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Evaluation of diffusion kurtosis and diffusivity from baseline staging MRI as predictive biomarkers for response to neoadjuvant chemoradiation in locally advanced rectal cancer

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Abstract

Purpose To evaluate the role of diffusion kurtosis and diffusivity as potential imaging biomarkers to predict response to neoadjuvant chemoradiation therapy (CRT) from baseline staging magnetic resonance imaging (MRI) in locally advanced rectal cancer (LARC).

Materials and methods This retrospective study included 45 consecutive patients (31 male/14 female) who underwent baseline MRI with high *b*-value sequences (up to 1500 mm/s^2) for LARC followed by neoadjuvant chemoradiation and surgical resection. The mean age was 57.4 years (range 34.2–72.9). An abdominal radiologist using open source software manually segmented T2-weighted images. Segmentations were used to derive diffusion kurtosis and diffusivity from diffusion-weighted images as well as volumetric data. These data were analyzed with regard to tumor regression grade (TRG) using the four-tier American Joint Committee on Cancer (AJCC) classification, TRG 0–3. Proportional odds regression was used to analyze the four-level ordinal outcome. A sensitivity analysis was performed using univariable logistic regression for binary TRG groups, TRG 0/1 (> 90% response), or TRG 2/3 (< 90% response). $p < 0.05$ was considered significant throughout.

Results In the univariable proportional odds regression analysis, higher diffusivity summary (D_{sum}) values were observed to be significantly associated with higher odds of being in one or more favorable TRG group (TRG 0 or 1). In other words, on average, patients with higher D_{sum} values were more likely to be in a more favorable TRG group. These results are mostly consistent with the sensitivity analysis, in which higher values for most D_{sum} values [all but region of interest (ROI)-max *D* median ($p = 0.08$)] were observed to be significantly associated with higher odds of being TRG 0 or 1. Tumor volume of interest (VOI) and ROI volume, ROI kurtosis mean and median, and VOI kurtosis mean and median were not significantly associated with TRG.

Conclusion Diffusivity derived from the baseline staging MRI, but not diffusion kurtosis or volumetric data, is associated with TRG and therefore shows promise as a potential imaging biomarker to predict the response to neoadjuvant chemotherapy in LARC.

Clinical relevance statement Diffusivity shows promise as a potential imaging biomarker to predict AJCC TRG following neoadjuvant CRT, which has implications for risk stratification. Patients with TRG 0/1 have 5-year disease-free survival (DFS) of 90–98%, as opposed to those who are TRG 2/3 with 5-year DFS of 68–73%.

Keywords Rectal cancer · Diffusion kurtosis · Diffusivity · Imaging biomarker · Neoadjuvant chemoradiation · Tumor regression grade

Introduction

Neoadjuvant chemoradiation for locally advanced rectal cancer (LARC) has become standard practice, as a number of trials have shown that its use is associated with decreased rates of local recurrence [1]. LARC includes those cases in which the tumor has spread beyond the wall of the rectum

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into the surrounding perirectal fat by at least 5 mm (T3c–d), when the tumor has invaded local adjacent structures (T4), or when there is involvement of locoregional lymph nodes (N1 or N2) [2]. Following neoadjuvant chemoradiation and surgical resection, the amount of tumor replaced by fibrosis is quantitated at pathology as the tumor regression grade (TRG). Although several scoring systems exist for classifying the TRG of a resected specimen, a significant correlation between the TRG and recurrence-free survival is seen across scoring systems [3]. The prognostic value of the TRG seen after neoadjuvant therapy in rectal cancer is significant, and an imaging biomarker that has the ability to predict a patient's TRG prior to initiating neoadjuvant chemoradiation may have clinical utility.

Diffusion kurtosis imaging (DKI), which reflects non-Gaussian distribution of diffusion values, has been described as a product of tissue microstructures [4]. It has shown promise as a biomarker in a variety of other cancers, where it has correlated with tumor aggressiveness in prostate cancer [5], as well as with histologic grade in breast cancer and gliomas [6–8]. Mean kurtosis values from DKI in gliomas have also been shown to be associated with progression-free and overall survival [9]. These findings have contributed to the growing research interest in oncologic applications of DKI.

Several authors have explored the potential role of DKI in imaging of LARC. Studies have shown correlations between kurtosis parameters and histologic subtypes and specific imaging features that have prognostic value [10–12], while others have shown associations with specific genetic phenotypes, including KRAS mutational status [13] or mismatch-repair (MMR) gene expression [14]. A handful of papers have also explored whether parameters derived from DKI may be useful in assessing a patient's response to neoadjuvant therapy [15–17].

In 2017, our institution began routinely acquiring *b* 1500 s/mm^2 on all rectal MR studies, as we find it useful in clinical practice. In this study, we examine whether parameters derived from DKI on the baseline magnetic resonance imaging (MRI) are associated with subsequent response to neoadjuvant chemoradiation as measured by the TRG.

Methods

The Institutional Review Board waived the requirement for informed consent for this Health Insurance Portability and Accountability Act (HIPAA)-compliant, retrospective study.

Patient selection

A total of 45 consecutive patients diagnosed with LARC, who underwent multiparametric MRI with at least three *b*-values, including *b* 1500 s/mm^2, followed by neoadjuvant chemoradiation and surgical resection, were included for analysis.

Image acquisition

MRI was performed with a 3-T whole-body MRI unit (Discovery MR750; GE Medical Systems, Waukesha, WI). A 32-channel phased array coil was employed for signal reception. Multiplanar T2-weighted images, dynamic contrast-enhanced (DCE), and diffusion-weighted images (DWIs) were acquired. DW-MRI was acquired at multiple *b*-values up to 1500 s/mm^2. Our standard institutional protocol for rectal MR on the 3-T scanner is included in the Appendix.

Image segmentation

Axial T2-weighted images from the baseline pretreatment MRI for all 45 patients were segmented by a board-certified radiologist fellowship trained in abdominal imaging with 2 years of experience (DB) on ImageJ software created by the National Institutes of Health [18]. The decision to use T2-weighted images was made because, in our experience, the margins of the tumor are most reliably identified on T2 images, as opposed to the DWI sequences. The segmentations were superimposed on axial DWIs to derive DKI parameters (Fig. 1).

Image analysis

Segmented images were postprocessed off-line using code written in MATLAB 7.0.1 (The Mathworks, Natick, MA, USA). To increase the signal-to-noise ratio, a Gaussian filter with a full-width at half-maximum of 3 mm was applied to all DWIs. Linear least square DKI fitting was used to solve for the coefficients of diffusivity (D_{app}) and apparent kurtosis (K_{app}) to the following equation [19]:

$$\ln\left(S_b\right) = \ln\left(S_0\right) \times \left[b \times D_{app} + 1/6 \times b^2 \times D_{app} \times K_{app}\right].$$

S_b and S_0 are the signal intensities at *b*-values of *b* and 0, respectively. K_{app} is a dimensionless statistical metric that quantitates the non-Gaussian diffusion behavior where the tissue diffusivity demonstrates a more peaked distribution. When $K_{app}=0$, the standard mono-exponential model is recovered reflecting Gaussian distribution.

Selection of tumor regression grade (TRG) system

Although a number of TRG models have been proposed, the four-tier American Joint Committee on Cancer (AJCC)

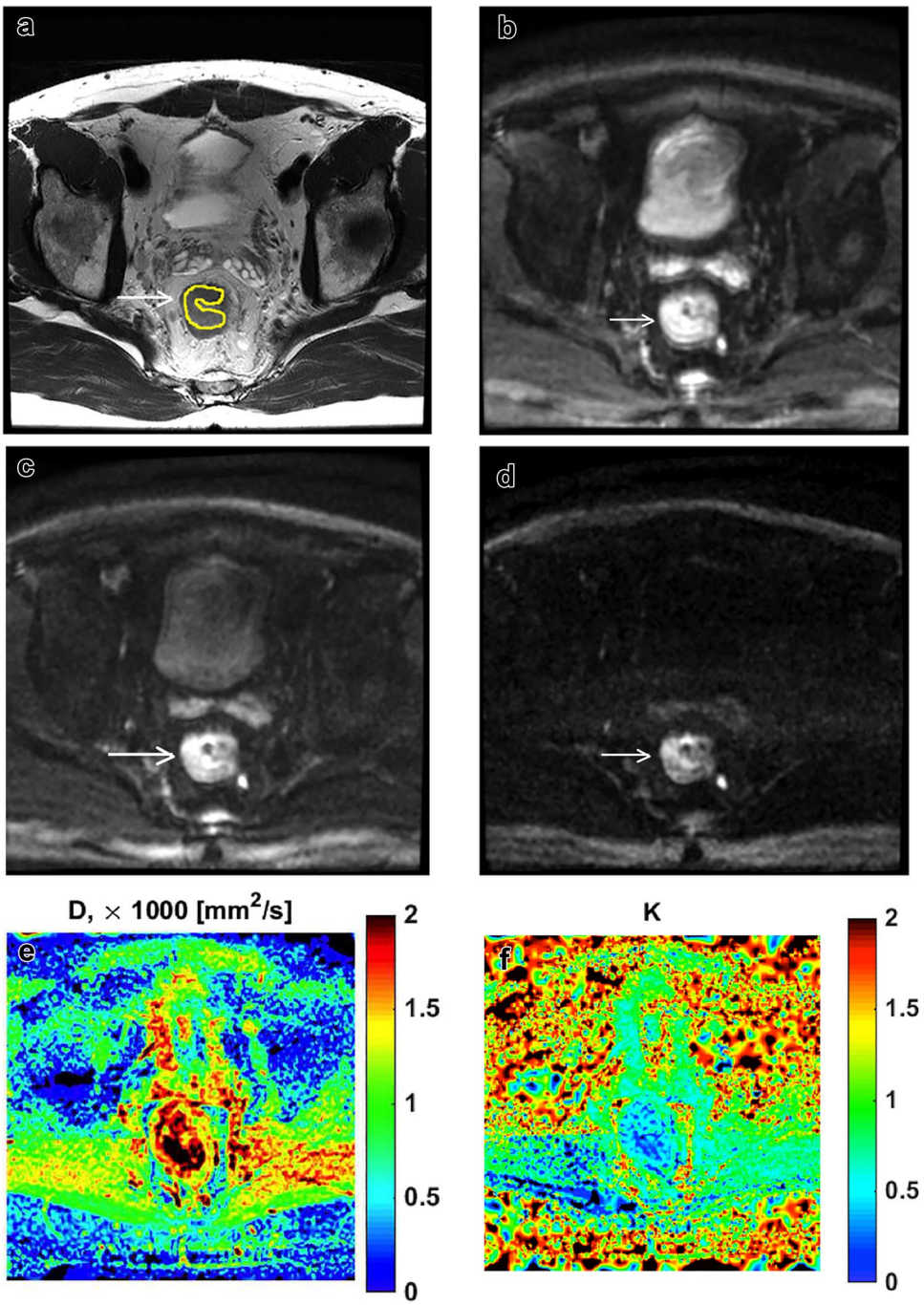

Fig. 1 50-year-old male with locally advanced rectal cancer. Axial T2-weighted image through the level of the tumor with segmentation (**a**), and corresponding diffusion-weighted images at b_{400}, b_{800}, and b_{1500} (**b**–**d**). Corresponding *D*- and *K*-maps from diffusion kurtosis imaging (**e**, **f**)

rectal cancer TRG system has been shown to be more accurate than other systems [3], and was therefore chosen for this study.

Statistical analysis

Tumors from 45 patients with rectal cancer were analyzed. Patients were categorized into one of four groups according to their approximate TRG values: TRG 0 (TRG = 100%), TRG 1 (90% ≥ TRG < 100%), TRG 2 (50% ≥ TRG < 90%), and TRG 3 (TRG < 50%). Considering low frequencies in some of the TRG groups, and TRG's association with recurrence-free survival [3], a binary outcome variable was created: TRG 0/1 (TRG ≥ 90%) and TRG 2/3 (TRG < 90%).

The relationships between the AJCC TRG groups were compared with diffusivity (*D*) and kurtosis (*K*) summary values, as well as with volumes from each tumor's volume of interest (VOI) and region of interest (ROI). The parameter *D* derived from DKI reflects the water molecule true diffusion where the non-Gaussian distribution of values has been

incorporated, and reflects complexity of tissue structures. It differs from the parameter *D* derived from intra-voxel incoherent motion (IVIM), which reflects the water molecular true diffusion, where the microcirculation perfusion, which reflects vascularization of tissue, has been separated. Summary values included mean and median diffusion and kurtosis values for tumor VOI and ROI.

In univariable analysis, a multinomial regression method was used, the proportional odds model, to analyze the four-level, ordinal outcome assuming the same effect of individual imaging value on each level of TRG group. As a sensitivity analysis, the relationships between the binary outcome and the explanatory variables of interest were tested using logistic regression. A significance level of 0.05 was used throughout.

All statistical computations were performed, and all output was generated using SAS Software Version 9.4 (The SAS Institute, Cary, NC).

Results

A total of 45 patients were included (31 male/14 female), mean age 57.4 years (range 34.2–72.9). The sample characteristics of the cohort and the frequency of TRG classification are summarized in Tables 1 and 2, respectively.

In the univariable proportional odds regression analysis, higher diffusivity summary (D_{sum}) values were observed to be significantly associated with higher odds of being in one or more favorable TRG group (TRG 0 or 1). This was true for the ROI-max *D* mean ($p = 0.002$), ROI-max *D* median ($p = 0.014$), VOI *D* mean ($p = 0.002$), and VOI *D* median ($p = 0.004$). In other words, on average, patients with higher D_{sum} values were more likely to be in a more favorable TRG group. These results are mostly consistent with the sensitivity analysis, in which higher values for most D_{sum} values, all except ROI-max *D* median ($p = 0.08$), were observed to be significantly associated with higher odds of being TRG 0 or 1 (Tables 3, 4).

Tumor VOI and ROI-max volume, ROI-max kurtosis mean and median, and VOI kurtosis mean and median were not associated with TRG and were therefore not significantly associated with the response to neoadjuvant chemoradiation.

Table 1 Sample characteristics ($N = 45$)

Variable	*N*	Median (min–max)
TRG proportion	45	0.7 (0.05 to 1)
ROI-max kurtosis mean	45	0.91837 (0.18113 to 1.86345)
ROI-max kurtosis median	45	0.85896 (1.335327E−10 to 1.39371)
ROI-max *D* mean	45	0.00175 (0.00077 to 0.003)
ROI-max *D* median	45	0.00167 (0.00088 to 0.00367)
ROI-max volume (cm^3)	45	3.96094 (0.82178 to 17.33643)
VOI kurtosis mean	45	0.90006 (0.10979 to 1.61107)
VOI kurtosis median	45	0.88078 (0.1012 to 2.06113)
VOI *D* mean	45	0.00159 (0.00088 to 0.00257)
VOI *D* median	45	0.00157 (0.00079 to 0.00277)
VOI volume (cm^3)	45	20.14993 (1.69629 to 84.54684)

Table 2 TRG group frequencies

		N (%)
Sample size		45
TRG group (ordinal)		
TRG 0	TRG = 100%	8 (17.8)
TRG 1	90% ≤ TRG < 100%	8 (17.8)
TRG 2	50% ≤ TRG < 90%	14 (31.1)
TRG 3	TRG < 50%	15 (33.3)
TRG group (binary)		
TRG 0/1	TRG ≥ 90%	16 (35.6)
TRG 2/3	TRG < 90%	29 (64.4)

Discussion

In our cohort of 45 patients, we found that diffusivity derived from DKI, but not kurtosis, was significantly associated with AJCC pathologic TRG. Specifically, almost all of the D_{sum} values derived from DKI were able to distinguish those patients with TRG 0 and 1—a more favorable response

Table 3 Univariable proportional odds (i.e. cumulative logit) regression model results

Variable	*N* used	OR [95% CI][a]	*p* value
ROI-max kurtosis mean[b]	45	0.908 [0.779–1.058]	0.22
ROI-max kurtosis median[b]	45	0.904 [0.759–1.078]	0.26
ROI-max *D* mean[c]	45	1.240 [1.084–1.417]	0.002
ROI-max *D* median[c]	45	1.127 [1.025–1.239]	0.014
ROI-max volume (cm^3)	45	1.048 [0.885–1.243]	0.59
VOI kurtosis mean[b]	45	0.916 [0.768–1.093]	0.33
VOI kurtosis median[b]	45	0.942 [0.812–1.091]	0.42
VOI *D* mean[c]	45	1.256 [1.090–1.446]	0.002
VOI *D* median[c]	45	1.184 [1.055–1.329]	0.004
VOI volume (cm^3)	45	1.012 [0.985–1.039]	0.39

Probabilities modeled are cumulated over the groups with lower TRG values

[a]Note that OR represents the odds ratio of being in one or more favorable TRG group(s) versus being in the rest [less favorable TRG group(s)] associated with a single unit increment in the variable

[b]Note that the increment unit for OR estimation is 0.1 for all kurtosis summary variables

[c]Note that the increment unit for OR estimation is 0.0001 for all diffusion summary variables

Table 4 Univariable logistic regression model results

Variable	*N* used	OR [95% CI]	*p*-value
ROI-max kurtosis mean[a]	45	0.931 [0.780–1.112]	0.43
ROI-max kurtosis median[a]	45	0.917 [0.749–1.123]	0.40
ROI-max *D* mean[b]	45	1.253 [1.051–1.494]	0.012
ROI-max *D* median[b]	45	1.102 [0.989–1.228]	0.08
ROI-max volume (cm^3)	45	1.091 [0.897–1.327]	0.39
VOI kurtosis mean[a]	45	0.963 [0.786–1.179]	0.72
VOI kurtosis median[a]	45	0.980 [0.827–1.161]	0.82
VOI *D* mean[b]	45	1.231 [1.042–1.454]	0.014
VOI *D* median[b]	45	1.147 [1.006–1.307]	0.041
VOI volume (cm^3)	45	1.025 [0.993–1.058]	0.12

Probability modeled is TRG group (binary) = TRG 0/1 (i.e. TRG ≥ 90%)

[a]Note that the increment unit for OR estimation is 0.1 for all kurtosis summary variables

[b]Note that the increment unit for OR estimation is 0.0001 for all diffusion summary variables

to neoadjuvant chemoradiation, from those with TRG 2 or 3—those with a less favorable response. This suggests that diffusivity derived from DKI may be able to risk stratify patients with rectal cancer on the baseline staging MRI for their subsequent response to neoadjuvant therapy.

Considering the results of our data in the context of the existing literature on DKI and rectal cancer provides perspective. The significant association of D_{sum} values with a patient's subsequent response to neoadjuvant therapy is not entirely unexpected, as diffusivity is a parameter closely aligned with apparent diffusion coefficient values, which have shown promise as an imaging biomarker to predict treatment response to neoadjuvant therapy and recurrence in rectal cancer [20]. Previously, authors have looked at a variety of diffusion and perfusion parameters on MRI before and after neoadjuvant short course radiotherapy (SCR) and found that some of the perfusion parameters, namely variable projection derived from IVIM, was a promising biomarker following SCR [15]. In another study, Zhu et al. found that kurtosis was more predictive of WHO tumor grade than ADC or diffusivity, and was also able to distinguish N0 from N1–2 disease [12]. Cui et al. found that diffusion kurtosis correlated with nodal status, tumor histologic grade, lymphangiovascular invasion, and involvement of the circumferential resection margin more than ADC or diffusivity [11]. Thus, our data add one more piece of information into the growing body of literature around the role of DKI as an imaging biomarker in the assessment of rectal cancer on MRI.

The ability to predict a patient's response to neoadjuvant therapy for rectal cancer based on data derived from the baseline rectal MRI may be of clinical utility. Diffusion kurtosis has gained considerable interest in recent years, due to its proven associations with tumor aggressiveness, histopathology, and disease-free survival across a range of malignancies [5–9]. Although *K* itself was not significantly associated with the subsequent response to neoadjuvant therapy in our cohort, *D* derived from DKI shows promise as an imaging biomarker in this setting. This distinction is not merely an academic question, as it has meaningful prognostic implications for a given patient. In an important study by Trakarnsanga et al. [3] that established the AJCC pathologic TRG model as the most accurate, patients who had TRG 0 and 1 after neoadjuvant therapy had 5-year recurrence-free survival rates of 98% and 90%, respectively. This contrasts with those patients who had AJCC TRG 2 and 3, who exhibited 5-year recurrence-free survival rates of 73% and 68%, respectively. Therefore, the D_{sum} parameters derived from a baseline rectal MRI could presumably stratify patients as being TRG 0/1, with significantly better disease-free survival rates, before neoadjuvant therapy is given. This information is readily available from baseline staging MRI studies if multiple *b*-values are acquired, including one high *b*-value that is at least 1000 s/mm^2, and may help medical oncologists and surgeons stratify patients up front.

This study has several limitations. First, this study is retrospective, which inherently limits the broad applicability of this data. Second, it is a relatively small cohort, with 45 patients. Lastly, our data are derived from a cohort of patients imaged at a single institution with a given set of MR parameters. As there is variability in MR scanning parameters across different institutions, this may limit reproducibility of our data.

As clinicians and radiologists investigate imaging biomarkers to help predict subsequent response to therapy in oncology, diffusivity values derived from DKI show potential in our cohort of rectal cancer patients, even though kurtosis values did not. Further investigation is needed in this area to establish the precise role D_{sum} may fill as a biomarker to stratify patients based on their expected response to neoadjuvant therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no relevant conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Written informed consent was waived by the Institutional Review Board.

Appendix

See Table 5.

Table 5 Standard protocol for rectal MRI used at our institution

Sequences	1	2	3	4	4		5	7	6	7	8
Series descriptor	Axial T2	Sagittal T2	Oblique axial T2	Oblique coronal T2 thru tumor	Oblique coronal T2 sphincter	G l u c a g o n I V	Axial *D*WI *b* 800	Focus *D*iffusion	Axial LAVA pre	Sagittal DCE pre and post	Axial LAVA post
Generic sequence name	FSE T2	FSE T2	FSE T2	FSE T2	FSE T2		2D	Focus diffusion	LAVA	3D FSPGR	LAVA
Plane	Axial	Sagittal	Oblique axial	Oblique coronal	Oblique coronal		Axial	Axial	Axial	Oblique through tumor	Axial
Options	Fast/NPW/ED	Fast/NPW/ED	Fast/NPW/ED	Fast/NPW/ED	Fast/NPW/ED		EPI, DIFF, ASSET	EPI, DIFF	ZIPX2/ACC/ED	Fast/NPW/EDR/MPh/Zip Off	ZIPX2/ACC/ED
Field of view (cm)	20–24	18	18	18	18		24	16	28–36	24	28–36
Slice thickness (mm)	5	4	3	3	3		5	5	3	5	3
Gap (mm)	1	1	1	1	1		1	1	NA	0	NA
b-value								1500			
Saturation pulse	S/I/A	A	S/I/A	A	A		N/A	N/A	Special	N/A	Special
TE1/2	110	102	102	102	102		Min	Min	In phase	Min	In phase
TR	4000–6000	4000–6000	4000–6000	4000–6000	4000–6000		6000	6000	Default	4	Default
Flip angle	90	90	90	90	90		N/A	N/A	15	30	15
Bandwidth (kHz)	32	32	32	32	32		N/A	N/A	62	62.5	62
ETL	24	24	24	24	24		N/A	N/A		N/A	
NEX	3	4	4	4	4	I	16	16	1	1	1
Frequency steps	320	320	320	320	320	E	128	70	320	320	320
Phase encoding steps	224	224	224	224	224	V	128	140	192	160	192
Frequency direction	A/P	A/P	A/P	A/P	A/P	N	R/L	R/L	R/L	R/L	R/L

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