

Image Quality Assessment of 2D versus 3D T2WI and Evaluation of Ultra-high b-Value ($b=2,000 \text{ mm/s}^2$) DWI for Response Assessment in Rectal Cancer

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Abstract. Aim: The purpose of this IRB-approved, retrospective study was to compare image quality between 2D and high-resolution 3D, T2-weighted (T2WI) magnetic resonance imaging (MRI) sequences and to investigate the additional value of ultra-high b-value diffusion-weighted imaging (DWI; $b=2,000 \text{ mm/s}^2$) for both rectal cancer staging and evaluating treatment response. Materials and Methods: From 12 February to 24 August 2016, 26 consecutive patients (22 males, four females; mean age: 61.9 ± 14.0 years) with histologically-proven rectal cancer. In total 31 examinations [12 prior to and 19 after chemoradiation (CRT)] were included. The patients underwent pelvic MRI on a 3.0-T scanner (Magnetom Skyra, Erlangen, Germany). Three radiologists (3, 4, and 5 years of experience in MRI, respectively) independently assessed all images and rated the image quality of DWI ($b=800 \text{ mm/s}^2$), apparent diffusion coefficient map, DWI ($b=2,000 \text{ mm/s}^2$), 3D sagittal T2WI, 3D axial T2WI, 2D sagittal T2WI, and 2D axial T2WI of each patient, respectively. In addition, signal intensity ratios (SIR) were calculated between rectal cancer and obturator internus muscle (background) in all patients after CRT on DWI ($b=2,000 \text{ mm/s}^2$) and correlated

with histopathological regression grade (RG). Results: Tumor delineation was significantly better by 2D T2WI than 3D T2WI both before and after CRT (before CRT: $Z=-3.2$, $p=0.02$; after CRT: $Z=-4.408$, $p<0.001$; all: $Z=-5.192$; $p<0.001$) and was the preferred method, although image quality ratings were not significantly different (3D sagittal: 4.00 ± 0.48 ; 2D sagittal: 4.03 ± 0.34 , $p=0.713$; 3D axial: 3.85 ± 0.61 , 2D axial: 3.78 ± 0.64 , $p=0.537$). Independent t-test showed significantly higher SIR between those with RG 1 or 2 (moderate response: mean score=2.02) and those with RG 3+4 (good response: mean score=0.8) ($t=3.044$, $p=0.011$). In those with RG 4 (complete response), SIR of b2000 was 0.946 compared to a 1.41 average of the whole cohort. In two patients, tumor was invisible on b2000 following CRT (RG 3 and 4, respectively). Interobserver agreement was mostly good ($\kappa \geq 0.6$) regarding image quality assessment, except for poor agreement ($\kappa=0.4$) in DWI (b2000) between the two less-experienced readers. Conclusion: In conclusion, 3D T2WI might be useful for evaluating response to neoadjuvant therapy in a comprehensive, cost-effective protocol, where 2D imaging seems to be preferable. In addition, DWI (b2000) may be beneficial in assessing both the primary and the residual tumor after CRT in rectal cancer and SIR may be helpful in assessing response to CRT.

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Key Words: Rectal cancer, image quality, diffusion-weighted imaging (DWI), b value, 2,000 s/mm^2 , 3-dimensional T2-weighted imaging (3D T2WI).

The prevalence of rectal cancer is not only relatively high (1, 2), but the disease is also associated with poorer prognosis and higher local recurrence rates than colon cancer (2, 3). However, standard care is total mesorectal excision (TME) with additional chemoradiation (CRT) in a selected group of patients with advanced tumors (4). Therefore, precise staging of rectal cancer is crucial for treatment decisions. Magnetic resonance imaging (MRI), with no ionizing radiation, is

Table I. Magnetic resonance imaging sequences parameters.

Parameter	Imaging method				
	Spin-echo EPI DWI		T2-Weighted turbo spin-echo		
	b800	b2000	3D	2D Sagittal	2D Axial
b-Value, s/mm ²	800	2000	-	-	-
Repetition time, ms	10,000	10,500	1,500	6,450	8,900
Echo time, ms	84	70	94	107	105
Slice thickness, mm	5	5	1	3	3
Spacing, mm	5.5	5.5	n.a.	3.3	3.3
ETL	59	33	60	15	15
Matrix	192×112	192×113	320×288	384×245	256×256
FOV	273×349	273×349	320×320	239×319	160×160
FA	900	900	900	1570	1640
Bandwidth	1860	1630	580	200	200
Acquisition time (min.)	n.a.	4:53	4:44	1:38	2:32

DWI: Diffusion-weighted imaging; TR: repetition time; ETL: echo train length; FOV: field of view; FA: flip angle.

regarded as an important method for both staging and re-staging after CRT prior to surgical resection (3, 5-7). Hence, the quality and accuracy of MRI are crucial.

High-resolution, 2-dimensional (2D) T2-weighted imaging (T2WI) is the most important sequence for tumor staging (1, 3). Nowadays, 3-dimensional (3D) T2WI is also gaining acceptance in abdominal imaging, such as for uterine disease, because of its thin slice thickness and the option of multiple planar reformations (8, 9). However, its value has never been reported in rectal cancer as far as we are aware.

Another aspect of the present study is to evaluate response to treatment using functional criteria. Several recent studies have confirmed the value of apparent diffusion coefficient (ADC) calculation or diffusion-weighted imaging (DWI)-based volumetry for response assessment following CRT (10). In this study, we also retrospectively investigate DWI (b-value=2,000 s/mm²) as a possible imaging biomarker for predicting treatment response.

DWI and high-resolution T2WI play a critical role in MRI sequences. The benefits of DWI and an accompanying ADC map lie in better tumor detection, especially of local recurrences (11). However, DWI is prone to susceptibility artifacts, which may adversely affect image quality. So far, the most widely used b-values for DWI in rectal cancer are 0-800-1,000 s/mm². Lower b-values are always associated with a risk of 'T2-shine-through' effects, which may reduce specificity in detecting malignant tissue properties with restricted diffusion. DWI with ultra-high b-values such as 2000 s/mm² (b2000) might allow for a better visualization of tumors due to a highly effective suppression of background signal. Recently, b2000 was applied for

imaging prostate cancer (12) and some promising results were gained. To the best of our knowledge, the value of a ultra-high b-value DWI has not been studied in rectal cancer.

Therefore, we selected a consecutive case series of rectal cancers with pre- and post-therapy MRI examinations to compare imaging quality between 2D and 3D T2WI sequences and to investigate the additional value of ultra-high b-value DWI in imaging rectal cancer for staging and for evaluating response to treatment.

Materials and Methods

Ethics statement. This study was approved by the local Ethics Committee (2008-338N-MA). The need for written informed consent was waived by the Institutional Review Board due to the retrospective design of the study.

Patient selection. From 12 February to 24 August 2016, 26 consecutive patients who had histopathologically-confirmed rectal cancer underwent pelvic MRI at our hospital. Two of these patients were examined before and after treatment and three of them were examined after treatment twice. In total, 12 of the examinations were conducted before and 19 after treatment.

MR acquisition. All MR images were acquired using a 3-T MR scanner (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany). The scan protocol comprised DWI (b=800 s/mm²), an ADC map, 2D sagittal T2WI and 2D axial T2WI, ultra-high b-value DWI (b=2000), and 3D T2WI with axial and sagittal reformations. The imaging parameters are detailed in Table I. MRI with b2000 was only acquired in 24 examinations and 3D T2WI in 28 examinations due to changes in the protocol during the retrospective observation period. All patients underwent rectal gel filling before the MRI examination.

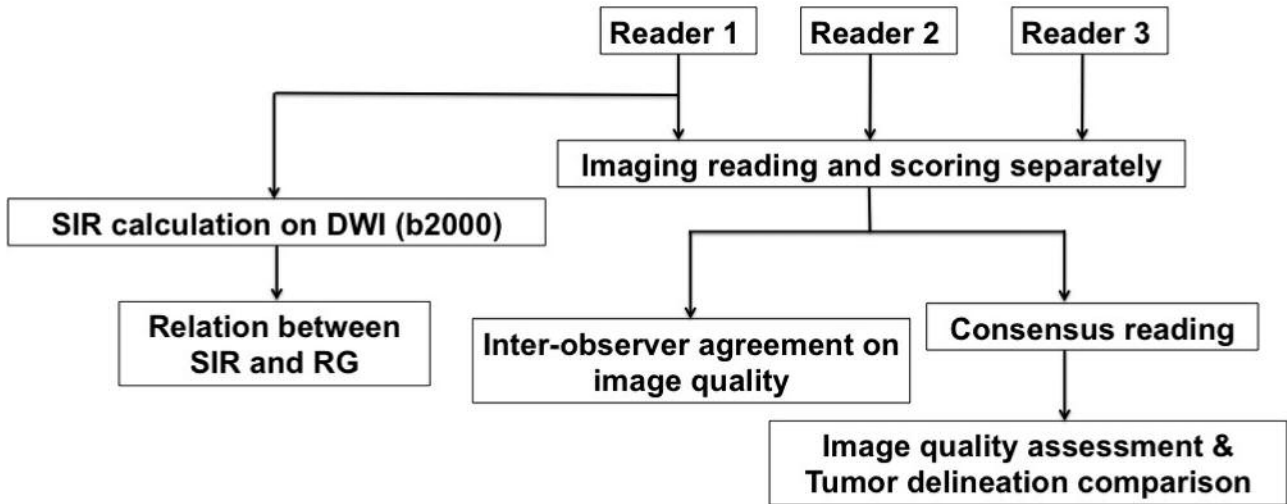


Figure 1. Workflow chart for imaging assessment. SIR: Signal intensity ratio, RG: regression grade.

Imaging quality assessment. Three radiologists (Reader 1, 2, and 3 with 3, 4, and 5 years of experience in MRI, respectively) who were unaware of the patients' clinical data independently assessed all images and rated the image quality of DWI ($b=800 \text{ s/mm}^2$), ADC map, DWI ($b=2,000 \text{ s/mm}^2$), 3D sagittal T2WI, 3D axial T2WI, 2D sagittal T2WI, and 2D axial T2WI of each patient, respectively.

Image quality was scored as follows: Score 1: Nondiagnostic image quality: serious artifacts, image distortion, or poor signal intensity. Score 2: Poor diagnostic image quality and diagnostic confidence of the readers: serious artifacts, image distortion pronounced, or relatively poor signal intensity. Score 3: Moderate image quality and confidence of the readers: some artifacts, moderate image distortion. Score 4: Good diagnostic image quality and confidence of the readers: few artifacts, slight image distortion, anatomic structures (e.g. rectal wall) well delineated. Score 5: Excellent image quality and strong confidence of the readers in the diagnosis: almost no artifacts or imaging distortion.

The radiologists also compared 2D T2W imaging with 3D T2W imaging and recorded which of these methods was preferred due to the quality of tumor delineation and image contrast.

All readers assessed the images separately in a blinded, randomized fashion. Interobserver agreement was assessed for evaluation of image quality. The discrepancies were resolved in a consensus reading. The results of the consensus reading were used for statistical analyses.

Calculation of signal intensity ratio (SIR) for b2000. One radiologist (3 years of experience in MRI) placed an oval-shaped region of interest (ROI) of approximately 1 cm^2 in rectal cancer and another ROI of the same size in the *obturator internus* muscle to calculate the ratio of the lesion: background signal intensity (SI) for all patients after CRT, with axial 2D T2WI as anatomical reference. SIR was calculated using the formula: $(SI_{\text{lesion}})/(SI_{\text{background}})$ for each patient. The value '0' was recorded if the tumor was not visible on b2000.

Histopathological results after CRT. Histopathological regression grades (RG) were determined according to the criteria of Dworak *et al.* (13) as 0: no regression; 1: predominantly tumor with significant fibrosis with/without vasculopathy; 2: predominantly fibrosis with scattered tumor cells (slightly recognizable histologically); 3: only scattered tumor cells in the space of fibrosis with/without acellular mucin; 4: no vital tumor cells detectable. These results were recorded and served as the gold standard for comparison with SIR in all the patients who received CRT and underwent resection at our hospital.

Statistical analyses. Interobserver agreement among the three readers was evaluated using SPSS 16.0 for DWI (b800), ADC map, DWI (b2000), sagittal 3D T2WI, 3D axial T2WI, 2D sagittal T2WI, and 2D axial T2WI, respectively ($\kappa \leq 0.4$: poor agreement, $\kappa = 0.4-0.6$: moderate agreement, and $\kappa \geq 0.6$: good agreement). Paired *t*-tests for image quality assessment were conducted to compare DWI (b800) and ADC map, DWI (b800) and DWI (b2000), DWI (b2000) and ADC map, 3D sagittal T2WI and 2D sagittal T2WI, 3D axial T2WI and 2D axial T2WI, respectively. Pearson correlation analysis was performed to evaluate SIR and RG. Two groups among the patients receiving CRT were defined according to grade: Group 1: RG 1+2, and group 2: RG 3+4. Independent *t*-test was applied to assess the relation between SIR and RG for these groups. Nonparametric statistical testing (Mann-Whitney *U*-test) was performed to compare the tumor delineation between 3D and 2D T2WI. The workflow chart is presented in Figure 1.

Results

Patients, MRI, and histopathology. In total, 26 consecutive patients (22 males, four females, mean age: 61.9 ± 14.0 years, range=33-90 years) with histopathologically-confirmed rectal cancer and a total of 31 MRI examinations were included in our study. Among them, 10 patients solely underwent a primary rectal cancer staging, two patients underwent two

Table II. Average scores of image quality for each reader and results of the inter-observer agreement.

Sequence	Average score			Interobserver agreement (κ value)		
	Reader 1	Reader 2	Reader 3	1&2	2&3	1&3
b800 DWI (n=31)	4.19±0.79	4.23±0.76	3.79±0.87	0.948	0.602	0.637
ADC map (n=31)	4.23±0.72	4.1±0.75	4.06±0.81	0.766	0.828	0.616
b2000 DWI (n=24)	3.83±0.87	4.04±0.62	3.88±0.80	0.4	0.723	0.69
3D Sagittal T2WI (n=28)	4.46±0.69	4.29±0.66	4.18±0.61	0.704	0.688	0.6
3D Axial T2WI (n=28)	4.04±0.74	3.93±0.66	3.93±0.66	0.713	0.753	0.6
2D Sagittal T2WI (n=31)	4.57±0.57	4.63±0.56	4.52±0.57	0.727	0.61	0.868
2D Axial T2WI (n=31)	4.03±0.84	3.87±0.72	3.84±0.69	0.76	0.838	0.712

ADC: Apparent diffusion coefficient; DWI: diffusion-weighted Imaging; 3D: 3-dimensional; 2D: 2-dimensional; T2WI: T2-weighted sequence.

Table III. Paired *t*-test for comparison of image quality scores.

Comparison	Total	Primary	After CRT
b800 DWI & ADC map			
No. of patients	31	12	19
Score for b800 DWI	3.74±0.72	3.42±0.79	3.95±0.62
Score for ADC map	3.74±0.63	3.50±0.80	3.89±0.46
<i>t</i>	0	-1	0.369
<i>p</i>	1	0.339	0.716
b800 & b2000 DWI			
No. of patients	24	8	16
Scores for b800	3.75±0.73	3.38±0.74	3.94±0.68
Scores for b2000	3.63±0.58	3.63±0.74	3.63±0.50
<i>t</i>	0.901	-1.528	1.775
<i>p</i>	0.377	0.17	0.096
ADC map & b2000 DWI			
No. of patients	24	8	16
Score for ADC map	3.83±0.56	3.50±0.76	4.00±0.37
Score for b2000 DWI	3.63±0.58	3.63±0.74	3.63±0.50
<i>t</i>	1.551	-0.552	2.423
<i>p</i>	0.135	0.598	0.029*
2D & 3D Sagittal T2WI			
No. of patients	28	9	19
Score for 3D	4.00±0.48	4.00±0.5	4.00±0.49
Scores for 2D	4.03±0.34	4.11±0.33	4.00±0.34
<i>t</i>	-0.372	-1	0
<i>p</i>	0.713	0.347	1
2D & 3D Axial T2WI			
No. of patients	28	9	19
Score for 3D	3.85±0.61	3.78±0.67	3.89±0.58
Scores for 2D	3.78±0.64	3.56±0.73	3.89±0.58
<i>t</i>	0.625	1.512	0
<i>p</i>	0.537	0.169	1

CRT: Chemoradiation; DWI: diffusion-weighted imaging, ADC: apparent diffusion coefficient; 2D: 2-dimensional; 3D: 3-dimensional; T2WI: T2-weighted sequence. *Significant *p*-value (<0.05).

MRI examinations both before and after CRT, 11 patients solely underwent one post-CRT scan, and three patients had two MRI examinations after CRT. All primary cancers were staged as T3 by histopathology.

Interobserver agreement on image quality. Almost all the interobserver agreement analyses showed a good agreement regarding image quality assessment, except for poor agreement in b2000 DWI between the two less-experienced readers (Reader 1 and reader 2, Table II). In addition, relatively higher scores were recorded by the less-experienced readers compared to the senior reader (Table II).

Significant differences were only obtained regarding the comparison between DWI (b2000) and ADC map in patients receiving CRT (Table III, Figure 2).

Comparisons of tumor delineation. Tumor delineation was significantly better on 2D T2WI images than on 3D T2WI images both before and after CRT (before CRT, *p*=0.02; after CRT, *p*<0.001; all: *p*<0.001; Figure 3, Table IV).

SIR. Histopathological results of three examinations after CRT were not available for evaluation. In three examinations, b2000 MRI was not obtained owing to technical problems. Consequently, 13 examinations in total were included in the SIR analysis. Pearson analysis showed no significant relationship between SIR and RG (*r*=-5.21, *p*=0.081). However, independent *t*-test showed significant positive correlation between SIR and RG for group 1 (RG 1+2, average score=2.02) (Figures 4 and 5, Table V) and group 2 (RG 3+4, average score=0.80) (*t*=3.044, *p*=0.011) (Figure 6, Table V).

In total, six patients showed a RG of 4 (complete response); SIR of b2000 MRI in this group was 0.95. In two patients, the tumor was invisible on b2000 MRI following CRT (RG 3 and 4, respectively).

Discussion

Despite MRI being a well-established technique for rectal cancer staging (1, 3) and response assessment, research is ongoing to further improve the technique and to optimize staging as prerequisite for an adequate choice of therapy and to predict the outcome of CRT before surgical resection.

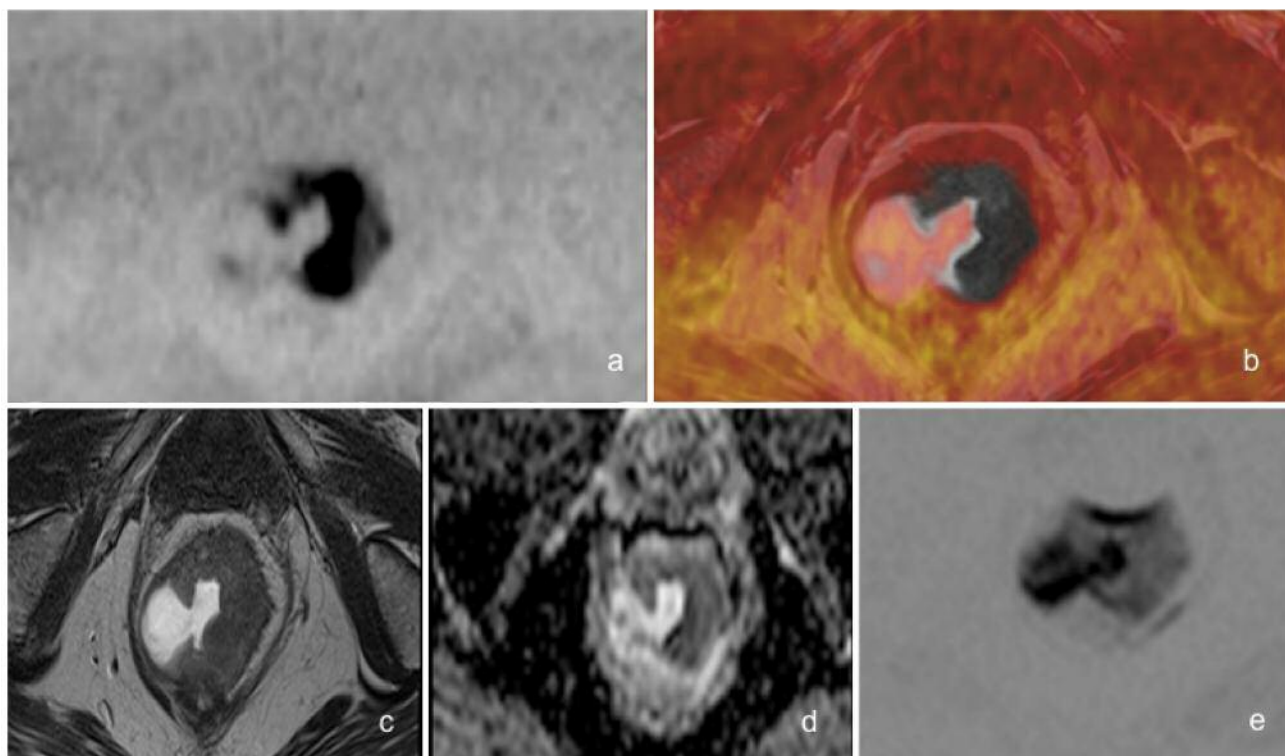


Figure 2. Imaging of primary rectal cancer (T3) in a 73-year-old man. *a*: The rectal cancer is clearly visible on b2000 diffusion-weighted imaging (DWI); *b*: fusion of b2000 DWI image with a 2D axial T2-weighted sequence (T2WI) adds morphological information of surroundings. *c*: 2D Axial T2WI for the same location as shown in (*a*). *d*: Apparent diffusion coefficient map also showed the tumor clearly. *e*: Slight image torsion and artifacts due to feces on b800 DWI.

Table IV. Tumor delineation comparisons between 3D and 2D T2-weighted images.

	3D Equivalent to 2D	3D Superior to 2D	3D Inferior to 2D	Z	p-Value
Total	n=4	n=4	n=20	-5.192	<0.001
Primary tumor	n=1	n=1	n=7	-3.2	0.02
After CRT	n=3	n=3	n=13	-4.408	<0.001

CRT: Chemoradiation.

Relatively new techniques such as isotropic, thin-sliced 3D sequences (8) were recently introduced that can be used to accurately assess penetration of the rectal wall and possible involvement of the mesorectal fascia, which is crucial for treatment decisions. Reformatting options can also be applied to shorten the protocol and consequently to increase the time- and cost-effectiveness of the examination.

3D T2WI has been successfully used in pelvic imaging, *e.g.* uterine imaging (8, 9). In this study, we explored the value of 3D T2WI in rectal cancer imaging for the first time. However, based on our initial results, tumor delineation was slightly inferior on 3D T2WI compared to 2D T2WI, which might be explained by an inferior in-plane resolution. Reducing the slice

thickness in 3D T2WI may also reduce the signal-to-noise ratio and consequently lower the contrast at tissue borders (*e.g.* tumor/rectal wall and surrounding perirectal fat tissue), which might possibly explain our results. On the other hand, a major advantage of 3D T2WI is the feasibility of reformatting virtually any slice direction. Slices need to be planned perfectly orthogonal to the tumor in order to accurately determine the tumor borders for correct T-staging (14). Planning these sequences can be challenging for the technician, especially at the rectosigmoidal junction. By using 3D T2WI, the correct angle for rectal wall assessment can be chosen retrospectively. Moreover, image quality was rated as nearly identical by all three readers. Therefore, and because of the potential time saved

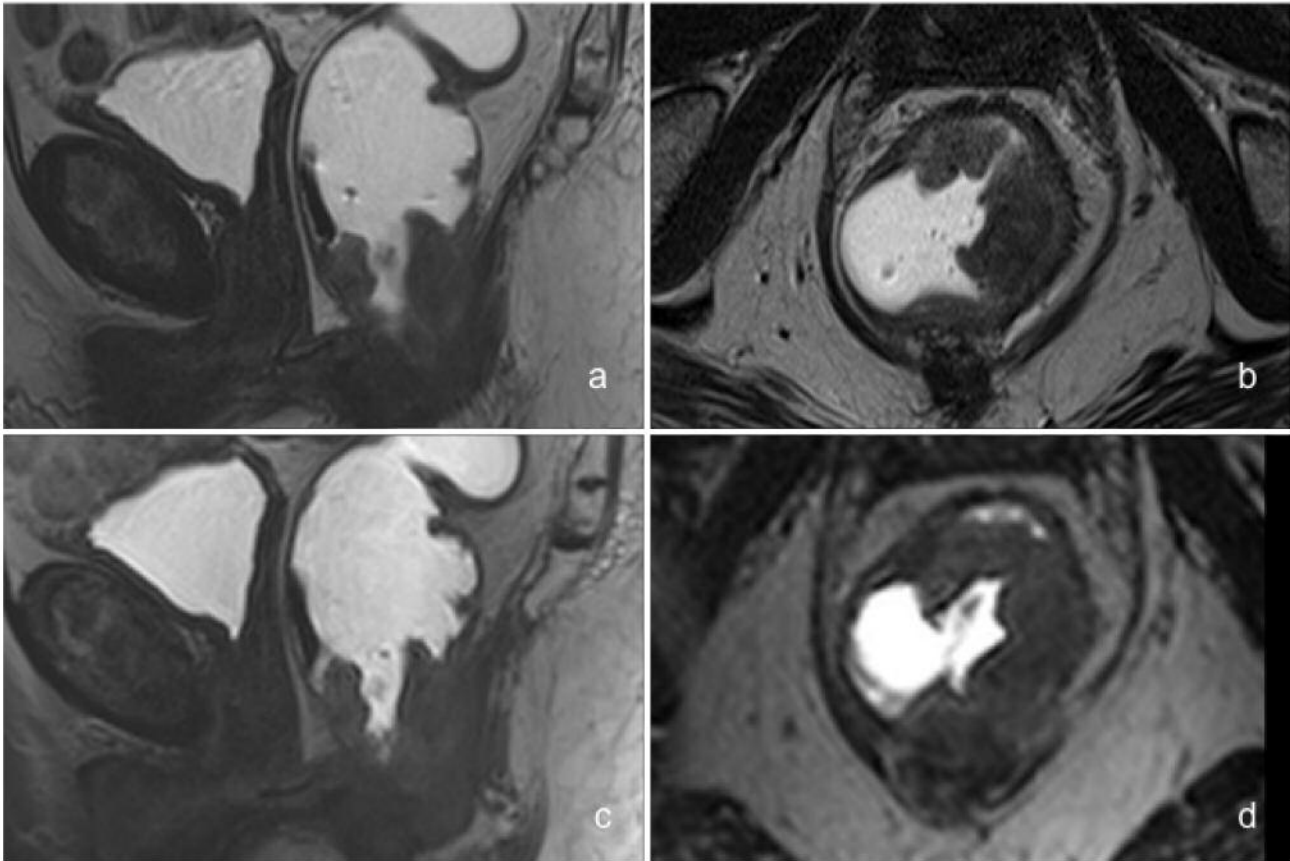


Figure 3. Imaging of primary rectal cancer (T3) in a 73-year-old man. a: 2D Sagittal T2-weighted sequence (T2WI); b: 2D axial T2WI. c: 3D sagittal T2WI. d: reformatted axial image of 3D T2WI. The delineation of tumor is superior on 2D T2WI.

in examination by a single 3D acquisition, 3D T2WI might represent a useful alternative to the conventional 2D approach.

Additionally, functional techniques such as DWI may facilitate prediction of early response and enable us to identify complete response, such that surgical resection may not affect patient outcome (7, 10).

Various previous studies have already investigated the use of DWI (b-value 800-1,000 mm²/s) as a tool for treatment response prediction and have shown that low pretreatment ADC values may correlate with a good response to CRT (15-19). For example, Intven *et al.* investigated 59 patients with locally advanced rectal cancer after CRT and suggested that both the pre-CRT ADC values and relative change in ADC were predictive for pathological response (cut-off value of 0.97×10⁻³ mm²/s) (15).

Another study also evaluated the relationship between the ADC parameters and tumor volume reduction or histopathological response to predict the therapeutic response to CRT in 35 patients (16). The authors showed that pre-CRT

Table V. Regression grade (RG) and signal intensity ratio (SIR) for each patient and statistical analysis.

RG	SIR	Average score	Results of <i>t</i> -test
3	0	Group 1, RG 1+2: 2.02 (n=6) Group 2, RG 3+4: 0.80 (n=7)	<i>t</i> =3.044 <i>p</i> =0.011*
1	0.988		
4	0		
4	0.909		
1	1.981		
1	1.793		
4	0.901		
2	2.598		
4	1.557		
2	3.309		
4	1.33		
4	0.98		
2	1.458		

*Significant *p*-value (<0.05).

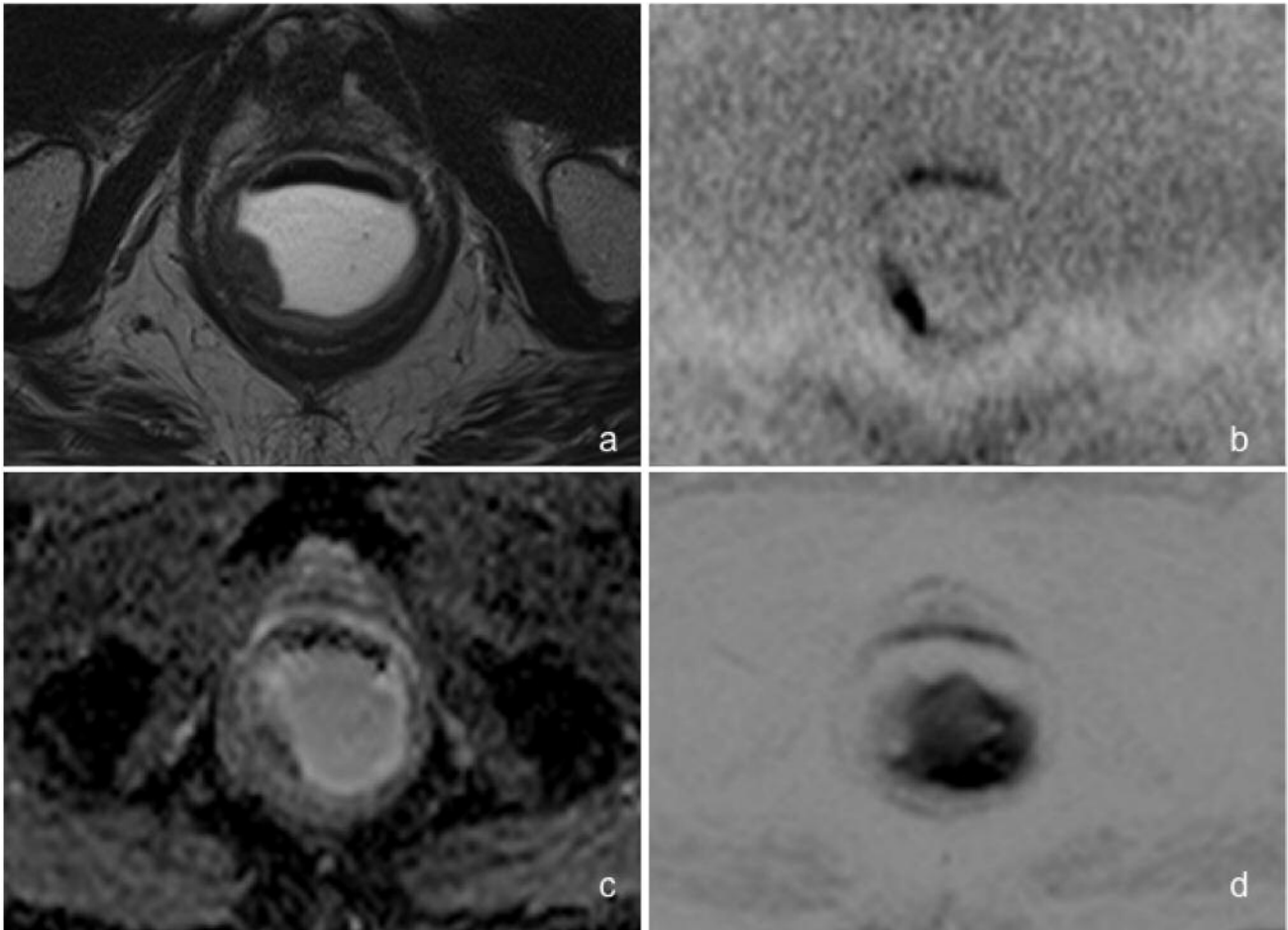


Figure 4. Imaging of a 67-year-old man with rectal cancer after chemoradiation (CRT) (regression grade 1). a: 2D Axial T2-weighted sequence depicts the tumor involving the right side of the rectal wall with soft-tissue signal intensity. b: On b2000 diffusion-weighted imaging (DWI) high signal intensity of tumor is seen, which suggests poor response to CRT and residual tumor. c: Apparent diffusion coefficient map. d: b800 DWI with poor visualization of the tumor (signal of rectal gel is not sufficiently suppressed).

ADC of responders was significantly lower than that of the non-responders ($p=0.034$). Relative change in ADC of the histopathological responders was significantly higher than that of nonresponders ($p<0.005$).

However, some studies have still proposed that ADC measurements fail to accurately distinguish complete responders from partial responders. Differences in the ROI size and positioning used for tumor ADC value calculation might explain these results (11, 20, 21).

DWI with a higher b-value (more than $1,000 \text{ s/mm}^2$) is a promising technique for detecting malignant tumors. In previous study, higher b-value DWI, such as a b-value of $1,400 \text{ s/mm}^2$, showed benefits in increasing rates of detection of prostate cancer (22). In our study, b2000 was applied in rectal cancer to our knowledge for the first time. Our results indicate that b2000 could be helpful in detecting tumors with a clear demarcation of

tumor borders, which can be attributed to a nearly perfect background suppression (almost no ‘T2-shine-through’) with high SIR between tumor and healthy tissue, although the image quality of b2000 DWI showed no significant differences when compared with b800 DWI and ADC map (Table III, Figure 1). In rectal cancer after CRT, b2000 DWI achieved only relatively low image quality scores compared to standard DWI and ADC maps. This might be attributed to the tremendous decrease in signal intensity after CRT and the lack of anatomical references for image assessment due to excellent background suppression (Figures 4 and 5). Consequently, b2000 DWI alone might not be suitable for reading and additional morphological sequences may be needed. Fusion of b2000 and T2WI may help to accurately assess cancer location.

Good response (RG 3 or 4) (Figure 6) usually results in development of fibrosis, which is not associated with

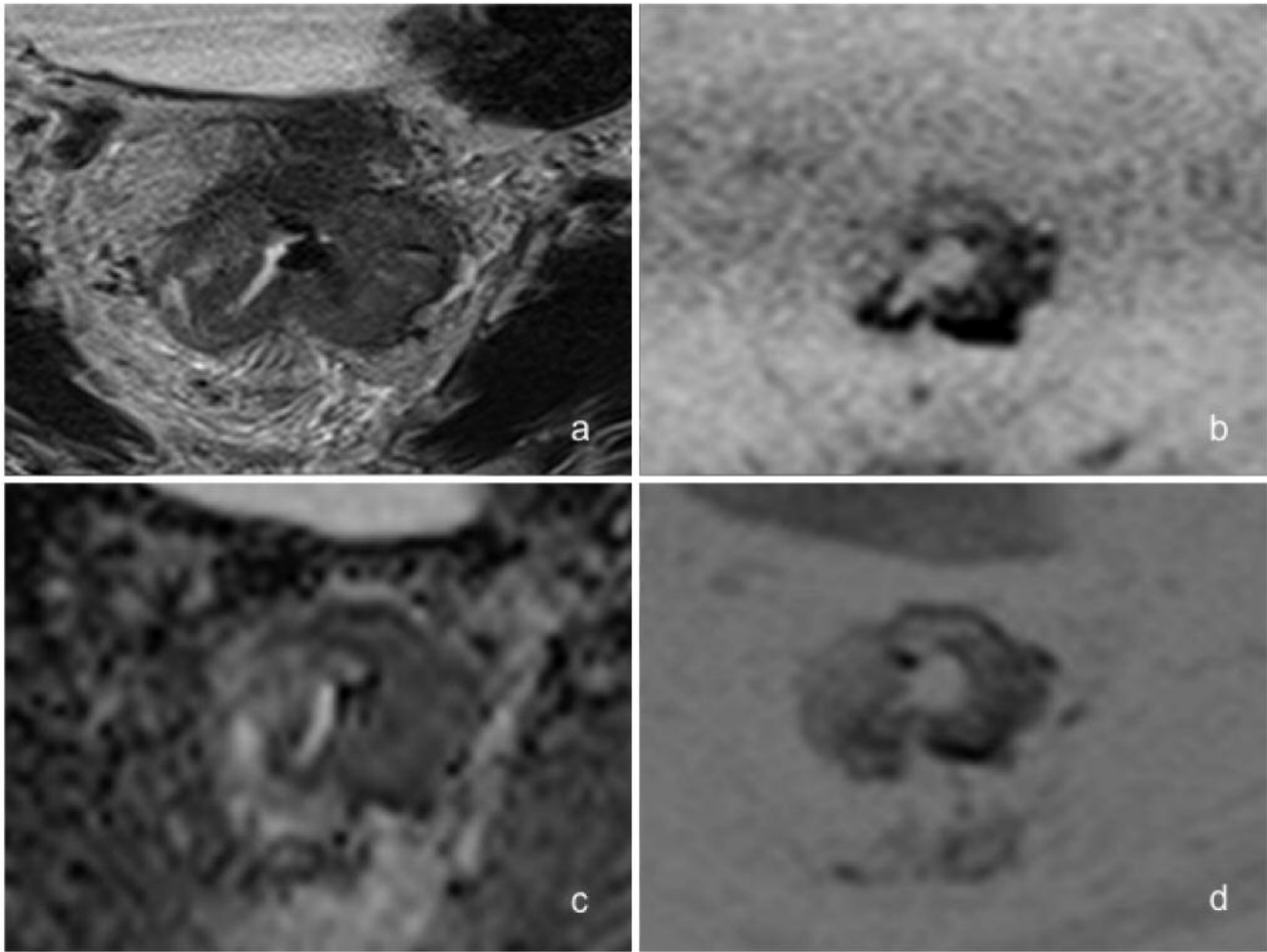


Figure 5. Imaging of a 56-year-old man with rectal cancer after chemoradiation (regression grade 2). a: On 2D axial T2-weighted sequence the tumor with soft-tissue signal intensity and invasion of the mesorectal fascia can be seen. b: b2000 Diffusion-weighted imaging (DWI) depicts high signal intensity of tumor, which suggests poor response to therapy and residual tumor. c, d: Apparent diffusion coefficient map and b800 DWI.

restricted diffusion and therefore displays a low signal intensity on b2000 MRI. Moderate to poor response (RG 1 or 2) (Figures 4 and 5) may result in a residual, increased cellularity due to dense tumor cells, which is associated with higher signal on high b-value MRI.

However, the initial statistical analysis of SIR (Table V) suggests benefits in predicting tumor response to CRT. Thus, it might be beneficial for assessing CRT response and identifying complete responders. Nevertheless, interobserver agreement between junior radiologists was not good for b2000 DWI, which might be due to unfamiliarity with the new sequence. Clearly, further technical developments are necessary in order to increase image quality. Zoomed techniques may also help to reduce artifacts and to increase diagnostic confidence (23).

Limitations. There are several limitations to our study: Firstly, the sample size is relatively small, especially for comparing SIR with different RG. However, as a pilot study for new sequences the results are of interest and should be confirmed in larger clinical studies. Secondly, the data distribution for statistical analyses is relatively heterogeneous due to the retrospective design of our study.

In conclusion, 3D T2WI can be obtained with high image quality in a comprehensive, time- and cost-effective protocol with the option of multiplanar reformations for accurate T-staging; however, the image quality of 2D T2WI seems to be preferable. MRI with b2000 is promising in both detecting tumors in the initial staging and assessing response, which also needs to be confirmed in larger studies.

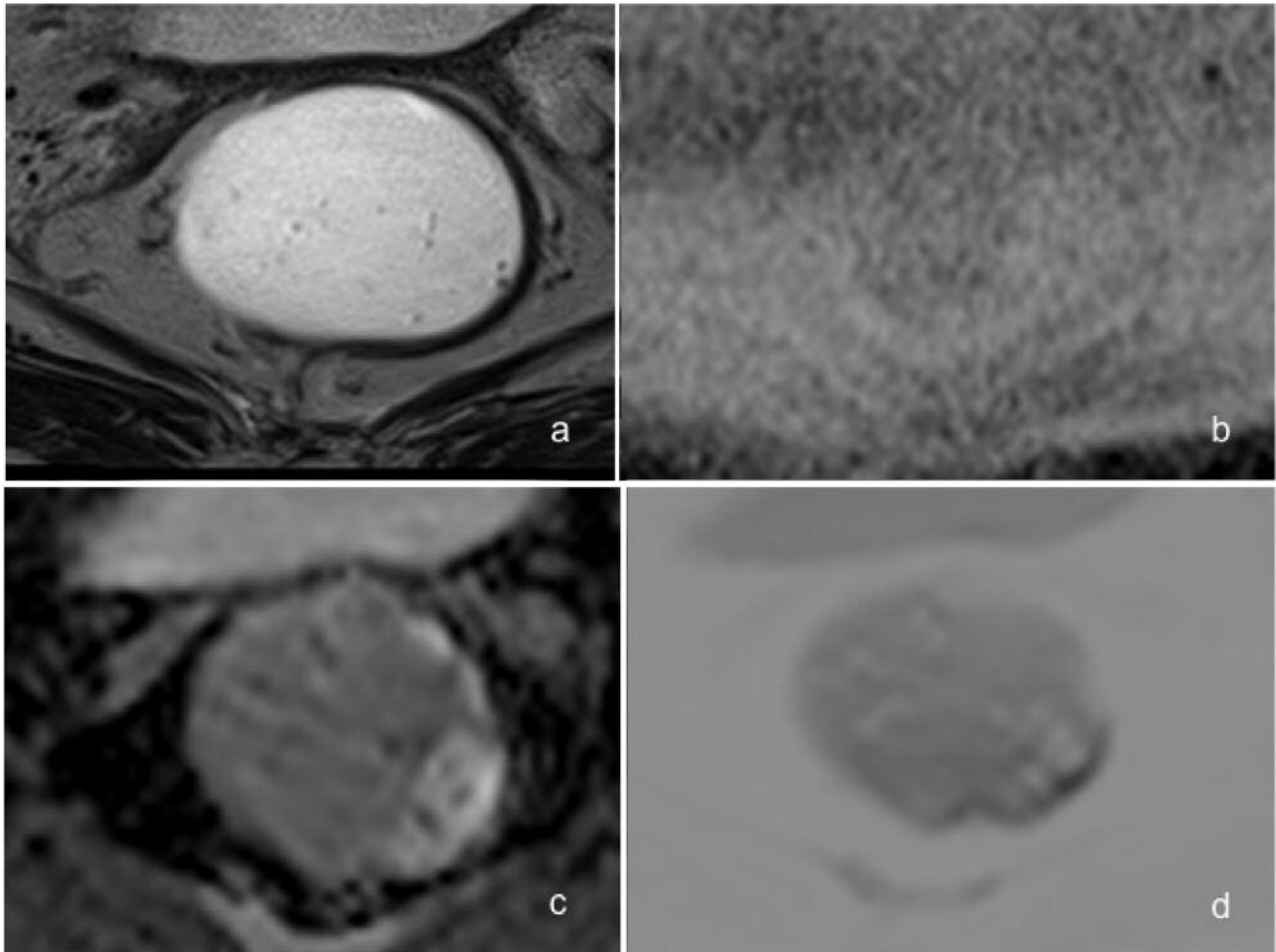


Figure 6. Imaging of a 5-year-old woman with rectal cancer after chemoradiation (Regression Grade 3). a: 2D axial T2-weighted sequence does not show visible tumor. b: b2000 Diffusion-weighted Imaging (DWI) is also negative. c, d: Apparent Diffusion Coefficient map and b800 DWI reveal inferior background suppression (e.g. 'T2-shine-through' of rectal gel) than b2000 DWI.

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Received November 14, 2017

Revised December 7, 2017

Accepted December 8, 2017