reports, and commentaries were excluded. A narrative synthesis of the evidence is presented.
Evidence synthesis: A total of 331 abstracts and 76 full-text articles were assessed; 34 studies met the inclusion criteria. Current methods of response assessment in RCC include anatomic methods—based on various criteria including Choi, size and attenuation CT, and morphology, attenuation, size, and structure—and functional techniques including dynamic contrast-enhanced (DCE) CT, DCE-magnetic resonance imaging, DCE-ultrasonography, positron emission tomography, and approaches utilising radiolabelled monoclonal antibodies.
Conclusions: Functional imaging techniques are promising surrogate biomarkers of response in RCC and may be more appropriate than anatomic CT-based methods. By enabling quantification of tumour vascularisation, functional techniques can directly and rapidly detect the biologic effects of antiangiogenic therapies compared with the indirect detection of belated effects on tumour size by anatomic methods. However, larger prospective studies are needed to validate early results and standardise techniques.

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1. Introduction

In the past few years, targeted agents that disrupt angiogenesis have been introduced for the treatment of metastatic renal cell carcinoma (mRCC). Approved agents include receptor tyrosine kinase inhibitors (TKIs), anti–vascular endothelial growth factor (VEGF) antibodies, and mammalian target of rapamycin inhibitors. Collectively, these agents have allowed for a substantial improvement in the treatment of the disease in terms of survival [1].

In contrast to tumour types in which biomarkers are used routinely to predict response to treatment, predictive biomarkers including imaging criteria are currently lacking in RCC. However, accurate and objective assessment of response is critical to ensure optimal use of targeted agents. Because antiangiogenic agents often cause decreased tumour vascularity and necrosis, traditionally used criteria involving measurement of tumour shrinkage (anatomic changes) may be inaccurate for assessing response to targeted agents [2]. Functional imaging, which tracks early changes in tumour physiology, may provide a more appropriate technique to monitor response to these therapies. Presently, there are no guidelines or general recommendations on the most suitable methods of response assessment for targeted therapy. We performed a systematic review of conventional and novel imaging methods for the assessment of response to targeted agents in RCC and discuss their use from a clinical perspective.

2. Evidence acquisition

2.1. Search strategy

The systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [3]. The databases searched were Medline (PubMed) and Google Scholar, covering the period from January 2006 to April 2013. Relevant articles were also identified using the related citations function of PubMed. In addition, abstracts from recent American Society of Clinical Oncology annual meetings and Genitourinary Cancers Symposia in 2011 and 2012 were searched. Additional sources of the search included the authors' personal knowledge of the literature. The search terms included these terms: *renal cell carcinoma, targeted therapy, imaging, ultrasound scanning, scintigraphy, magnetic resonance imaging (MRI), computed tomography (CT)*, and *response and assessment* (see Supplement for full Medical Subject Headings search). Only English-language articles were included. All abstracts and full-text articles were screened independently. Disagreement was resolved by discussion.

2.2. Types of included study designs

Included were randomised controlled trials, nonrandomised controlled studies, retrospective case series, and cohort studies. Exclusion criteria were studies published before January 2006, systematic and narrative reviews, animal and preclinical studies, case reports, and commentaries.

2.3. Data analysis

Baseline characteristics of studies included were collected for authors, types of studies, number of participants, types of imaging modalities, and outcome measures. A meta-analysis and an assessment of risk of bias were not planned due to the lack of randomised studies from a prior scoping exercise. A narrative synthesis of the evidence is presented instead. The Oxford Centre for Evidence Based Medicine 2011 level of evidence (OLoE) was used as a basis for the evidence synthesis (http://www.cebm.net/index.aspx?o=5653).

3. Evidence synthesis

The study selection process is outlined in the PRISMA diagram (Fig. 1). Thirty-seven studies met the inclusion criteria (3 phase 2 randomised studies, 19 nonrandomised comparative studies, 11 retrospective comparative studies, and 4 retrospective noncomparative studies). The baseline characteristics and OLoE of the included studies are displayed in Supplemental Table 1.

3.1. Anatomic-based current methods of response assessment

3.1.1. Computed tomography

Response to treatment has traditionally been based on measurements of tumour size reduction (≥30%) using the Response Evaluation Criteria in Solid Tumors (RECIST) [4]. In clinical practice, CT is the main technique used to evaluate RECIST response (Table 1) [4–7]. However, it can also be used to assess lesion attenuation, and degree and

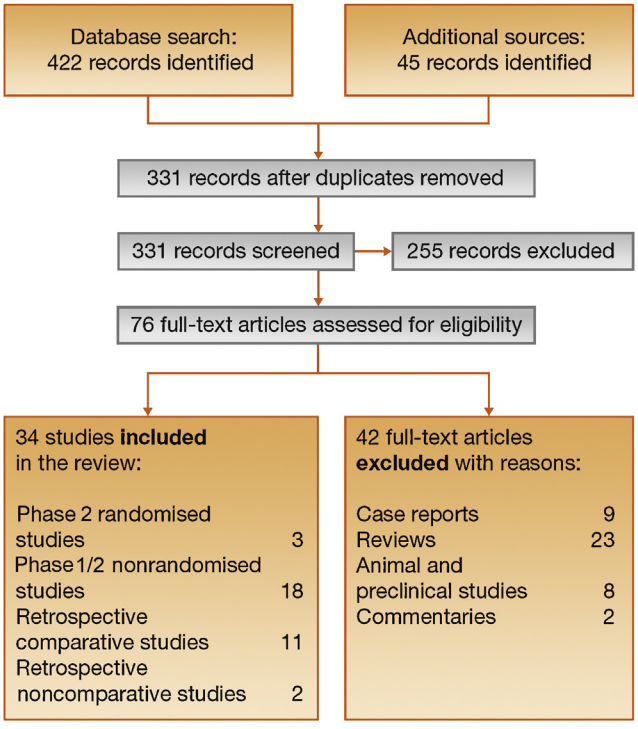

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis diagram outlining the study selection process.