Dynamic Contrast-enhanced Magnetic Resonance Imaging in the Early Evaluation of Anti-angiogenic Therapy in Metastatic Renal Cell Carcinoma

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Abstract. *Aim: To evaluate the efficacy of dynamic contrast-enhanced magnetic resonance (DCE-MR) in the response to anti-angiogenic-targeted agents in patients with metastatic renal cell cancer (mRCC). Patients and Methods: Twenty-eight consecutive patients with sub-diaphragmatic metastases from mRCC were included in the protocol after signed informed consent. Baseline characteristics were collected and patients were first evaluated with a baseline computed tomography (CT) and DCE-MR, subsequently with a new DCE-MRI after 28 days of therapy and followed-up with CT until progression. Treatments were administered at standard doses. The changes of peak enhancement (ΔPE) and of the sum of longest tumor diameters (ΔLTD) were related to progression-free survival (PFS) and overall survival (OS). Results: The median PFS was 11.4 months [95% Confidence Interval (CI): 7.9-14.7 months) and the parametric two-tailed Pearson's test showed a positive correlation between the median ΔPE and the median PFS (rp=0.809; p=0.015); no significant correlation was found between the median ΔLTD and the median PFS (rp=–0.446; p=0.27). The median OS was 23.3 months (95% CI: 13.6–33.0 months) and no significant correlation was found with the median ΔPE (rp=0.218; p=0.60) or with the median ΔLTD (rp=0.012; p=0.98). Conclusion: The ΔPE but not the ΔLTD was found to be significantly related to PFS; these preliminary results suggest extending the number of patients and investigating the possible relationship with other tumor characteristics and MRI parameters.*

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Metastatic renal cell carcinoma (mRCC) is a fatal urological cancer with 5-year survival rates approximately 10% (1, 2). Treatment of mRCC has improved in the past decade because of the availability of targeted agents, such as the (VEGF)VEGFR inhibitors sorafenib, sunitinib, pazopanib, axitinib, tivozanib and bevacizumab (in combination with interferon), and (mTOR) inhibitors temsirolimus and everolimus.

In recent years, several nomograms were developed to predict prognosis in patients affected by mRCC treated with immunotherapy (3, 4) or with targeted agents (5-7), but these are not validated as predictive factors. Moreover, a recent retrospective analysis reported some adverse events related to the mechanism of action of targeted agents, including arterial hypertension, which impacted on treatment efficacy and patient survival (8).

Despite the effect of targeted agents on tumor angiogenesis being well-known, this is not the used for evaluation of treatment efficacy in clinical practice, where the evaluation of morphological changes of tumor metastases is still the standard reference. In order to investigate the predictive role of angiogenic changes, we correlated these with the outcomes in a selected group of patients who received targeted agents as first-line therapy for mRCC.

Patients and Methods

Twenty-eight consecutive patients with diagnosis of mRCC and sub-diaphragmatic metastases located in the abdomen or pelvis were enrolled in the present study. All patients signed an informed consent. Patients enrolled in the study underwent an MRI examination on a 1.5-Tesla scanner (Magnetom Avanto, Siemens, Germany) equipped with a double surface-phased array coil (abdomen and pelvis); sequences were acquired before and after intravenous contrast agent administration (10 ml of Gadobutrol, 1 M). MRI examination was performed at baseline and after four weeks of therapy (Figure 1). Fifteen patients received sunitinib-plus-interferon, nine sorafenib-plus-temsirolimus, and the remaining four received bevacizumab-

plus-pazopanib (Table I). The scan protocol included morphological imaging with (TSE) T2-weighted sequences on the axial, sagittal and coronal planes and dynamic contrast-enhanced imaging (DCE-MR) using 3D (GRE) T1-weighted sequence. Patterns of vascularity of the lesion were evaluated by placing the region of interest (ROI) at the level of evaluating structures; a semi-quantitative evaluation was performed by computing intensity/time curves. The longest tumor diameter (LTD) and the peak enhancement (PE) were evaluated for each lesion and related to progression free-survival (PFS) and overall survival (OS). The choice of anti-angiogenic drug was at the attending physician's discretion and given according to standard recommendation until three days after the baseline MRI. Patients were followed-up with CT scans at baseline and every three months until progression of disease defined per Response Evaluation Criteria in Solid Tumors (RECIST) (9).

Statistics. Baseline values were expressed as median values with respective ranges. Baseline was defined as the date of the initial MRI. The changes in PE and LTD were expressed as a percentage compared to baseline PFS. PFS was defined as the time from treatment beginning to the first documentation of disease progression or to death from any cause, whichever occurred first. Disease progression was defined as an increase of the sum of the longest tumor diameter (SLD) by 20% or more as per the RECIST criteria (9). The OS was defined as the time from treatment beginning to death or last follow-up. The PFS and OS were estimated using the Kaplan–Meier method with Rothman's 95% confidence intervals (95% CI). The correlations between the changes in PE and LTD and the median PFS or OS were evaluated by parametric Pearson's rank test.

All values of p less than 0.05 was considered statistically significant. Analysis was performed using Predictive Analytics Software (PASW v 18; IBM, SPSS, Chicago, Illinois, USA).

Results

A total of 43 lesions were evaluated (Table I). At baseline the median LTD was 35.0 mm (range=10.0-58.0 mm) and the median PE was 153.7 (range=40.1-421.0). After 28 days of therapy, the median LTD was 25.0 mm (7-38 mm), the median PE was 120.0 (16.6-258.8) and the median change in PE from baseline was –27.2% (–58.6 to 12.5). At the time of analysis, only one patient did not have disease progression; the median PFS was 11.4 months (95% CI=7.9-14.7 months) and the parametric two-tailed Pearson's test showed positive correlation between the changes in PE and the median PFS (r_p=0.809; p=0.015), but no significant correlation was found between the median changes of LTD and the median PFS (r_p=–0.446; p=0.27). At the time of analysis, four patients were dead, the median OS was 23.3 months (95% CI=13.6-33.0 months) and no significant correlation was found between the OS and the changes in PE (r_p=0.218; p=0.60) or in LTD (r_p=0.012; p=0.98).

At the first evaluation during therapy, only one patient had a partial response, with a decrease of the sum of the LTDs of targeted lesions of 30% or more, and three patients had a decrease of the sum of LTDs of 20% or more. No differences in terms of PFS were found between patients with or without a response of 20% or more. On the contrary, we found that a decrease of PE of 20% or more was related to shorter median PFS (4.7 *vs*. 11.6 months; p=0.004) compared to a reduction of 10% or 30%. Interestingly, the patient with the greatest reduction of PE (58.6%) is the only patient remaining free of progression after 36 months of therapy.

Table I. *Main characteristics of the patients*.

Characteristic	Patients n=28
Median age, years (range)	58 (44-74)
Male gender	85%
Nephrectomy	100%
Histology	
Clear cell	93%
Papillary	7%
Extra-abdominal disease	60%
Abdominal sites of metastases	
Kidney	32%
Liver	23%
Adrenal gland	15%
Pancreas	15%
Lymph nodes	15%
Baseline MRI	
Median LTD, mm (range)	35 (10-58)
Median PE (range)	153.7 (40.1-421.0)
Treatment	
Sunitinib + interferon	15
Sorafenib + temsirolimus	9
Bevacizumab + pazopanib	4

MRI: Magnetic resonance imaging; LTD: longest tumor diameter; PE: peak enhancement.

Discussion

The RECIST is the most common measurement system in clinical practice and is based on the sum of the longest diameters of the target lesions (9). Target therapies have a different pattern of tumor response compared to traditional cytotoxic chemotherapy: lesions show increase of central tumor necrosis and a smaller decrease in LTD, typically less than 30% at early evaluation. In fact, anti-angiogenic agents mainly act on tumor endothelium and only indirectly on tumor cells; hence the decrease of tumor dimensions is a late effect. Nevertheless, treatment-induced necrosis is not considered by RECIST and may even simulate progressive disease.

This study reports that the evaluation of the efficacy of targeted agents may be performed independently of the extension of targeted lesions and with a direct evaluation of treatment activity on reduction of angiogenesis. We found that the greater the reduction of tumor vascularization, the longer the PFS was and we suggest at least 20% as the threshold value for decrease.

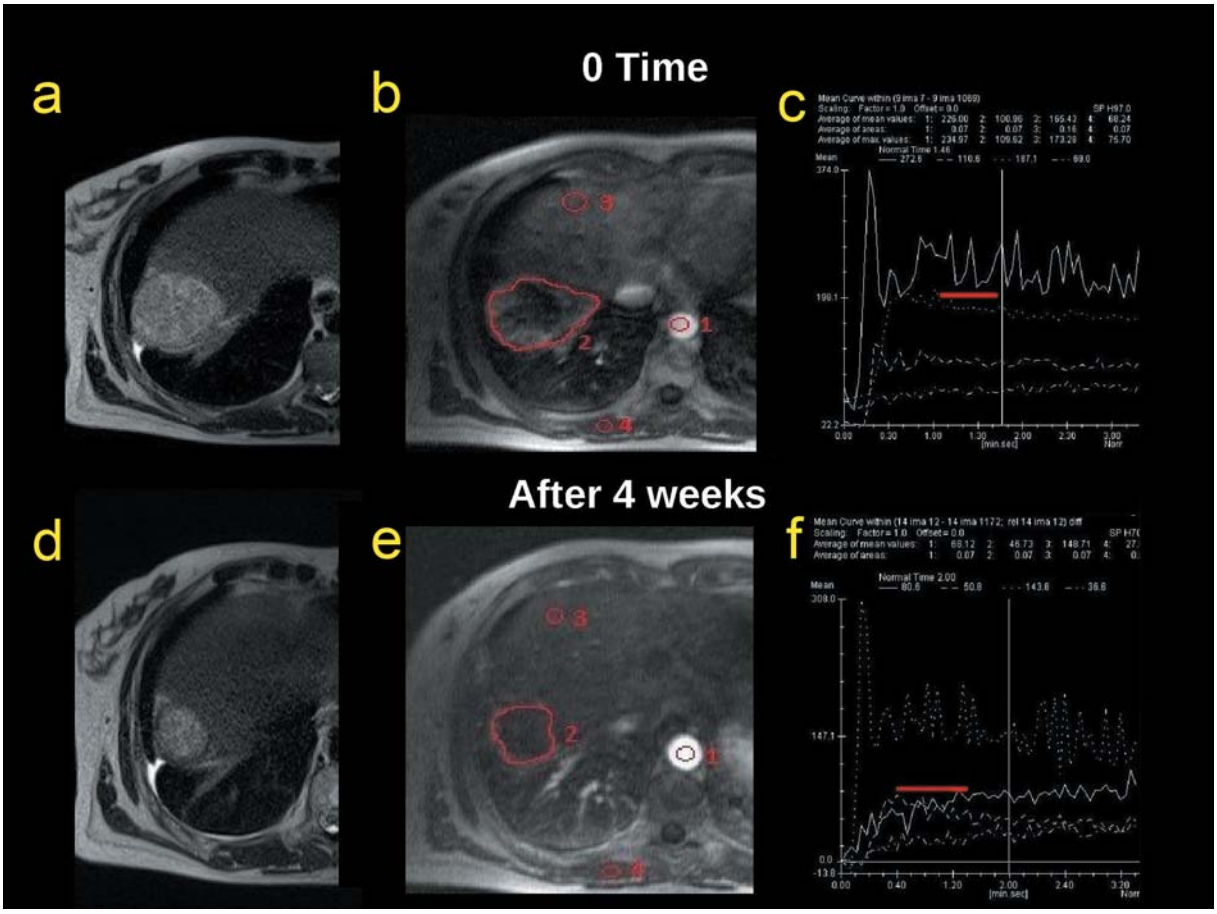

Figure 1. *MRI of a female patient showing a metastatic lesion in the VII-VIII segment before treatment (a-c) and after four weeks of treatment (d-f). a: T2-weighted sequences show a inhomogeneous hyperintense mass of 4 cm in maximum diameter. b: Qualitative assessment of perfusion images show the same lesion as a hypointense zone with peripheral vascularization; regions of interest were plotted on the lesion, abdominal aorta, liver and muscle. c: Semi-quantitave analysis using intensity/time curves highlights the grade of vascularization of the lesion. d: T2-weighted sequences showing a slight dimensional reduction of approximately 0.5 cm of the metastatic lesion after four weeks of treatment. e: Qualitative assessment using perfusion images depicting the reduction of vascularization of the lesion; regions of interest were plotted on the metastasis, aorta, liver and muscle. f: Semi-quantitative approach revealing the lesion's behavior compared to the aorta, liver and muscle. The semi-quantitave analysis by means of intensity/time curves adds important functional information to morphological criteria, which only indicates dimensional reduction; the former highlights the reduction of neoangiogenesis and therefore the response to anti-angiogenic therapy.*

In the era of targeted-therapies, several methods for response evaluation based on different parameters have been proposed, such as the Choi criteria, which measure the decrease of Hounsfield units evaluated by CT (10). In a retrospective analysis, Krajewsky *et al*. demonstrated that only the reduction in the LTD of more than 10% is an early predictor of outcome, while the RECIST and Choi criteria are not directly correlated with time-to-treatment failure (11). The main limitation of this study is the evaluation of morphological response of target lesions, but not the functional aspects. Furthermore, CT is a widely available and reproducible method, but its use is limited by the need for exposure to ionizing radiation (11).

Diagnostic imaging that reports changes in tumor vascularization may show earlier treatment effects and such changes could be related to efficacy. Contrast-enhanced ultrasonography (CEUS) found a threshold of a more than 10% decrease in contrast medium uptake, with either stability or decrease in tumor volume after three or six weeks of treatment with sorafenib, to be a predictive factor for PFS in patients with RCC (12). Unfortunately, their study used tumor volume for evaluation of anti-angiogenic agent activity and CEUS has several limitations such as restricted depth penetration, limited resolution and high operator dependence, and it may be adversely affected by the presence of bowel gas (13).

MRI is an interesting modality for evaluating anti-angiogenic therapies: it is widely available and does not use ionizing radiation. In a previous study, 17 patients treated with sorafenib for mRCC were evaluated by DCE-MRI (14). During treatment, significant changes in tumor vascular permeability were observed. Furthermore, the percentage decline of volume transfer constant of contrast agent (K_{trans}) and high baseline K_{trans} was predictive of longer PFS (14). A similar relationship between baseline K_{trans} and PFS was observed in another prospective study by Hahn *et al*. (15), where 56 patients affected by RCC were evaluated by DCE-MRI during treatment with sorafenib. Conversely, a decrease of K_{trans} and the area under the contrast concentration versus time curve for 90 sec after contrast injection were not predictive of PFS in this population, probably due to high patient variability of these two measures.

Our study also has several limitations: firstly, the low number of patients included that limits drawing any definitive conclusion; secondly, the heterogeneity of treatments used; thirdly, we used a 28-day interval from baseline for evaluation of response but there is no evidence that this is the best timing. Nevertheless, DCE-MRI can be considered an attractive and non-invasive method to evaluate *in vivo* changes in tumor vascularization. Furthermore, it is a reproducible method, without exposure to ionizing radiation, and MRI examination on 1.5 Tesla scanners is widely used. Unlike other diagnostic imaging techniques, MRI provides both morphological and functional evaluation of target lesions. Our preliminary results suggest extending the study to a greater number of patients and investigating the possible relationship with other tumor characteristics and MRI parameters.

Conflicts of Interest

The Authors declare that there are no conflicts of interests

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