Full length article

Measurements of metastatic renal cell tumours as determined by diffusion weighted imaging or computed tomography are in close agreement, a pilot study

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ABSTRACT

Background: Diffusion weighted magnetic resonance imaging (DWI) provides both functional and anatomical information regarding tumours but can also be used for tumour detection. Today, tumour treatment response in clinical trials is mainly assessed on Computed Tomography (CT) using established criteria. Despite availability of dedicated software, CT still requires significant manual work for selection and measurement in treatment response evaluation of solid tumours.

Purpose: To compare the maximum diameter of tumour lesions on CT with the corresponding measurements on diffusion weighted images.

Materials and methods: In this prospective cohort, metastatic lesions were identified on CT and on DWI in five patients with metastatic renal cell carcinoma before and after three months of treatment with pazopanib. Two radiologists independently measured the same lesions on axial CT images and separately also on axial DWI images. The measurements were compared between CT and DWI with respect to the number of target lesions measured, size of the lesions, size reduction due to treatment and the inter-observer variability. Wilcoxon signed rank test, linear regression and Bland-Altman plots were used for statistical analyses.

Results: In this pilot study, there was no significant inter-observer variability in terms of numbers of lesion selected between CT and DWI. A significant reduction of lesion size was observed both for CT and DWI when post-treatment scans were compared to pre-treatment scans. There was no significant difference in measurement of lesion size on both pre- and post treatment scans between CT and DWI (p = 0.099 and p = 0.388 respectively).

Conclusion: Measurement of the size of metastatic lesions on the basis of axial DWI images are in close agreement with measurement based on conventional axial CT images, the most often employed approach in clinical trials today. The results in this pilot study can be used to estimate sufficient sample size in a larger trial with adequate power, were the results can be confirmed in a wider range of cancers other than renal cell carcinoma.

Background

The Response Evaluation Criteria in Solid Tumours (RECIST) is currently the most widely accepted procedure for assessment of therapeutic tumour response on the basis of radiological examinations in connection with clinical trials. RECIST was updated in 2009 [1] and the resulting RECIST 1.1 is an accepted international standard for evaluation of treatment of solid tumours in clinical trials today. This assessment involves repeated anatomical measurement of selected lesions most often employing computed tomography (CT). CT is a rapid and standardized technique for evaluation of treatment response and has therefore become the predominant radiological modality for monitoring cancer. At the same time CT has its drawbacks including repeated exposure of the patient to radiation, dependent on intravenous

contrast agents, considerable manual work in selection and measurement of lesions as well as inter-observer variability in the assessment [2]. There is also limited functional information concerning the disease.

Diffusion-weighted magnetic resonance imaging (DWI) has recently become both a robust and routinely used technique when performing body magnetic resonance imaging (MRI). DWI enables visualization of areas within the body where water diffusion is altered as well as providing functional information based on the random motion of water molecules in both the intra- and extracellular spaces. Takahara and colleagues first described the concept of free-breathing DWI with background body signal suppression in 2004 [3] and showed that head-to-toe DWI examinations were possible to detect tumours in a whole body examination. This technique can be employed to highlight tumour lesions within the body [4] and to detect physiological effects within the tumour due to treatment [5–7]. Thus, employing DWI as a biomarker in cancer is currently under active investigation.

The obvious advantage of DWI over CT is the functional information the former supplies concerning physiological changes within the tumour. Restricted diffusion can be calculated and visualized as an apparent diffusion coefficient (ADC) map, which has resulted in considerable focus on quantitative changes in the diffusivity of the tumour.

In addition to the functional information, it is also possible to measure tumour lesions on axial DWI images in the manner as traditional response evaluation is carried out on CT. The potential advantage with only DWI would be that it is less time consuming than a full MRI examination (including T1 and T2 sequences), provides easier identification and measurement of lesions with low water diffusivity due to the high contrast to noise background. This potential has previously been little explored. Here, we hypothesize as a first step towards implementation of DWI for such evaluation that the size of tumour lesions can be determined as accurately on the basis of axial high b-value DWI images as with axial CT images. We also evaluate the inter-observer variability associated with these two procedures.

1. Methods

After providing informed consent, five patients (median age 67.6 years range 61–73 years) met the inclusion criteria i.e. they had a histologically confirmed metastatic renal clear cell carcinoma (1), were scheduled to begin treatment with a tyrosine kinase inhibitor (2), and had not previously been treated with any chemotherapeutic drug (3), entered this prospective cohort study. The drug of choice was first-line treatment with Pazopanib (800 mg once daily). The study protocol was pre-approved by the regional ethical review board (Dnr 2012/2223-31/1). Each patient entering the study conducted both a CT and DWI examination pre-treatment and another CT and DWI after three months of treatment according to the experimental flow-chart (Fig. 1).

1.1. Imaging protocol

DWI was carried out with a 1.5T MRI system (Siemens Aera, Siemens AG Erlangen Germany). Free breathing echo planar imaging with suppression of background body signals was performed with multiple phased-array body-coils covering the thorax and abdomen. The MRI-protocol consisted of trans axial DWI-sequences only, with a total acquisition time of 15–20 min (average 18 min). ADC-maps were generated from the b50, b400 and b800 sequences. In addition, three dimensional maximum-intensity projection images were also reconstructed from the b800 images. The parameters utilized for DWI imaging are summarized in Table 1. No premedication was administered.

CT examinations of the thorax and abdomen were performed on a 64-slice scanner (LightSpeed General Electric Healthcare, Milwaukee, WI). Thin-collimation helical scanning was employed with a 40 mm detector coverage, 0.625 mm helical thickness, a 65.62 mm/sec table

speed and a pitch of 0.984. Images were reformatted prior to interpretation into 5 mm thickness with 2.5 mm intervals using a volume-averaging algorithm. In this context three of the patients received an intravenous contrast agent in parenchymal phase, but two others with reduced renal function (eGFR below 45) could not. Injected contrast media was ioversol (Optiray, Mallinckrodt Imaging, Hazelwood, Missouri) with 350 mgl/mL iondine content and at the speed of 4 mL/s.

1.1.1. Image analysis

Each DWI and CT examination was separately reviewed independently in a blinded random fashion both by modality and with respect to time point before or after treatment by two radiologists (C.S. and L.B.), with more than seven and 20 years of experience in body MR-imaging respectively (flow chart displayed in Fig. 1). Reviewers were only aware of the inclusion criteria but did not know whether each single examination was baseline or follow-up. Metastatic lesions were selected for assessment only if the reviewer was certain of their malignancy, i.e., the CT morphology of the lesion was obviously malignant and the lesion gave a high signal on b800 DWI images and exhibited markedly reduced diffusion on the ADC map. For statistical reasons, the longest dimension of as many as 10 metastatic lesions (none < 1.0 cm) in the transverse plane was determined at each time point by each reviewer. A subgroup analysis of pulmonary lesions was performed to determine whether those lesions had larger differences due to free-breathing artefacts. A third investigator analysed the results including saved screen shots with annotated images for each target lesion selected for each modality by each reviewer (J.F.).

1.1.2. Statistical analysis

Utilizing the Wilcoxon signed rank test, target lesions were analysed with respect to the number chosen by each reviewer, length before and after treatment and the inter-observer differences in measurement. Bland-Altman plots of the measurements pre- and post-treatment by DWI and CT were created and linear regression performed to investigate proportional bias. A p-value < 0.05 was considered statistically significant. Since this was a pilot study with no information on patient outcome, a power calculation was not applicable. All statistical analyses were conducted with the SPSS software version 21.0 (IBM).

2. Results

All patients underwent both CT and DWI examinations prior to (median 0, range 0–22 days prior to treatment initiation) and after three months treatment. All five patients had a stable disease after 3 months on follow-up CT examinations. Metastatic lesions were distributed as displayed in graph (Fig. 2).

A total number of 106 lesions were measured independently on pre- and post-treatment CT (the two different reviewers measured 78 and 70 lesions respectively) and 90 lesions were measured independently on pre- and post-treatment DWI (68 and 67 lesions respectively). The same lesion was selected for measurement by both reviewers in 42 cases on CT (21 lesions pre- and 21 post-treatment) and in 45 cases on DWI (25 lesions pre- and 20 post-treatment). The median number of lesions per subject measured pre- and post-treatment by the two reviewers on the basis of CT and DWI scans did not differ significantly.

Tumour lesion size was significantly reduced by treatment when the same reviewer assessed a lesion before and after treatment on CT or DWI independent of each other (the Wilcoxon sign rank test reveal p = 0.001 and 0.000 respectively; Fig. 3). As determined by CT the median size was 32 mm pre-treatment (mean 37.9 and range 11–105) and 29 mm post-treatment (mean 35.3 and range 8–88) and the corresponding values for DWI was 30 mm (mean 36.5 mm and range 12–94) and 28 mm (mean 34.1 and range 10–83).

The agreement between the CT and DWI was evaluated by comparing the longest diameter of each separate lesion when the same lesion