Physics and Imaging in Radiation Oncology 33 (2025) 100720

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Technical Note

Repeatability of rectal cancer apparent diffusion coefficient measurements on a 1.5 T MR-linac☆

Hidde Eijkelenkamp [a,*], Guus Grimbergen [a], Brigid McDonald [b], Reijer Rutgers [a], Tim Schakel [a], Casper Beijst [a], Marielle Philippens [a], Gert Meijer [a], Martijn Intven [a]

[a] University Medical Center Utrecht, Department of Radiotherapy, Utrecht, the Netherlands
[b] University of Texas MD Anderson Cancer Center, Department of Radiation Oncology, Houston, USA

ARTICLE INFO

Keyword:
Apparent diffusion coefficient (ADC)
Diffusion-weighted imaging (DWI)
Repeatability MR-guided radiotherapy
Rectal cancer

ABSTRACT

The repeatability of the apparent diffusion coefficient (ADC) during radiotherapy for rectal cancer on a 1.5 T MR-linac was investigated by acquiring two sequential diffusion-weighted imaging (DWI) sequences at each fraction. In 109 treatment sessions involving 22 patients, tumors were separately delineated on the b500 images. ADC maps were generated with all b-values (0, 30, 150, and 500 s/mm^2) on the MR-linac, and the median ADC values were used in Bland-Altman analyses. A relative repeatability coefficient of 17.0 % was determined, providing a threshold to differentiate between measurement variability and true treatment response. This threshold can be used for potential response monitoring and personalized treatment adjustments.

1. Introduction

Diffusion-weighted imaging (DWI) is a functional magnetic resonance imaging technique (fMRI) commonly used in oncology. DWI offers insight into tissue characteristics by measuring the diffusion of water molecules, which is expressed as the apparent diffusion coefficient (ADC). This ADC serves as a potential quantitative imaging biomarker for oncologic treatment outcome prediction and response assessment and might be used in personalized cancer treatment [1].

In rectal cancer, the value of ADC has been widely researched with diagnostic MRI pre- and post-treatment to assess and predict the response of chemotherapy and radiotherapy (RT). A low pretreatment ADC and an increased post-treatment ADC are both correlated with good response rates after RT [2]. Furthermore, a low pretreatment ADC is correlated with increased complete and good response rates after chemoradiotherapy [3]. However, while these studies address the potential of ADC in rectal cancer response prediction, their impact on clinical decision-making is limited because they mostly contain only pre- and post-treatment measurements with long intervals between them. In other tumor sites, mid-treatment ADC measurements have demonstrated effectiveness and potential in early response prediction [4–6]. This absence of comprehensive ADC data throughout treatment in rectal cancer is a limitation but might be resolved by regularly measuring the ADC during the course of treatment.

MRI-guided radiotherapy (MRgRT) has this capability with fMRI opportunities at each fraction. Daily ADC measurements have shown a prognostic role at some tumor sites [7–9]. More robust ADC information potentially enhances response monitoring and enables personalized treatment adjustments for rectal cancer [10,11]. Serial ADC acquisition is feasible on MR-linac systems for rectal cancer, but these measurements must be reliable to distinguish between therapy-related responses and measurement variations before they can be integrated into personalized treatment [8,12]. For diagnostic MRI-systems the repeatability of ADC values for rectal cancer is described for several setups [13]. However, due to differences in acquisition and system design, this repeatability might be different for MR-linac systems [14,15]. Therefore, this study aimed to determine the ADC repeatability during clinical use by assessing ADC values in rectal cancer, with normal prostate tissue as reference, using sequential DWI scans on a 1.5 T MR-linac.

2. Methods

2.1. Patients

Twenty-two consecutive patients with rectal cancer were treated on a 1.5 T MR-linac (Unity, Elekta AB, Stockholm, SW) between September

☆ This article is part of a special issue entitled: 'MR in RT 2024' published in Physics and Imaging in Radiation Oncology.

* Corresponding author.
E-mail address: h.eijkelenkamp@umcutrecht.nl (H. Eijkelenkamp).

https://doi.org/10.1016/j.phro.2025.100720
Received 3 July 2024; Received in revised form 26 January 2025; Accepted 28 January 2025
Available online 30 January 2025

2021 and December 2022. All patients were diagnosed with rectal cancer (stage cT3c-d (MRF-) N0M0 or cT1-3 (MRF-) N1M0) and received short-course neoadjuvant radiotherapy with 25 Gy delivered in five fractions. Eight patients participated in a dose escalation study (pre-RADAR) and received two to four additional fractions of 5 Gy [16]. Consent was given through the Dutch Prospective Data Collection Initiative on Colorectal Cancer (PLCRC; NCT02070146) or the Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac (MOMENTUM; NCT04075305) studies, both approved by the Medical Research and Ethics Committee of the University Medical Centre Utrecht, the Netherlands.

2.2. Imaging and processing

During procedure on the MR-linac, a transverse T2-weighted and two directly sequential DWI sequences with b-values of 0, 30, 150, and 500 s/mm^2 were acquired before dose delivery (Fig. 1). The scanning DWI sequence parameters are detailed in Supplementary Table 1. Single-shot spin-echo EPI (ssSE-EPI) was used for the readout. ADC maps (Fig. 1) were calculated on the MR-linac with a mono-exponential model of all b-values by fitting the data with signal intensity (S) to the following equation: $S(b) = S_0 \bullet e^{-ADC \bullet b}$.

After imaging, all sequences were transferred to an in-house tool for processing [17]. Tumors were delineated on the high b-value (b500) images of every DWI sequence [15]. For the purpose of providing reference values in the prostate, the central zone of the prostate gland was delineated on the T2w scan with a 1 cc cylindrical contour in all male patients, created by placing concentric circular contours of radius 7.5 mm on three adjacent slices, expanded with a 5 mm margin. Contours were propagated to the ADC maps (Supplementary Fig. 1).

2.3. Statistical analysis

Data were presented as median with interquartile range (IQR), as mean with standard deviation (SD) or as frequencies with percentages, depending on their distribution.

Bland-Altman analysis was performed to compare the two sequential DWI sequences by using the median ADC from each region of interest [18]. The repeatability coefficient (RC) was calculated from the within-subject standard deviation (wSD) at a confidence level of 95 %: $RC = 2.77 * wSD$.

Because the RC is an absolute measure and is therefore dependent on the magnitude of the ADC measurements, the relative repeatability coefficient (%RC) was calculated from the within-subject coefficient of variation (wCV): $\%RC = 2.77 * wCV$ [19].

Data were visualized using R studio version 4.2.2.

3. Results

3.1. Patients

Baseline patient and tumor characteristics are summarized in Supplementary Table 2. The cohort was primarily male (77 %) and had an average age of 63 years, ranging from 43 to 81 years. A total of 109 treatment sessions included two sequential DWI sequences, with 70 sessions containing a prostate contour. One treatment session was excluded before analysis due to a technical failure in one of the DWI scans, rendering it unreadable.

On the b500 image of the DWI sequences, tumor contours had a median volume of 15.05 cc with an IQR of 14.64 cc and a median ADC of 1.23×10^{-3} mm^2/s with an IQR of 0.30×10^{-3} mm^2/s. Prostate contours had a median volume of 4.98 cc with an IQR of 0.41 cc and a median ADC of 1.55×10^{-3} mm^2/s with an IQR of 0.20×10^{-3} mm^2/s.

For rectal tumors, the bias in ADC values was -0.01×10^{-3} mm^2/s and the limits of agreement ranged from -0.21 to 0.20×10^{-3} mm^2/s (Fig. 2). The RC was 0.21×10^{-3} mm^2/s and the %RC was 17.0 %.

For the normal prostate tissues, the bias was 0.01×10^{-3} mm^2/s and the limits of agreements ranged from -0.15 to 0.16×10^{-3} mm^2/s (Fig. 2). The RC was 0.08×10^{-3} mm^2/s and the %RC was 5.4 %.

4. Discussion

In this study, a relative repeatability coefficient of 17.0 % for rectal cancer ADC measurements on a 1.5 T MR-linac was found. When using serial ADC measurements on a 1.5 T MR-linac for response monitoring in rectal cancer, it is crucial to account for this repeatability coefficient to differentiate between measurement variability and actual treatment response. Additionally, serial ADC measurements from an MR-linac have the potential to enhance response monitoring and personalize treatment for rectal cancer.

The repeatability coefficient was higher for the rectal tumor compared to the coefficient measured in the prostate region (17.0 % vs 5.4 %), which is consistent with findings in diagnostic MRI studies [13]. This difference is attributed to rectal motion and the passage of gas

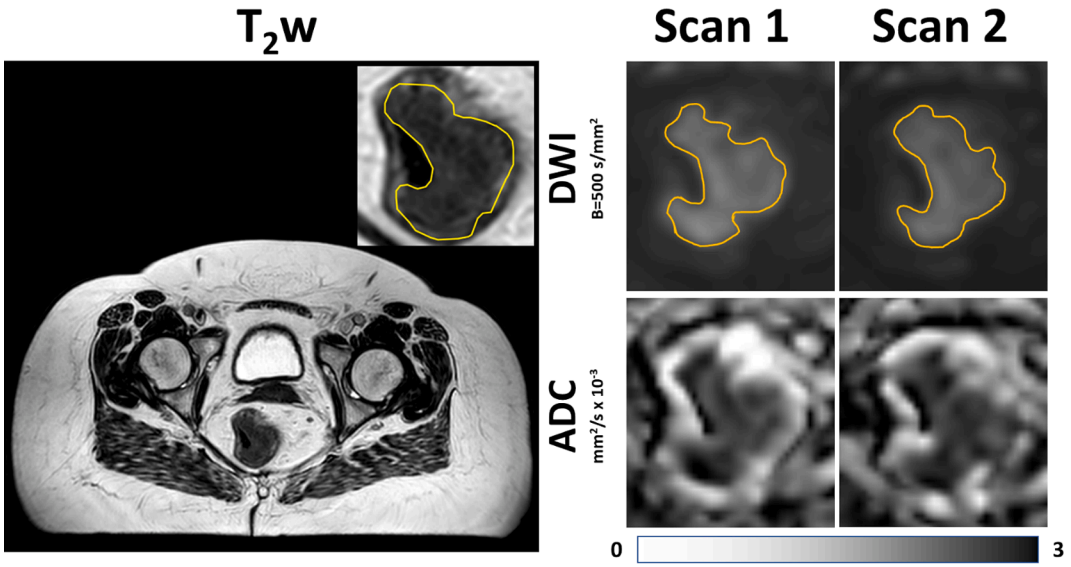

Fig. 1. MRI images during a treatment session on a 1.5 T MR-linac for rectal cancer. On the left, a T_2 weighted scan with the tumor volume delineated (yellow). On the top right, the tumor illustrated on the b = 500 of two sequential DWI scans, with below, two ADC maps calculated from the DWI.

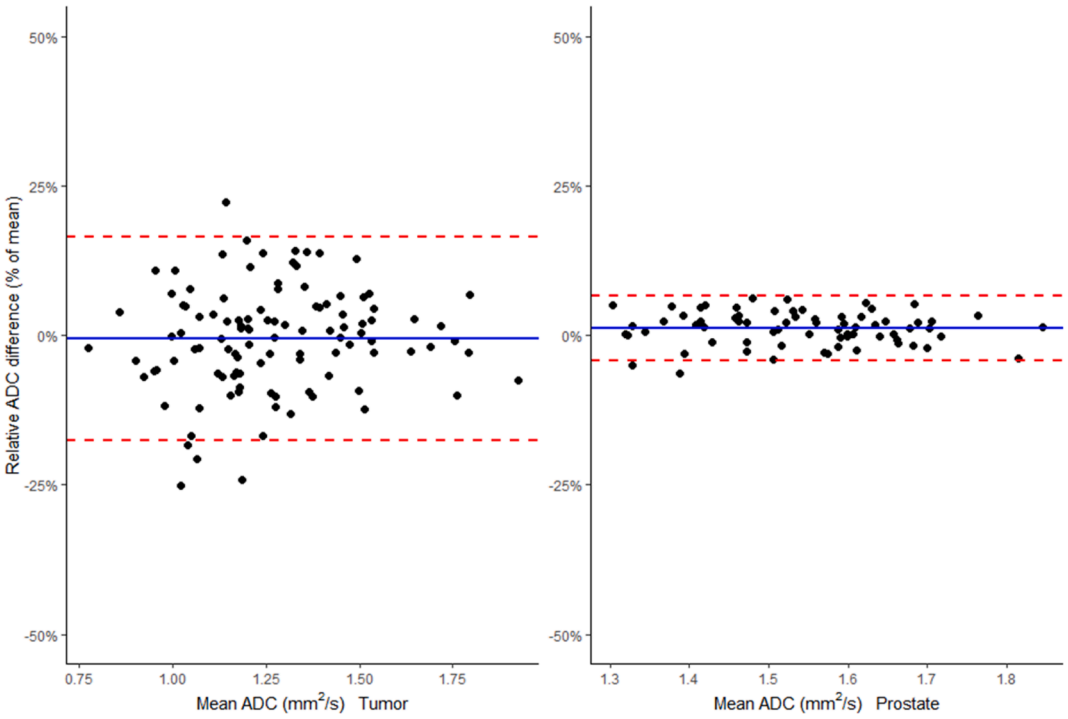

Fig. 2. Two Bland-Altman plots illustrating the agreement between two sequential DW-MRI scans for rectal tumors (left) and normal prostate tissues (right). The bias (blue lines) and limits of agreement (red dotted lines) for rectal tumors were 0.01×10^{-3} mm^2/s, with limits of -0.22 to 0.21×10^{-3} mm^2/s. For the normal prostate tissues, the bias was 0.01×10^{-3} mm^2/s, with limits of -0.15 to 0.16×10^{-3} mm^2/s.

though the rectum during DWI acquisition. This was confirmed after visual inspection of the separate b-value scans, which showed anatomical differences between the different b-values in the patients with the largest ADC repeatability. These occurrences illustrate the added challenge when performing fMRI in tumor sites with anatomical motion. Deformable image registration of individual b-value images could potentially improve ADC repeatability for rectal tumors, but it is difficult due to the low signal-to-noise ratio and limited anatomical features inherent in ADC images, which might lead to registration errors. Furthermore, different ADC calculation methods might improve repeatability, such as choosing between region-of-interest analysis or voxel-based analysis, selecting different b-values, or using alternative software [20,21]. Another option would be to reduce the acquisition time by modifying sequence parameters such as numbers of averages and number of b-values. Faster acquisition would reduce the chance of capturing unexpected movement in the rectum [22]. The DWI sequence of this study follows recommendations for consistent and accurate ADC measurements on Unity MR-Linac systems [15]. We therefore believe that sequence-related contributions to ADC variability have been confined to a minimum.

In a prior study of our group, a 9.8 % ADC repeatability coefficient was found for rectal cancer on a diagnostic 1.5 T MRI unit (Gyroscan NT Intera, Philips) [13]. While a 1.5 T MR-linac has the same field strength, it is important to recognize that its hardware design (e.g. split gradient coils, reduced number of receive channels) reduces the signal to noise ratio of especially the high b-value images, which might negatively impact the ADC repeatability [14]. As expected, the repeatability coefficient was higher in this study. Furthermore, like most other quantitative MRI measurements, the exact MR acquisition parameters also play an important role in the degree of ADC repeatability. The split gradient system of Elekta Unity systems (leading to a reduced gradient strength and ramp up time) requires different diffusion gradient characteristics compared to diagnostic MRI systems, and these must be considered for ADC measurements.

Although ADC repeatability has been tested before on the 1.5 T MR-Linac, this is the first study to have done so for rectal tumors. Hence, comparison is limited to different tumor groups. ADC repeatability studies for head and neck cancer (HNC) on MR-linac systems found repeatability coefficients between 26.7 % and 31.3 % using similar methods as the current study [23,24]. These numbers are higher than our RC for rectal cancer. Kooreman et al. studied ADC measurements during different treatment scenarios of prostate cancer on a Unity system [15]. They reported absolute ADC repeatability coefficients of 0.34 $\times 10^{-3}$ mm^2/s and 0. 22 $\times 10^{-3}$ mm^2/s in the first and second fraction, respectively. However, they looked at the ADC difference between the gantry on and off, and they did not discuss this difference in repeatability between the first and second fraction. This study examined repeatability before dose delivery, likely clarifying our lower RC.

Diagnostic MRI systems generally have a better ADC repeatability compared to MR-linac systems for rectal cancer. However, the advantage of an MR-linac lies in its scan opportunity at each treatment fraction. Despite less accurate individual measurements, the abundance of estimations from serial scans allows for a more comprehensive understanding of ADC dynamics. This increased sample size could offer a more refined prediction of the ADC compared to a single diagnostic MRI measurement. This can be especially helpful in longer RT schemes, like chemoradiation for locally advanced rectal cancer. In such situations, adequate response monitoring with ADC during radiotherapy might lead to personalized treatment adjustments such as dose-(de)escalation, dose-painting, or selective boosts. Additionally, outcome predictions based on serial ADC tilt might assist in decision making for a wait-and-see strategy to postpone surgery. However, longer treatment schemes may present additional challenges to ADC, such as radiotherapy-induced edema at the tumor site. Focusing on relevant ADC values for analysis or using other ADC calculation methods might address this issue. In the current study, the median ADC value was used to mitigate the impact of outliers.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to improve grammar. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

CRediT authorship contribution statement

Hidde Eijkelenkamp: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Guus Grimbergen:** Methodology, Validation, Data curation, Writing – review & editing. **Brigid McDonald:** Writing – review & editing. **Reijer Rutgers:** Writing – review & editing. **Tim Schakel:** Methodology, Validation, Writing – review & editing. **Casper Beijst:** Methodology, Validation, Writing – review & editing. **Marielle Philippens:** Methodology, Validation, Writing – review & editing. **Gert Meijer:** Methodology, Validation, Writing – review & editing, Supervision. **Martijn Intven:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: B. A. McDonald is supported by an Image Guided Cancer Therapy T32 Training Program Fellowship (T32CA261856).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2025.100720.

References

[1] Prestwich RJD, Vaidyanathan S, Scarsbrook AF. Functional imaging biomarkers: potential to guide an individualised approach to radiotherapy. Clin Oncol 2015;27:588–600. https://doi.org/10.1016/j.clon.2015.06.008.

[2] Joye I, Deroose CM, Vandecaveye V, Haustermans K. The role of diffusion-weighted MRI and 18F-FDG PET/CT in the prediction of pathologic complete response after radiochemotherapy for rectal cancer: a systematic review. Radiother Oncol 2014;113:158–65. https://doi.org/10.1016/j.radonc.2014.11.026.

[3] Staal FCR, van der Reijd DJ, Taghavi M, Lambregts DMJ, Beets-Tan RGH, Maas M. Radiomics for the prediction of treatment outcome and survival in patients with colorectal cancer: a systematic review. Clin Colorectal Cancer 2021;20:52–71. https://doi.org/10.1016/j.clcc.2020.11.001.

[4] Xie T, Ye Z, Pang P, Shao G. Quantitative multiparametric MRI may augment the response to radiotherapy in mid-treatment assessment of patients with esophageal carcinoma. Oncol Res Treat 2019;42:326–33. https://doi.org/10.1159/000499322.

[5] Tangyoosuk T, Lertbutsayanukul C, Jittapiromsak N. Utility of diffusion-weighted magnetic resonance imaging in predicting the treatment response of nasopharyngeal carcinoma. Neuroradiol J 2022;35:477–85. https://doi.org/10.1177/19714009211055191.

[6] John NO, Irodi A, Thomas HMT, Abraham V, Sasidharan BK, John S, et al. Utility of mid-treatment DWI in selecting pathological responders to neoadjuvant chemoradiotherapy in locally advanced esophageal cancer. J Gastrointest Cancer 2023;54:447–55. https://doi.org/10.1007/S12029-022-00818-Y.

[7] Bisgaard ALH, Brink C, Schytte T, Bahij R, Weisz Ejlsmark M, Bernchou U, et al. Prediction of overall survival in patients with locally advanced pancreatic cancer using longitudinal diffusion-weighted MRI. Front Oncol 2024;14:1401464. https://doi.org/10.3389/FONC.2024.1401464/BIBTEX.

[8] van Houdt PJ, Saeed H, Thorwarth D, Fuller CD, Hall WA, McDonald BA, et al. Integration of quantitative imaging biomarkers in clinical trials for MR-guided radiotherapy: conceptual guidance for multicentre studies from the MR-Linac Consortium Imaging Biomarker Working Group. Eur J Cancer 2021;153:64. https://doi.org/10.1016/J.EJCA.2021.04.041.

[9] Kooreman ES, van Houdt PJ, Nowee ME, van Pelt VWJ, Tijssen RHN, Paulson ES, et al. Feasibility and accuracy of quantitative imaging on a 1.5 T MR-linear accelerator. Radiother Oncol 2019;133:156–62. https://doi.org/10.1016/J.RADONC.2019.01.011.

[10] Boldrini L, Intven M, Bassetti M, Valentini V, Gani C. MR-guided radiotherapy for rectal cancer: current perspective on organ preservation. Front Oncol 2021;11. https://doi.org/10.3389/fonc.2021.619852.

[11] Gani C, Boldrini L, Valentini V. Online MR guided radiotherapy for rectal cancer. New opportunities. Clin Transl Radiat Oncol 2019;18:66–7. https://doi.org/10.1016/j.ctro.2019.04.005.

[12] Ingle M, Blackledge M, White I, Wetscherek A, Lalondrelle S, Hafeez S, et al. Quantitative analysis of diffusion weighted imaging in rectal cancer during radiotherapy using a magnetic resonance imaging integrated linear accelerator. Phys Imaging Radiat Oncol 2022;23:32–7. https://doi.org/10.1016/J.PHRO.2022.06.003.

[13] Intven M, Reerink O, Philippens MEP. Repeatability of diffusion-weighted imaging in rectal cancer. J Magn Reson Imaging 2014;40:146–50. https://doi.org/10.1002/JMRI.24337.

[14] Tijssen RHN, Philippens MEP, Paulson ES, Glitzner M, Chugh B, Wetscherek A, et al. MRI commissioning of 1.5T MR-linac systems – a multi-institutional study. Radiother Oncol 2019;132:114–20. https://doi.org/10.1016/J.RADONC.2018.12.011.

[15] Kooreman ES, van Houdt PJ, Keesman R, Pos FJ, van Pelt VWJ, Nowee ME, et al. ADC measurements on the Unity MR-linac – a recommendation on behalf of the Elekta Unity MR-linac consortium. Radiother Oncol 2020;153:106–13. https://doi.org/10.1016/j.radonc.2020.09.046.

[16] Verweij ME, Tanaka MD, Kensen CM, van der Heide UA, Marijnen CAM, Janssen T, et al. Towards Response ADAptive Radiotherapy for organ preservation for intermediate-risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial. BMJ Open 2023;13:e065010. https://doi.org/10.1136/BMJOPEN-2022-065010.

[17] Bol GH, Kotte ANTJ, van der Heide UA, Lagendijk JJW. Simultaneous multi-modality ROI delineation in clinical practice. Comput Methods Programs Biomed 2009;96:133–40. https://doi.org/10.1016/J.CMPB.2009.04.008.

[18] Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999;8:135–60. https://doi.org/10.1177/096228029900800204.

[19] Shukla-Dave A, Obuchowski NA, Chenevert TL, Jambawalikar S, Schwartz LH, Malyarenko D, et al. Quantitative imaging biomarkers alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials. J Magn Reson Imaging 2019;49:e101–21. https://doi.org/10.1002/JMRI.26518.

[20] Bisgaard ALH, Keesman R, van Lier ALHMW, Coolens C, van Houdt PJ, Tree A, et al. Recommendations for improved reproducibility of ADC derivation on behalf of the Elekta MRI-linac consortium image analysis working group. Radiother Oncol 2023;186:109803. https://doi.org/10.1016/J.RADONC.2023.109803.

[21] Bisgaard ALH, Brink C, Fransen ML, Schytte T, Behrens CP, Vogelius I, et al. Robust extraction of biological information from diffusion-weighted magnetic resonance imaging during radiotherapy using semi-automatic delineation. Phys Imaging Radiat Oncol 2022;21:146–52. https://doi.org/10.1016/J.PHRO.2022.02.014.

[22] Eijkelenkamp H, Boekhoff MR, Verweij ME, Peters FP, Meijer GJ, Intven MPW. Planning target volume margin assessment for online adaptive MR-guided dose-escalation in rectal cancer on a 1.5 T MR-Linac. Radiother Oncol 2021;162. https://doi.org/10.1016/j.radonc.2021.07.011.

[23] McDonald BA, Salzillo T, Mulder S, Ahmed S, Dresner A, Preston K, et al. Prospective evaluation of in vivo and phantom repeatability and reproducibility of diffusion-weighted MRI sequences on 1.5 T MRI-linear accelerator (MR-Linac) and MR simulator devices for head and neck cancers. Radiother Oncol 2023;185:109717. https://doi.org/10.1016/J.RADONC.2023.109717.

[24] Habrich J, Boeke S, Nachbar M, Nikolaou K, Schick F, Gani C, et al. Repeatability of diffusion-weighted magnetic resonance imaging in head and neck cancer at a 1.5 T MR-Linac. Radiother Oncol 2022;174:141–8. https://doi.org/10.1016/j.radonc.2022.07.020.