Clin Neuroradiol
DOI 10.1007/s00062-015-0381-3

ORIGINAL ARTICLE

Between-Scanner and Between-Visit Variation in Normal White Matter Apparent Diffusion Coefficient Values in the Setting of a Multi-Center Clinical Trial

J. Huo · J. Alger · H. Kim · M. Brown · K. Okada · W. Pope · J. Goldin

Received: 6 August 2014 / Accepted: 24 February 2015

Abstract
Purpose To study the between-scanner variation and the between-visit reproducibility of brain apparent diffusion coefficient (ADC) measurements in the setting of a multi-center chemotherapy clinical trial for glioblastoma multiforme.
Methods and Materials ADC maps of 52 patients at six sites were calculated in-house from diffusion-weighted images obtained by seven individual scanner models of two vendors. The median and coefficient of variation (CV) of normal brain white matter ADC values from a defined region of interest were used to evaluate the differences among scanner models, vendors, magnetic fields, as well as successive visits. All patients participating in this study signed institutional review board approved informed consent. Data acquisition was performed in compliance with all applicable Health Insurance Portability and Accountability Act regulations. The study spanned from August 1, 2006, to January 29, 2008.
Results For baseline median ADC, no difference was observed between the different scanner models, different vendors, and different magnetic field strength. For baseline ADC CV, a significant difference was found between different scanner models ($p=0.0002$). No between-scanner difference was observed in ADC changes between two visits. For between-visit reproducibility, significant difference was seen between the ADC values measured at two successive visits for the whole patient group.
Conclusion The CVs varied significantly between scanners, presumably due to image noise. Consistent scanner parameter setup can improve reproducibility of the ADC measurements between visits.

Keywords ADC · Normal white matter · Between-scanner variation · Between-visit reproducibility

J. Huo (✉)
TeraRecon Inc.,
4000 E 3rd Ave., Suite 200,
94404 Foster City, CA, USA
e-mail: jinghuo@gmail.com

J. Alger, PhD · H. Kim · M. Brown · W. Pope · J. Goldin
Department of Radiological Science,
University of California in Los Angeles,
924 Westwood Blvd, Suite 650,
90024 Los Angeles, CA, USA

K. Okada
Department of Computer Science,
San Francisco State University,
San Francisco, USA

Introduction

Diffusion-weighted (DW) magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) can measure the Brownian motion of water molecules at the microscopic level and thus can detect relatively small changes in tissue structure in solid tumors before tumor size change is visible [1–3, 18, 20, 24, 26]. Apparent diffusion coefficient (ADC) map, calculated from DW-MR or DTI images, is reported to be inversely correlated with tumor cellularity [12, 22] and is being explored as a surrogate marker for monitoring the treatment response to therapeutic interventions in many studies [7, 16, 22].

Ongoing studies are using ADC as a biomarker to assess treatment response to glioblastoma multiforme (GBM) tumors [6, 17, 21]. Quantitative and qualitative analysis is predicated on either treatment prediction using baseline ADC data [28] or treatment response detection using ADC changes between baseline and follow-up(s) [6, 17, 21]. In the setting of a multi-center, multi-scanner chemotherapy

Published online: 20 March 2015

clinical trial, it is necessary to evaluate the reproducibility of ADC measurements to reliably use ADC values as biomarker to evaluate GBM tumor treatment response.

Padhani et al. [19] emphasized that centers should demonstrate the reproducibility of their clinical measurements, and major sources of error should be identified. Different factors affecting ADC values and reproducibility are being evaluated. Steens et al. examined different *b*-values and scan-rescan reproducibility on whole-brain ADC histogram [25]. Kubo et al. compared different ADC calculating methods: two-point method and multi-point method [13]. Others studied the effects of field strength [10], number and strength of *b*-values [15], and aging [5, 8]. Xing et al. [27] studied the effect of diffusion weighting on the precision of ADC measurements. Farrell [14] and Lanman [9] studied effects of diffusion scheme and the signal-to-noise ratio (SNR) on the reproducibility of ADC derived from DTI images. These studies were all single-scanner studies. Koizumi et al. studied the ADC reproducibility on four 1.5 T different scanners by GE and Siemens using a phantom [11]. Sasaki et al. evaluated the inter-imager, inter-vendor, and inter-institute variability of brain ADC values using healthy volunteers [23].

The aims of our study were to evaluate between-scanner and between-visit variation of ADC measurement of real-world patients group with variable scanner parameter setup. The setting is a multi-center drug clinical trial where multiple centers and multiple scanners were involved. Even following radiation and variable chemotherapy these patients still appeared to have consistent normal brain white matter (WM) ADC values by visual check. In our study, we evaluated whether a variety of clinical MRI scanner models produced consistent measures of brain WM ADC, and whether between-visit ADC measurements were reproducible at two visits for different scanner models. We examined not only absolute ADC values, but also the dispersion of ADC measurements. Data was obtained from a multi-center clinical trial for treatment of GBM.

Methods and Materials

Patient Group

A total of 68 patients with GBM brain tumors from six medical centers were obtained.

The patient selection criteria were: (1) no visible T2-weighted signal change in the WM used for region of interest (ROI) analysis as determined by a neuroradiologist; (2) no significant magnetic susceptibility artifacts and (3) normal brain structures clearly identifiable on the ADC map. Eleven patients did not satisfy the criteria. As a result, we had 57 patients with usable baseline scans.

The scanner selection criteria were: (1) scanners which scanned at least five patients to ensure substantial statistical power; (2) scanners which scanned the same patient at least two times (for the between-visit variation study).

As a result, we included 52 patients (31 men and 21 women; age range 19–78 years old; mean age, 52 years old) by seven scanner models for between-scanner variation study, and 40 patients by five scanner models for the between-visit ADC reproducibility study. Age information for seven groups is: (1) 26–71; (2) 48–69; (3) 36–63; (4) 19–64; (5) 37–70; (6) 39–69; (7) 25–78. These patients were treated with radiation and chemotherapy, with normal appearing brain WM visually.

Scanner Protocol

Seven scanners from six centers with variability in scanner parameter setup built the setting of the real-world ADC variation study. The seven scanners were two 3 T scanners (Siemens TrioTim at two sites) and five 1.5 T scanners (GE SIGNA HDx at two sites, GE SIGNA EXCITE, Siemens Avanto, Siemens Symphony). The protocol required the use of DW spin-echo echo-planar imaging technique (TR = 4000–12,000 ms, TE = 60–110 ms) using a *b*-factor between 700 and 1000 s/mm^2; 22–36 axial slices were acquired, with FOV = 220–240 mm, slice gap 5–7 mm, slice thickness 5–7 mm, and acquired matrix size 128 × 128, 256 × 192, or 256 × 256. The number of diffusion sensitization directions was from 3 to 30. The details of the scanner parameters are shown in Table 1. The data were anonymized and collected in the digital imaging and communications in medicine format.

Image Analysis

All ADC maps were calculated from DW images with the same in-house software using a two-point method as shown in the following equation: $ADC = -\ln[S(b)/S(0)]/b$, with b being the diffusion sensitivity factor ranging between 700 and 1000 s/mm^2, $S(0)$ and $S(b)$ being the image intensity when $b = 0$, and 700 s/mm^2 or $b = 1000$ s/mm^2. DW, trace DW or DT images were used to derive ADC values based on their availability. For diffusion-weighted imaging (DWI) trace images, we calculated ADC maps from DW images by the equation above. For DTI, we calculated ADC for each orientation and average them as the ultimate ADC map. Figure 1 shows two example ADC maps.

Study Design

A fixed size circular 2D ROI (radius = 7 pixels) was manually drawn on the normal-appearing brain WM above ventricles and confirmed by board-certified neuroradiologist.

Table 1 Detailed protocols of the MR scanners

	Scanner model	Number of patients	Field strength (T)	DWI or DTI	Number of diffusion directions	Acquired matrix size	Slice thickness (mm)
1	GE SIGNA HDx at site 1	8	1.5	DWI or DTI	6 for DTI and N/A for DWI	256×256	5
2	GE SIGNA HDx at site 2	7	1.5	DWI	N/A	256×256	5
3	GE SIGNA Excite	5	1.5	DWI	N/A	256×256	5
4	Siemens Symphony	5	1.5	DTI	6	128×128 or 256×256	5
5	Siemens Avanto	9	1.5	DTI	6	256×192 or 256×256	5
6	Siemens TrioTim at site 3	10	3	DTI	30	128×128	5
7	Siemens TrioTim at site 4	8	3	DWI	3	128×128	7

MR magnetic resonance, *DWI* diffusion-weighted imaging, *DTI* diffusion tensor imaging

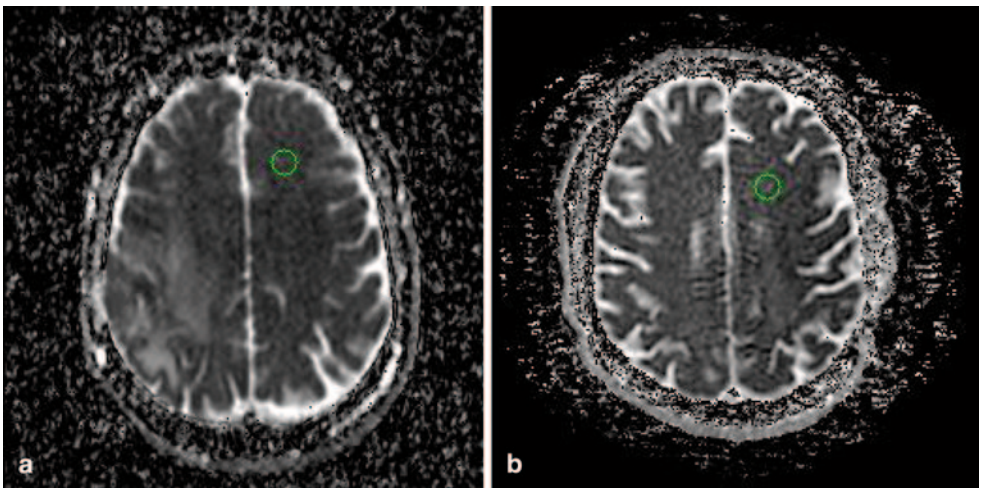

Fig. 1 Two example apparent diffusion coefficient (ADC) maps with brain white matter (WM) region of interests (ROIs). The window level and width are set to 2800 and 1500×10^{-6} mm^2/s, respectively. The median and coefficient of variation (CV) for each ROI is as follows: (**a**) median = 721×10^{-6} mm^2/s, CV = 0.11; (**b**) median = 884×10^{-6} mm^2/s, CV = 0.18

For each ROI, ADC median, and coefficient of variation (CV) were calculated. Median ADC value was used to represent the whole ROI ADC measurements to compare the absolute ADC value across different scanner models. CV, defined as the ratio of standard deviation (STD) to the mean, was used to evaluate the dispersion of the whole ROI ADC measurements. Median was used here instead of mean to avoid random noise. CV was used instead of STD, because the STD of data should be understood in the context of the mean of the data. Figure 1 shows two images with different image quality, and thus different CVs and medians. Yasemin Bilgili et al. reported that varying ROI sizes in brain WM did not yield statistically different ADC values [4].

Baseline ROI median and CV were used to explore the ADC variation across different scanners. Furthermore, the median change and CV change between two visits (typically 5–7 weeks apart) were calculated for each brain WM ROI, and differences across scanners were compared. What is more, between-visit reproducibility of ROI median and CV were evaluated for the whole patient group.

Statistical Analysis

Box-Cox transformation followed by Shapiro–Wilk normality test was used to meet normality assumption in ADC median and CV. For baseline inter-scanner variation analysis, differences in baseline ROI ADC median and CV were examined by the analysis of variance (ANOVA) test among different scanners, different magnetic fields, and different vendors.

For the between-visit ADC change analysis, differences in the ROI ADC median change and CV change among different scanners were examined by the ANOVA test. Between-visit ADC measurement agreement at two visits was examined by using an intra-class correlation coefficient (ICC), and difference between the two visits in ADC measurements was evaluated by using a paired *t*-test.

Results

The Shapiro–Wilk normality test showed that the ROI ADC median ($p = 0.0014$) and CV ($p = 0.0065$) were not normally distributed. After log transformation of CV and inverse transformation of the median based on the Box-Cox model, data were normally distributed and thus eligible for the ANOVA test.

The results showed that there was no significant difference in median ADC ($p = 0.165$) between any two of the seven scanner models. However there was a significant difference in CV ($p = 0.0002$). Multiple comparison test by was Tukey's honest significant difference method

was conducted. The result showed that the differences came from the following scanner pairs with significance levels: 1–7($p=0.033$), 2–7($p=0.002$), 3–7($p=0.00007$), 5–7($p=0.009$), 6–7($p=0.023$), with the scanner index numbers corresponding to those in Table 1. Figure 2 displays the box plots of the seven-patient groups.

For inter-vendor difference, we combined the three 1.5 T GE scanners (#1, 2, 3) patients into one group and the two 1.5 T Siemens scanners (#4, 5) patients into another. We applied the ANOVA test to compare the difference in ROI median and CV between the two groups. There was no significant difference in either the median ($p=0.30$) or CV ($p=0.21$) for the two groups. Figure 3 displays the box plots of the aggregated groups.

We also evaluated the intra-vendor difference in ADC values when different magnetic field strength were used. We combined the two 1.5 T Siemens scanners into one group and the two 3.0 T Siemens scanners into another. The ANOVA test showed that there was no significant difference in terms of brain WM ROI median ($p=0.16$). However, the test demonstrated a significant difference in brain WM ROI CV between different magnetic fields ($p=0.04$). Figure 4 shows the box plots of the two groups.

For the between-visit reproducibility analysis, we had 40 patients by 5 scanner models with both baseline and follow-up data usable. The days between two visits are 34.35 + 6.42, and the range is 27. For each patient, we calculated the ADC changes in ROI median and CV, and compared the difference across different scanners. The ANOVA test showed that there was no significant difference among the five scanners in median change ($p=0.62$), and CV change ($p=0.71$). Figure 5 displays the box plots of the five patient groups.

When the 40 patients were combined, a paired *t*-test showed that there was no significant difference between baseline and follow-up ADC values in CV ($p=0.44$), but significant difference in median ($p=0.01$). The ICC was 0.58 for median, and 0.56 for CV. Figure 6 shows the Bland–Altman plot to visualize the agreement between the ADC values measured at two-time points before and after treatment.

Three of the patients from scanner 1 did not have consistent scanner parameter setup (number of diffusion sensitization directions) for baseline and follow-up scans. With these three patients excluded, the paired *t*-test between baseline and follow-up median ADC values showed that the significance level of $p=0.05$ for the rest 37 patients. Figure 7 shows the box plot of the rest 37 patients.

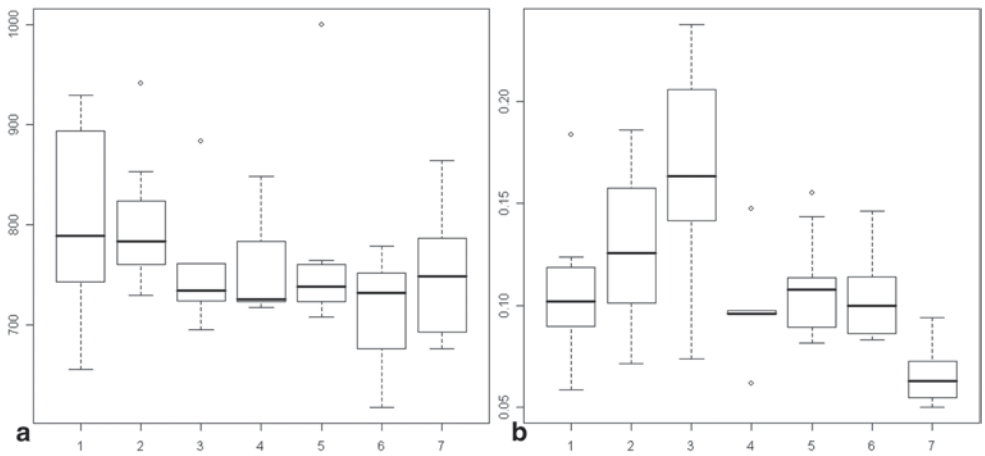

Fig. 2 Box plots of the baseline brain white matter (WM) apparent diffusion coefficient (ADC) (units of 10^{-6} mm^2/s) median and coefficient of variation (CV): (**a**) brain WM region of interest (ROI) median; (**b**) brain WM ROI CV

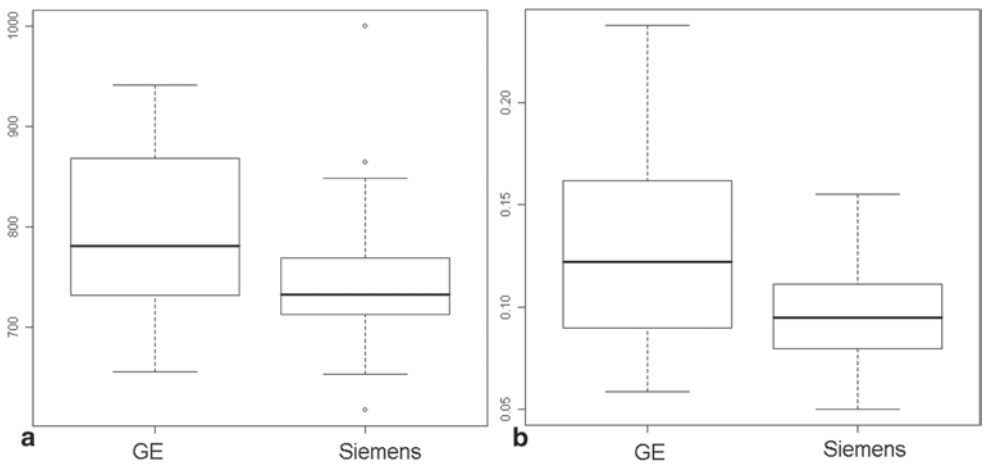

Fig. 3 Box plots of the baseline brain white matter (WM) apparent diffusion coefficient (ADC) (units of 10^{-6} mm^2/s) median and coefficient of variation (CV) for all 1.5 T GE and all 1.5 T Siemens scanners: (**a**) brain WM region of interest (ROI) median; (**b**) brain WM ROI CV

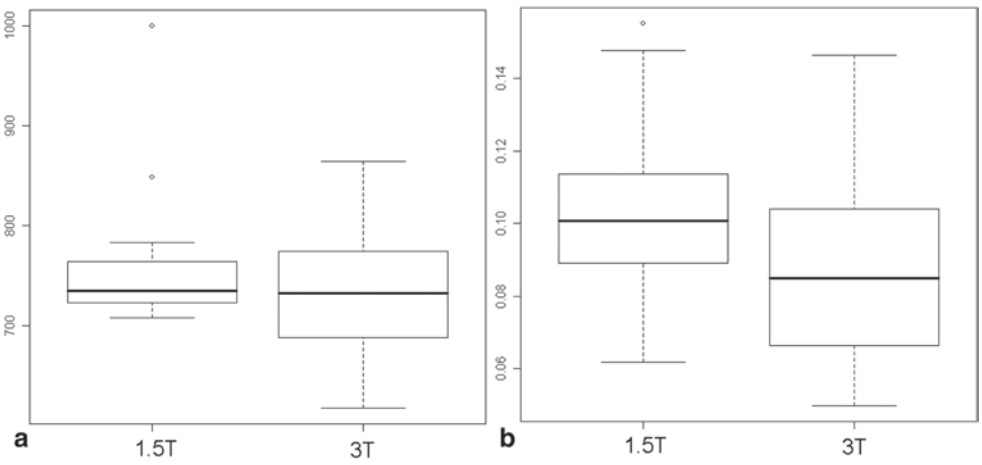

Fig. 4 Box plots of the baseline brain white matter (WM) apparent diffusion coefficient (ADC) (units of 10^{-6} mm^2/s) median and coefficient of variation (CV) by magnetic field strength for all Siemens scanners: (**a**) brain WM region of interest (ROI) median; (**b**) brain WM ROI CV

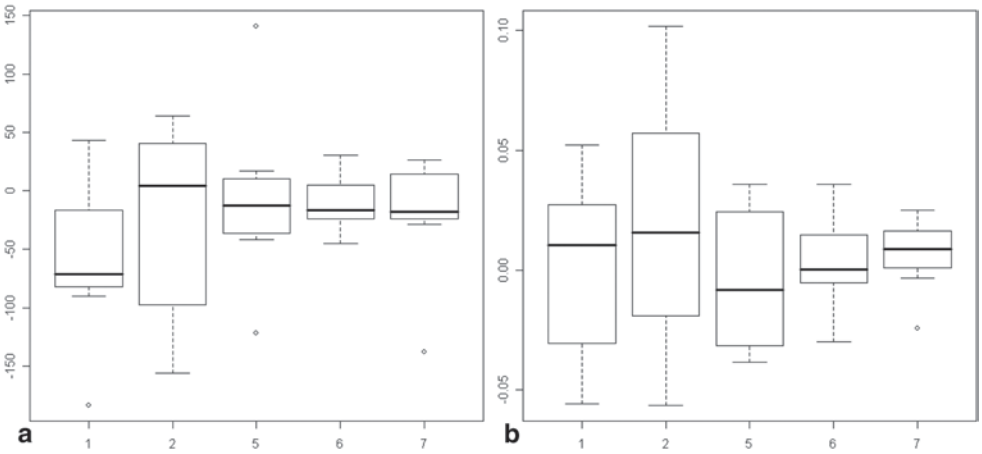

Fig. 5 Box plots of the apparent diffusion coefficient (ADC) changes for each patient between two visits: (**a**) brain white matter (WM) region of interest (ROI) median change by scanner; (**b**) brain WM ROI coefficient of variation (CV) change by scanner. The number of patients involved here are: scanner 1: $n=7$; scanner 2: $n=7$; scanner 5: $n=9$; scanner 6: $n=9$; scanner 7: $n=8$. Scanners number corresponds to Table 1. ADC values are in the units of 10^{-6} mm^2/s

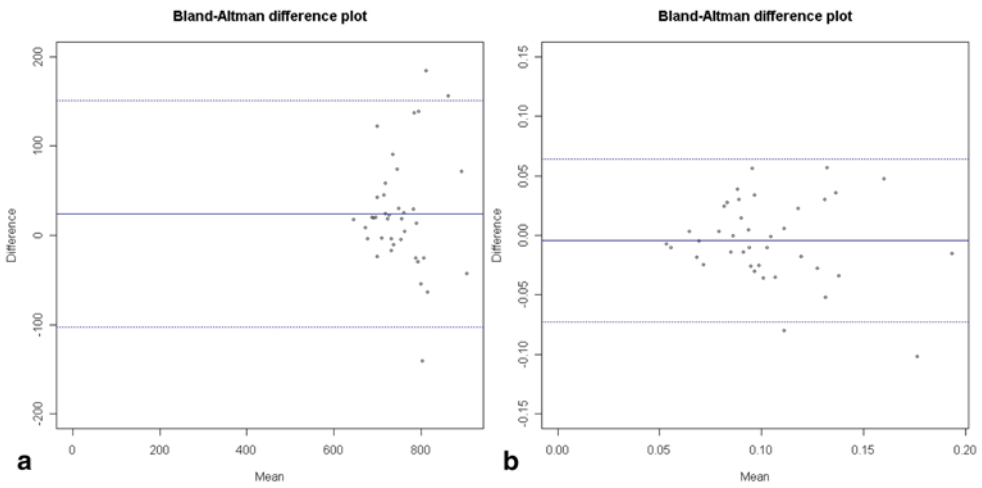

Fig. 6 Bland–Altman plots to visualize the agreement between the apparent diffusion coefficient (ADC) values measured at two-time points before and after treatment: (**a**) median, mean difference = 23.87, upper agreement limit = 150.51, lower agreement limit = −102.77; (**b**) coefficient of variation (CV), mean difference = −0.004, upper agreement limit = 0.06, lower agreement limit = −0.07. ADC values are in the units of 10^{-6} mm^2/s.

Discussion

In this study, we compared brain WM ADC measurements of patients with GBM tumors among different scanner models from different vendors at different medical sites with different field strengths and different acquisition styles. We acquired patient scans from a GBM drug clinical trial. The treatment of radiation and chemotherapy may affect the ADC values and make them change over time, reflecting real-world conditions in which patient treatment can be highly variable.

Others have found a small but significant difference in ADC values between scanners [23]. We did not observe a significant difference in median ADC values across differ-

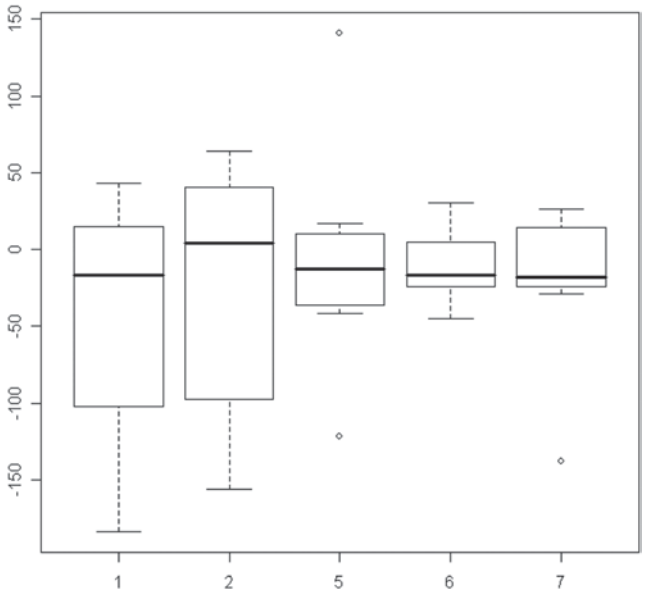

Fig. 7 Box plots of the brain white matter (WM) region of interest (ROI) median changes by scanner between two visits with 37 patients. Apparent diffusion coefficient (ADC) values are in the units of 10^{-6} mm^2/s.

ent scanner models. The power analysis showed that 52% power was achieved at the 0.05 level of alpha to detect differences in median ADC values among scanners, and that we needed 13 patients per scanner to have enough statistical power to detect the difference in ROI median. We cannot conclude whether this is because there was truly no difference, or because we did not have enough statistical power to detect a small change. Another possible reason is that we found the intra-scanner CV is in the range of 5−25%, while Sasaki et al. [23] reported 2–8%. The higher CV in our study might attribute to the fact we did not find an inter-scanner difference in mean ADC.

In contrast to median ADC, we found significant difference in CV of ADC measurements. This may be due to variability in image noise. Image noise can stem from many factors. First of all, different scanners from different vendors have different radiofrequency coil designs which can affect the accuracy of ADC values [23]. Second, different magnetic field strength will lead to different SNRs, and thus different image quality (see below). Moreover, different acquisition techniques may result in different sensitivity. For instance, DTI technique applies six or more gradient orientations to obtain the images, whereas DWI technique uses three gradient orientations and obtains the averaged signal. Additionally, the total number of diffusion sensitization directions also may affect the accuracy of ADC measurement. In this study, there were both DWI and DTI scans with number of diffusion sensitization directions varying from 3 to 30, as shown in Table 1. Moreover, different fields of view and slice thicknesses make a single voxel represent a different physical volume, resulting in a different SNR. Another possible cause for different noise level comes from different *b*-values. Lastly, image post processing, including image interpolation, filtering to improve image quality, etc. may have variable effects.

For inter-vendor variability, we compared the 1.5 T Siemens scanners and 1.5 T GE scanners and did not observe significant difference in median or CV of ADC measurements. Our observation agrees with the report by Koizumi et al. [11]. Koizumi et al. also reported a good relationship in ADC values between scanners given a proper b factor in their phantom study [11].

For ADC variability between different magnetic field strengths, we compared the 1.5 T and 3 T scanners from the same vendor (Siemens). We observed no difference in median ADC values, consistent with prior studies [10, 23]. However, we observed that CV of ADC measurements from 1.5 T Siemens scanners was larger than 3.0 T Siemens scanners, which meant, ADC measurements from 1.5 T scanners were more dispersed than 3.0 T scanners. The result is logical since SNR gets higher with higher magnetic field strength. Higher SNR leads to less noise and less dispersion. Interestingly, with our pooled data, the 1.5 T Siemens scanners used a DTI acquisition technique and post-processed the images with interpolation, while the 3.0 T Siemens scanners used a DWI acquisition technique without interpolating the raw images. Both of these factors may affect the dispersion of the brain WM ADC values. With our data, we were not able to evaluate their separate effects.

Besides analyzing between-scanner ADC variation with baseline data, we also explored the between-visit ADC variation among multiple scanners and ADC reproducibility between two successive visits. The interval between two visits ranged from 4 to 8 weeks. We found no significant difference across different scanner models in median change or CV change between successive visits.

As for the between-visit reproducibility, ADC measurements did not show high reproducibility for the whole 40 patients. Three of the patients from scanner 1 did not have consistent scanner parameter setup (number of diffusion sensitization directions) for baseline and follow-up scans. With these three patients excluded, the paired *t*-test between baseline and follow-up median ADC values showed that the level of significance was decreased from 0.01 to 0.05. We conclude that consistent scanner parameters are necessary to achieve good between-visit reproducibility.

These data suggests that ADC measurements can have good reproducibility between two successive visits with exactly the same scanner parameters. The between-visit ADC change does not vary significantly among scanners.

The limitation of our study is that relatively a few patients available for each scanner model, diminishing the statistical power of our analysis, and thus the ability to detect small

changes. For future studies, a larger subject population is required to increase statistical power to detect more pairwise differences. Moreover, we were not able to tell the degree of between-scanner ADC variation due to a lack of a controlled (phantom) study. Lastly, inconsistent between-scanner parameters (DW gradient orientations, number of *b*-factor, and in-plane image resolution) may introduce bias to the study. Moreover, due to the different imaging resolution, the actual ROI size is different, and thus the CV values may be significantly affected. In the future, an interesting study would be to interpolate images to achieve the same image resolution. By such a method, the effects of data interpolation can also be evaluated. However, in a real-world multi-center clinical trial, it is possible that scanner parameters are set different among different medical sites.

In conclusion, we performed a comparison study in a real-world clinical trial to determine if ADC measurements were consistent across different scanners between different visits. For between-scanner ADC variation, the results suggested that CV difference in ADC measurements was found across different scanners. Median difference of ADC measurements might be found given more patients and more statistical power. Moreover, CV difference was reported for different magnetic field strength and CV was smaller for 3 T than 1.5 T. For between-visit ADC variation, the ADC measurements could have good reproducibility with consistent scanner parameters between two successive visits 4–8 weeks apart. Furthermore, the ADC measurement changes did not vary significantly across scanners in terms of both median change and CV change. This implies that ADC changes before and after treatment have potentials as surrogate endpoints. For studies using baseline ADC as treatment predictors, we suggest evaluating image quality by use of brain WM.

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Bammer R. Basic principles of diffusion-weighted imaging. Eur J Radiol. 2003;45:169–84.
2. Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis—a technical review. NMR Biomed. 2002;15:456–67.
3. Bihan D Le, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H. Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging. 2001;13(4):534–46.
4. Bilgili Y, Unal B. Effect of region of interest on interobserver variance in apparent diffusion coefficient measures. Am J Neuroradiol. 2004;25:108–11.
5. Bonekamp D, Nagae LM, Degaonkar M, Matson M, Abdalla WM, Barker PB, Mori S, Horská A. Diffusion tensor imaging in children and adolescents: reproducibility, hemispheric, and age-related differences. NeuroImage. 2007;34:733–42.
6. Chenevert TL, McKeever PE, Ross BD. Monitoring early response of experimental brain tumors to therapy using diffusion magnetic resonance imaging. Clin Cancer Res. 1997;3:1457–66.
7. Chenevert TL, Stegman LD, Taylor JM, Robertson PL, Greenberg HS, Rehemtulla A, Ross BD. Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. J Natl Cancer Inst. 2000;92:2029–36.
8. Engelter ST, Provenzale JM, Petrella JR, DeLong DM, MacFall JR. The effect of aging on the apparent diffusion coefficient of normal-appearing white matter. AJR Am J Roentgenol. 2000;175:425–30.
9. Farrell JA, Landman BA, Jones CK, Smith SA, Prince JL, van Zijl PC, Mori S. Effects of signal-to-noise ratio on the accuracy and reproducibility of diffusion tensor imaging-derived fractional anisotropy, mean diffusivity, and principal eigenvector measurements at 1.5 T. J Magn Reson Imaging. 2007;26:756–67.
10. Huisman TA, Loenneker T, Barta G, Bellemann ME, Hennig J, Fischer JE, Il'yasov KA. Quantitative diffusion tensor MR imaging of the brain: field strength related variance of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) scalars. Eur Radiol. 2006;16(8):1651–8.
11. Koizumi K, Masuda K, Komizu M, Ikemoto Y, Yoshimura M, Iguchi H, Hiraga A, Kobayashi A. Report on the ECR2003 (European Congress of Radiology): comparison of apparent diffusion coefficient (ADC) between different MRI scanners. Nihon Hoshasen Gijutsu Gakkai Zasshi. 2003;59(7):825–6. (Japanese).
12. Kono K, Inoue Y, Nakayama K, Shakudo M, Morino M, Ohata K, Wakasa K, Yamada R. The role of diffusion-weighted imaging in patients with brain tumors. AJNR Am J Neuroradiol. 2001;22:1081–8.
13. Kubo H, Maeda M, Araki A. Comparison of apparent diffusion coefficients between two-point and multi-point analyses using high-b-value diffusion MR imaging. Jpn Soc Radiol Technol. 2001;57(6):634–8.
14. Landman BA, Farrell JA, Jones CK, Smith SA, Prince JL, Mori S. Effects of diffusion weighting schemes on the reproducibility of DTI-derived fractional anisotropy, mean diffusivity, and principal eigenvector measurements at 1.5 T. NeuroImage. 2007;36:1123–38.
15. Melhem ER, Itoh R, Jones L, Barker PB. Diffusion tensor MR imaging of the brain: effect of diffusion weighting on trace and anisotropy measurements. AJNR Am J Neuroradiol. 2000;21:1813–20.
16. Moffat BA, Chenevert TL, Meyer CR, McKeever PE, Hall DE, Hoff BA, Johnson TD, Rehemtulla A, Ross BD. The functional diffusion map: an imaging biomarker for the early prediction of cancer treatment outcome. Neoplasia. 2006;8(4):259–67.
17. Mardor Y, Pfeffer R, Spiegelmann R, Roth Y, Maier SE, Nissim O, Berger R, Glicksman A, Baram J, Orenstein A, Cohen JS, Tichler T. Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. J Clin Oncol. 2003;21:1094–100.
18. Neil JJ. Diffusion imaging concepts for clinicians. J Magn Reson Imaging. 2008;27:1–7.
19. Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, Dzik-Jurasz A, Ross BD, Van Cauteren M, Collins D, Hammoud DA, Rustin GJ, Taouli B, Choyke PL. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia. 2009;11(2):102–25.
20. Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. Radiology. 1996;201:637–48.
21. Pirzkall A, Ozturk E, Lee MC, Lupo J, Crawford FW, Chuang CF, Nelson SJ. Assessing tumor response in GBM following concurrent radiation and chemotherapy by means of novel MR based imaging methods characterizing metabolic and physiologic changes. In Proceedings of the American Society for Therapeutic Radiology and Oncology 47th Annual Meeting; 2005 (Oct 1: S66–7).

22. Ross BD1, Moffat BA, Lawrence TS, Mukherji SK, Gebarski SS, Quint DJ, Johnson TD, Junck L, Robertson PL, Muraszko KM, Dong Q, Meyer CR, Bland PH, McConville P, Geng H, Rehemtulla A, Chenevert TL. Evaluation of cancer therapy using diffusion magnetic resonance imaging. Mol Cancer Ther. 2003;2:581–7.
23. Sasaki M, Yamada K, Watanabe Y, Matsui M, Ida M, Fujiwara S, Shibata E; Acute Stroke Imaging Standardization Group-Japan (ASIST-Japan) Investigators. Variability in absolute apparent diffusion coefficient values across different platforms may be substantial: a multivendor, multi-institutional comparison study. Radiology. 2008;249(2):624–30.
24. Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. Radiology. 2000;217(2):331–45.
25. Steens SC, Admiraal-Behloul F, Schaap JA, Hoogenraad FG, Wheeler-Kingshott CA, le Cessie S, Tofts PS, van Buchem MA. Reproducibility of brain ADC histograms. Eur Radiol. 2004;14:425–30.
26. Stejskal E, Tanner J. Spin diffusion measurements: spin echos in the presence of time-dependent field gradient. J Chem Phys. 1965;42:288–92.
27. Xing D, Papadakis NG, Huang CL, Lee VM, Carpenter TA, Hall LD. Optimised diffusion-weighting for measurement of apparent diffusion coefficient (ADC) in human brain. Magn Reson Imaging. 1997;15(7):771–84.
28. Pope WB1, Kim HJ, Huo J, Alger J, Brown MS, Gjertson D, Sai V, Young JR, Tekchandani L, Cloughesy T, Mischel PS, Lai A, Nghiemphu P, Rahmanuddin S, Goldin J. Recurrent glioblastoma multiforme: ADC histogram analysis predicts response to bevacizumab treatment. Radiology. 2009 Jul;252(1):182-9.