European Journal of Radiology Open 4 (2017) 45–49

Contents lists available at ScienceDirect

European Journal of Radiology Open

journal homepage: www.elsevier.com/locate/ejro

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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ARTICLE INFO

Keywords:
DWI
CT
RECIST1.1
Biomarker
Clinical trials

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

Abbreviations: DWI, Diffusion weighted magnetic resonance imaging; CT, Computed Tomography; RECIST, The Response Evaluation Criteria in Solid Tumours (RECIST); MRI, Magnetic Resonance Imaging; ADC, Apparent Diffusion Coefficient

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http://dx.doi.org/10.1016/j.ejro.2017.03.003
Received 29 November 2016; Received in revised form 29 March 2017; Accepted 31 March 2017
Available online 14 April 2017

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 mgI/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

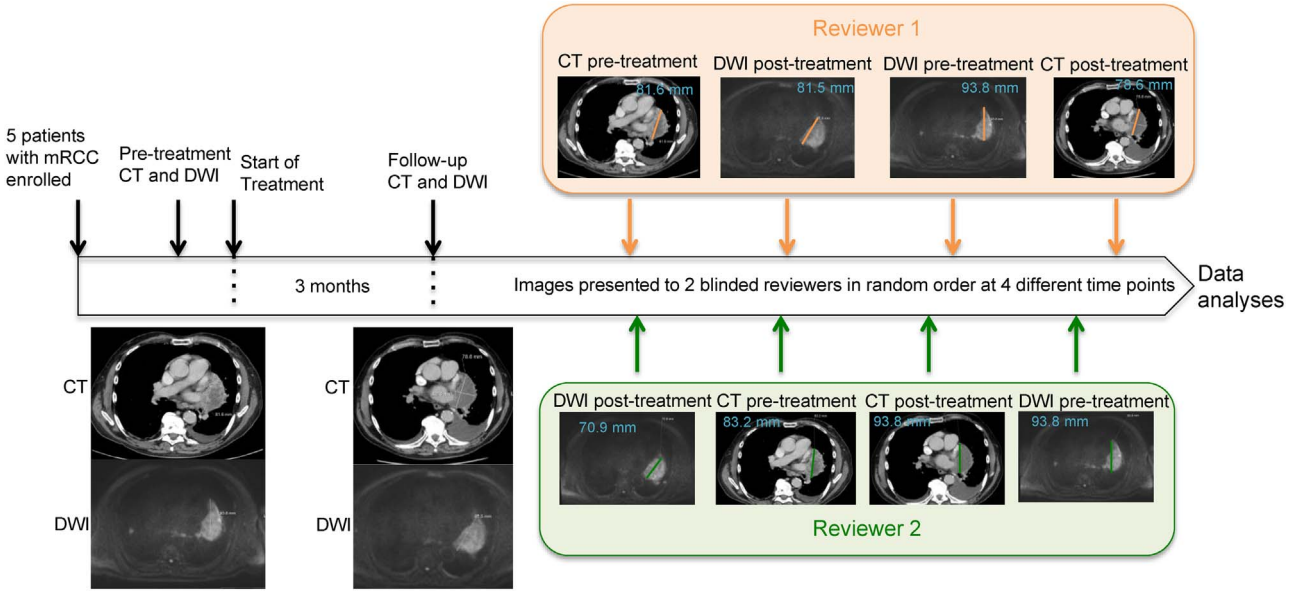

Fig. 1. Experimental flow-chart. CT and DWI examinations are performed before and after treatment. All 20 examinations (ten CT and ten DWI) were randomly presented to two radiologists who independently identified and measured up to ten tumour lesions. Data was collected and analysed by a third radiologist.

Table 1
DWI-parameters.

TR	5600 ms
TE	60 ms
Field of view	380 × 380
Pixel size	2 × 2 × 5 mm
b-values	50/400/800
Nr of signal averages	4
Receiver bandwidths	1736 Hz/pixel
Fat suppression	STIR
Scan time	3 min 51 sec/station
Station length	18 cm
Number of stations	4/5

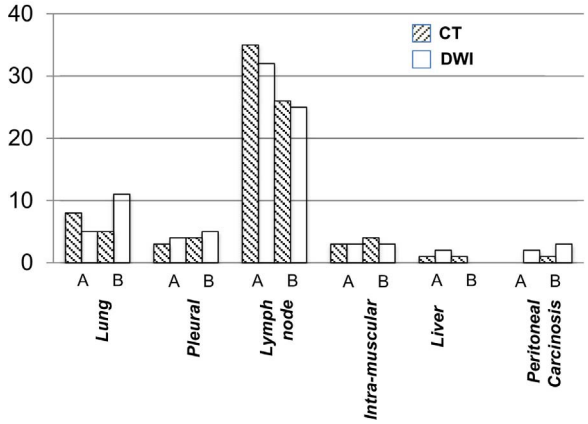

Fig. 2. Distribution of metastases identified by the two different reviewers labelled A and B. Reviewer B identified no lesion in the liver on DWI and reviewer A identified no peritoneal carcinosis lesion on CT.

was chosen by either reviewer on CT and DWI, either pre- or post-treatment or both (a total of 76 lesions; 41 pre-treatment and 35 post-treatment). The Wilcoxon signed rank test reveals no statistical difference in tumour diameter between CT and DWI neither in total, nor pre- or post-treatment ($p = 0.065$, $p = 0.099$ and $p = 0.388$ respectively). This agreement is emphasized by the two Bland-Altman plots in Fig. 4, which reveal no systematic bias and linear regression showing no proportional bias ($p = 0.98$ pre-treatment and $p = 0.077$

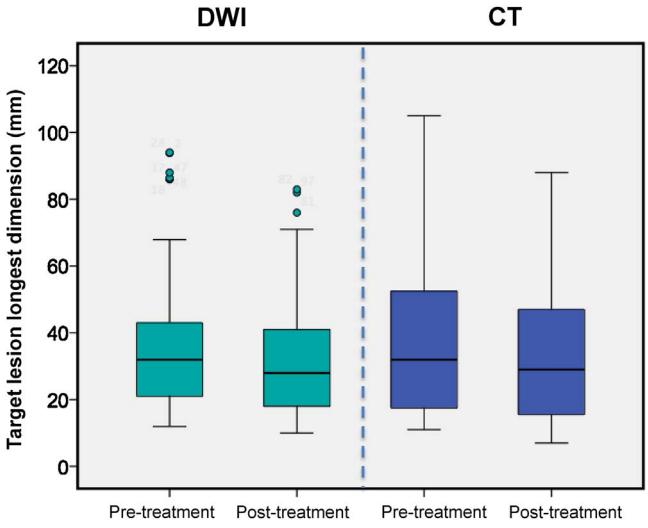

Fig. 3. Box-plot diagram of the size of target lesions as assessed by DWI or CT prior to and after 3 months of treatment. The line within the box represents the median value. The Wilcoxon signed rank test reveal significant differences in lesion dimension by either DWI or CT.

post-treatment). The mean difference between the size of the same lesion measured by CT and DWI was 1.31 mm pre-treatment and 1.76 mm post-treatment.

There was no significant difference in lesion dimension on pre-treatment CT and pre- and post-treatment DWI between the two reviewers. However, there was a significant difference in tumour size between the reviewers when the same lesion was assessed on post-treatment CT examinations (Table 2).

In additional comparison of pulmonary lesions, there was no statistical difference in size between CT and DWI ($p = 0.128$), but the numbers of cases were limited to twelve. The median size of pulmonary lesions was 18.5 mm for CT (range 10–83 mm) and 19 mm for DWI (range 10–94 mm).

3. Discussion

To date, most use of DWI to monitor cancer drug response has focused on changes in the ADC [5,8,9]. Here, we document good

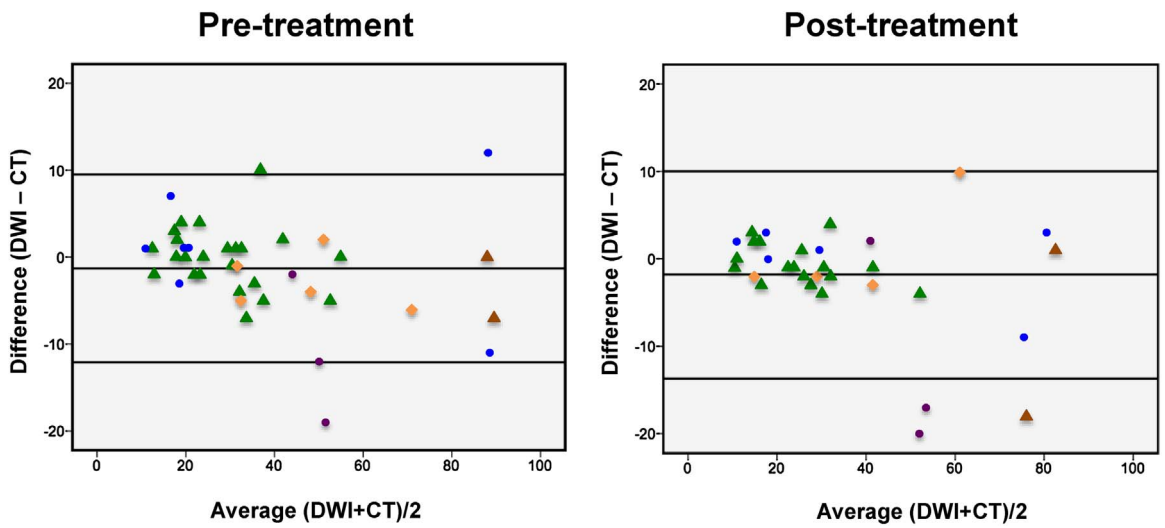

Fig. 4. Bland-Altman plots illustrating the agreement between DWI and CT measurements both pre- and post-treatment. The lines represent means and 95% confidence intervals. Symbols represent the metastatic location (green triangles are lymph node, blue circles are pulmonary, yellow cubes are pleural, pink circles are intramuscular and brown triangles are peritoneal). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
P-values for the median difference in the size of target lesions as assessed by reviewers 1 and 2 on the basis of DWI and CT scans before and after treatment, analysed with the Wilcoxon signed rank test.

	Pre-treatment	Post-treatment
DWI	0.843	0.216
CT	0.583	0.019*

* p-value < 0.05 (indicates a significant difference at a significance level of 0.05).

concordance between determination of the longest diameter of target tumour lesions based on high b-value DWI images or CT (presently the predominant modality in clinical trials). Although this was a small group of patients, response to treatment was similar between the two methods. Intentionally, we report no information on changes in the ADC in order to avoid measurement bias.

Issues with inter-observer variability in radiological response assessments have been addressed before [1,2,10–13]. Previous reports indicate that one-dimensional measurement in solid tumours is as accurate as two-dimensional or volumetric measurement [1,10,14] and should be used in tumour response assessments. Our study, although not proven in this pilot study, indicates the probability that similar disagreement between observers can be achieved when one-dimensional DWI is utilized compare to one-dimensional CT. A potential concern that needs to be addressed further is the lower spatial resolution provided by DWI compared to CT. This is extra problematic in the case of pulmonary metastases, being under influence of potential artefacts related to free breathing, particularly those smaller than 20 mm. An example of this is shown in Fig. 5 were a pulmonary lesion displays a rather large disparity on post-treatment CT compared to on DWI. Besides motion artefacts signal suppression due to treatment induced necrosis can also cause underestimation of the lesion volume on DWI. Before implementation of DWI in clinical trials it will be critical to show in a large cohort that not only measurements have a high agreement but also that the response ratio between CT and DWI and classification according to RECIST1.1 are in close agreement.

If CT is to be replaced by an alternative imaging modality in clinical trials, this alternative would not only have to be more accurate, but also as rapid and not more complicated to use. The drawbacks of MRI in comparison to CT (the former being contraindicated for patients with metallic implants, claustrophobia etc.) are offset by the fact that it requires no intravenous contrast agent or no ionising radiation.

Another advantage of DWI is the ability to enhance the signal by suppressing normal tissue background and causing tumour tissue to stand out clearly, which is not the case with CT. Accordingly, our radiologists experienced it subjectively easier to identify tumour lesions with DWI than with CT. It seems likely that tumour assessment could also be performed employing two dimensional maximal intensity projection images in a very rapid fashion, although this would require localization of the lesion on the ADC map for purpose of verification.

There are certain obvious limitations to the present study. First, this was a pilot study involving only five patients. Although, as many as ten lesions per patients were analysed (giving a total of 75 lesions for assessment by CT and DWI), this limited number of patients reduces the statistical power. Five patients with little variation in treatment response between the subjects narrowed the range of changes in lesion size. Secondly, an intravenous contrast agent was not used in two patients, which might have influenced their CT measurements. Third, although our ambition was to examine all of the patients on one and the same day, there was a mean time lapse of 5.6 days between DWI and CT examinations. And finally, all the potential inter- and intra-observer bias known to be associated with RECIST was possible here as well [2], of which only the inter-observer variability was assessed in the current study.

In conclusion, in this pilot study measurements of metastatic lesions on axial DWI images were in close agreement with measurements on axial CT images. Our present results can be used for estimation of sample size in a larger study that explores whether DWI can replace CT in clinical trials of solid tumours such as renal cell carcinoma.

Conflict of interests

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

The study protocol was pre-approved by the regional ethical review board (Dnr 2012/2223-31/1) in Stockholm Sweden.

Consent for publication

The participants gave written informed consent.

Availability of data and materials

Raw data can be presented upon request to the corresponding

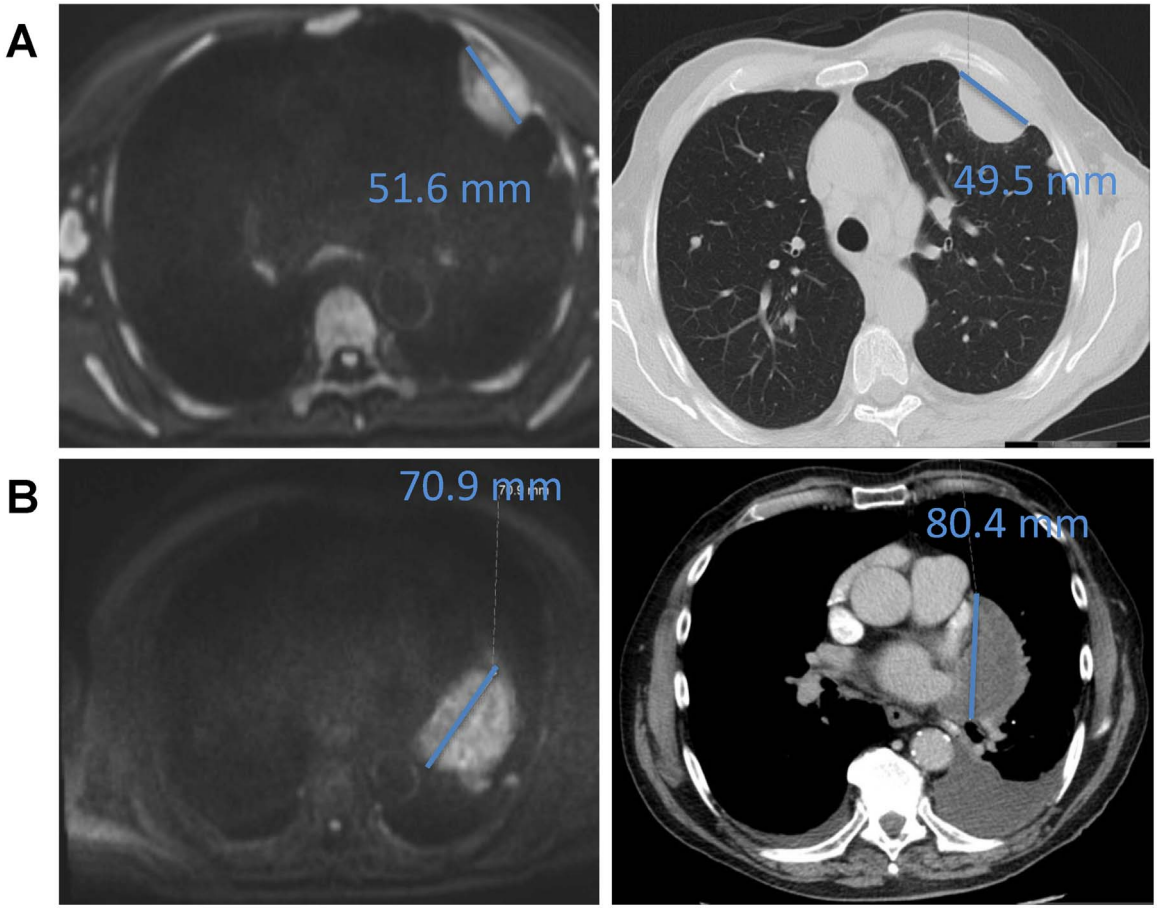

Fig. 5. Two examples of different disparity between CT and DWI. A represents a pleural lesion pre-treatment and B a pulmonary lesion post-treatment.

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Funding

The study was partly funded by VINNOVA (Swedish Governmental Agency for Innovation Systems) and partly by Stockholms läns landsting.

Author's contribution

JF had access to all data. Study concept and design: JF, PS and LB. Acquisition of data: RV-P. Tumor measurements: CH and LB. Analyses and interpretation of data: JF and LB. Writing manuscript: JF and LB.

Acknowledgements

This study was supported by the Swedish Governmental Agency for Innovation System (VINNOVA).

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