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Inter-reader reproducibility of dynamic contrast-enhanced magnetic resonance imaging in patients with non-small cell lung cancer treated with bevacizumab and erlotinib

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ABSTRACT

Objectives When evaluating anti-tumor treatment response by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) it is necessary to assure its validity and reproducibility. This has not been well addressed in lung tumors. Therefore we have evaluated the inter-reader reproducibility of response classification by DCE-MRI in patients with non-small cell lung cancer (NSCLC) treated with bevacizumab and erlotinib enrolled in a multicenter trial.

Materials and methods: Twenty-one patients were scanned before and 3 weeks after start of treatment with DCE-MRI in a multicenter trial. The scans were evaluated by two independent readers. The primary lung tumor was used for response assessment. Responses were assessed in terms of relative changes in tumor mean trans endothelial transfer rate (K^{trans}) and its heterogeneity in terms of the spatial standard deviation. Reproducibility was expressed by the inter-reader variability, intra-class correlation coefficient (ICC) and dichotomous response classification.

Results: The inter-reader variability and ICC for the relative K^{trans} were 5.8% and 0.930, respectively. For tumor heterogeneity the inter-reader variability and ICC were 0.017 and 0.656, respectively. For the two readers the response classification for relative K^{trans} was concordant in 20 of 21 patients ($k = 0.90$, $p < 0.0001$) and for tumor heterogeneity in 19 of 21 patients ($k = 0.80$, $p < 0.0001$).

Conclusions: Strong agreement was seen with regard to the inter-reader variability and reproducibility of response classification by the two readers of lung cancer DCE-MRI scans.

1. Introduction

A challenge in using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for evaluating anti-tumor treatment response is to assure its validity and reproducibility. In short, DCE-MRI measures signal changes over time in a selected volume of tumor tissue and in blood (e.g. arteries) before and after intravenous contrast agent injection. These measurements render pharmacokinetic parameters, such as the endothelial transfer rate K^{trans} that reflects the hyper-permeability in the tumor. The potential strength

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of DCE-MRI is that vascular biologic effects of anti-vascular and anti-tumor treatments are measured potentially before morphologic changes occur and a reduction in size becomes apparent. In lung cancer the use of DCE-MRI seems promising for the follow-up of lung tumors after treatment [1,2].

For lung cancer treatment, the use of novel targeted agents has widely expanded in recent years [3–6]. For example, the anti-vascular agents such as bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF), has shown activity in non-small cell lung cancer (NSCLC) [7,8]. As with other tumor types, it has been proposed that the morphology based response criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST) [9], should be complemented, if not replaced by surrogate markers such as measures derived from DCE-MRI [2,10].

Apart from the apparent potential of DCE-MRI in cancer imaging, practical challenges are currently recognized as well [11]. In particular, correct identification of the tumor margins and selection of the appropriate region of interest (ROI) on a viewing workstation are crucial for the outcome of the DCE-MRI measurements. For multicenter trails this is particularly important as images might be interpreted by different medical specialists. As with conventional measurements such as RECIST, one should be aware of variations in measurements that affect conclusions regarding treatment response [12,13]. In several cancer types, issues such as contouring the tumor have been well addressed [14,15]. However, for lung tumors it remains thus far unknown to what extent variations in tumor contouring effects the response results. The aim of this study is to evaluate the inter-reader variability and response classification of DCE-MRI in patients with advanced NSCLC treated with bevacizumab and erlotinib.

2. Material and methods

2.1. Study design and Eligibility criteria

Chemo naive patients with advanced NSCLC were included in a prospective multicenter phase II study of first-line erlotinib and bevacizumab [16]. The study protocol was approved by the institutional medical ethics review board of each of the three participating medical centers and patients gave written informed consent. The study was in accordance with the Helsinki Declaration as revised in 2000. All patients were evaluated using an extensive imaging protocol, including Chest CT, DCE-MRI, H_2O_{15} Positron Emission Tomography (H_2O_{15}-PET) and ^{18}F-FDG Positron Emission Tomography (^{18}F-PET).

Of the forty-seven patients enrolled in the phase II study a total of twenty-one patients could be included for this inter-reader reproducibility study with an DCE-MRI evaluation at baseline and week 3 after treatment onset (Fig. 1)

2.2. Study treatment

All patients received bevacizumab 15 mg/kg as an intravenous infusion every 3 weeks and erlotinib 150 mg orally daily. Patients remained on treatment until disease progression, unacceptable toxicity and/or patient refusal.

2.3. Imaging schedule and parameter

DCE-MRI scans were performed at baseline and after three weeks of treatment. K^{trans} was determined as the pharmacokinetic parameter of choice to characterize the functional status of tumor micro-vessels and represents a combined measure of microvascular flow, permeability and surface area [17].

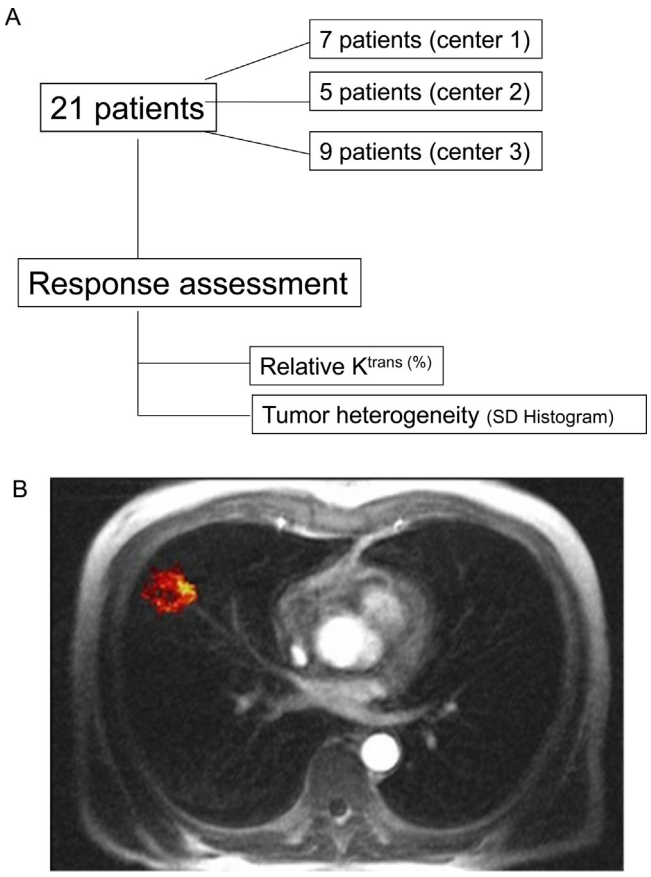

Fig. 1. (A) CONSORT diagram. Twenty one patients included from three different medical centers. (B) Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) images of a tumor. The color scale-coded tumor K^{trans} maps, showing substantial heterogeneity within the tumor lesion.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Image acquisition

DCE-MRI was performed on 1.5 Tesla clinical MRI systems in three University Medical Centers utilizing two Siemens Sonata systems (Erlangen, Germany) and one Intera Philips system (Best, the Netherlands). All DCE-MRI acquisitions were performed under breath-hold in a transverse plane (five 10-mm thick slices) and included five pre-contrast T1-weighted (3D spoiled gradient echo sequences) measurements with different flip angles (FA 35°, 25°, 15°, 10°, 8°, 4°, and 2°) to determine the T1 relaxation time in blood and tumor tissue before contrast arrival. Next, 0.1 mmol/kg body weight Gadolinium-based contrast agent (Gd-DTPA, Magnevist, 0.5 mol/L) was intravenously injected with an injection rate of 3.0 mL/s and flushed with 15 mL saline. This was followed by the DCE series using the same sequence as the five pre-contrast T1 weighted measurements, but with a FA of 35°, containing 30–35 scans of 2 s each. The dynamic acquisition period was started before the bolus arrival under breath hold instructions to minimize motion artifacts during the first pass of the contrast agent [18,19]. Patients were asked to breathe shallowly when breath holding was no longer possible. All three sites were trained for the scan timing protocol. To reduce cardiac motion artifacts in the lung volume as much as possible the phase encoding direction was set to the anterior–posterior direction. On the Siemens scanners the acquisition parameters were TR/TE/FA = 2.84 ms/1.0 ms/35° and FOV 350 mm, and matrix 263 × 350 or TR/TE/FA = 1.93–2.17 ms/0.75 ms/35°, FOV 350 mm,