BJR

https://doi.org/10.1259/bjr.20180655

Received: 27 July 2018 | Revised: 19 October 2018 | Accepted: 31 October 2018

Cite this article as:
Schurink NW, Lambregts DM.J, Beets-Tan RG.H. Diffusion-weighted imaging in rectal cancer: current applications and future perspectives. *Br J Radiol* 2019; **92**: 20180655.

REVIEW ARTICLE

Diffusion-weighted imaging in rectal cancer: current applications and future perspectives

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ABSTRACT

This review summarizes current applications and clinical utility of diffusion-weighted imaging (DWI) for rectal cancer and in addition provides a brief overview of more recent developments (including intravoxel incoherent motion imaging, diffusion kurtosis imaging, and novel postprocessing tools) that are still in more early stages of research. More than 140 papers have been published in the last decade, during which period the use of DWI have slowly moved from mainly qualitative (visual) image interpretation to increasingly advanced methods of quantitative analysis. So far, the largest body of evidence exists for assessment of tumour response to neoadjuvant treatment. In this setting, particularly the benefit of DWI for visual assessment of residual tumour in post-radiation fibrosis has been established and is now increasingly adopted in clinics. Quantitative DWI analysis (mainly the apparent diffusion coefficient) has potential, both for response prediction as well as for tumour prognostication, but protocols require standardization and results need to be prospectively confirmed on larger scale. The role of DWI for further clinical tumour and nodal staging is less well-defined, although there could be a benefit for DWI to help detect lymph nodes. Novel methods of DWI analysis and post-processing are still being developed and optimized; the clinical potential of these tools remains to be established in the upcoming years.

INTRODUCTION

Over the last decade, more than 140 papers have been published on diffusion-weighted imaging (DWI) for rectal cancer varying from small, purely technical and pre-clinical studies to multicentre clinical patient studies in cohorts of up to 128 patients. Increasing evidence shows that DWI provides added benefit compared to conventional morphological sequences, in particular for the assessment of treatment response. The routine use of DWI for rectal cancer restaging was recently also recommended in the expert consensus guidelines of the European Society of Gastrointestinal Abdominal Radiology[1] and DWI is increasingly incorporated in clinical rectal MRI exams worldwide. Figure 1 illustrates how the research on rectal DWI has evolved over the years and what have been the main topics under investigation. Initially, the main focus of research was the role of DWI for qualitative (visual) assessment of rectal cancer for either staging or response assessment. This focus has slowly shifted towards more quantitative methods of DWI assessment, including a large number of studies on the use of the apparent diffusion coefficient (ADC), the main quantitative measure of DWI. More recently, several papers have been published on more advanced DWI models and post-processing methods such as histogram analysis, intravoxel incoherent motion (IVIM), diffusion kurtosis imaging (DKI), and automated DWI tumour segmentation.

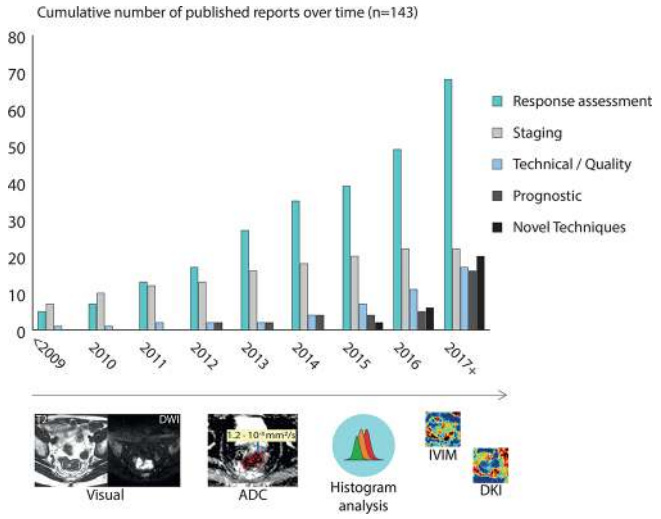
This paper aims to give an overview of the various clinical applications of DWI and discuss their potential role for rectal cancer imaging.

PRIMARY RECTAL CANCER STAGING

Rectal tumour detection

The main goal of MRI for rectal cancer is staging rather than tumour detection, since typically the presence of tumour has already been established by endoscopy or CT-colonography.[2] It is probably therefore that only a few studies have focused on DWI for the primary detection of rectal cancer.[3–10] Nevertheless, published reports have shown consistently good results for DWI to detect rectal tumours. In a recent meta-analysis, albeit focusing on colorectal tumours in general and not specifically on rectal cancer, pooled sensitivity, specificity and area under the curve (AUC) were 95%, 93% and 0.98, respectively.[11]

Figure 1. Overview of the cumulative number of studies published on DWI and rectal cancer in the last decade. The majority focused on response assessment to CRT, initially followed by studies on DWI for staging though now overtaken by studies focusing on new techniques. Over time, the focus of research has shifted from simple qualitative evaluation to increasingly advanced quantitative methods, which is also reflected by the increased proportion of studies focusing on the development of novel DWI models such as IVIM and DKI. Technical/Quality papers indicate papers that focusing on image quality or protocol development. ADC, apparent diffusion coefficient; CRT, chemoradiotherapy; DKI, diffusion kurtosis imaging; DWI, diffusion-weighted imaging; IVIM, intravoxel incoherent motion.



The few studies that did specifically focus on rectal cancer detection found similar high sensitivities of 86–100%, specificities of 84–100%, and AUCs of 0.96–0.99.[3–6] These results indicate that overall, the detection level of DWI is high, with a low risk for false positive findings, although these may occur, *e.g.* because DWI can also result in high signal in non-malignant colorectal polyps.[6,7] In practice, DWI may mainly be helpful in some specific more difficult cases, to help direct the eye of the radiologist, *e.g.* in the case of small tumours (Figure 2) or when tumours are obscured by large amounts of faeces. DWI is less useful for the detection of mucinous rectal tumours as due to their high mucin content, these tumours show less restricted diffusion and assessment is limited by T_2 effects.[12] They typically show a relatively low signal on high *b*-value DWI with corresponding high signal on the ADC-map.[12] Mucinous type rectal tumours are generally better appreciated on routine T_2W-MRI because their high mucin content results in markedly high T_2 signal intensity.[13,14]

Tumour staging

DWI appears to have only a minor role in the primary staging of rectal tumours. Two groups studied the added benefit of DWI for T-staging of rectal cancer, compared to routine staging using T_2W-MRI.[15,16] They found no clear benefit: for T1-2 tumours sensitivity was 64–90% for DWI *vs* 60–80% for T_2W-MRI and specificity was 83–100% for DWI *vs* 78–92%; for T3-4 tumours sensitivity was 50–100% for DWI *vs* 50–100% for T_2W-MRI and specificity was 83–100% for DWI *vs* 77–100% for T_2W-MRI. Differences in staging performance all lacked statistical significance. To the best of our knowledge, no papers have specifically focused on using DWI for other primary staging outcomes such as mesorectal fascia (MRF) involvement and extramural venous invasion (EMVI).

Lymph node staging

Nodal staging, remains one of the most challenging tasks for radiologists.[17] Traditionally, nodal staging relied heavily on nodal size as the main criterion. Additional morphological criteria such as nodal border, shape and signal intensity have been shown to be helpful and are now commonly employed, although these criteria may be difficult to evaluate in very small nodes.[18–20] Two meta-analyses reported suboptimal sensitivities and specificities in the range of 55–78% for nodal staging with standard (T_2 weighted) MRI.[21,22] The use of DWI for lymph node staging is appealing, since owing to the high cellular density of lymphoid tissue, nodes should typically be well detectable on DWI (Figure 3). Indeed, a 10–83% increase in the overall number of detected lymph nodes has been reported when using DWI compared to T_2W-MRI to detect pelvic lymph nodes.[23–26]

Figure 2. T_2 weighted MRI (a) and b1000 s mm^{-2} DWI images (b) of a male patient with a small tumour (white arrowhead) that is hard to detect and initially missed on T_2 weighted MRI, but is clearly visible on DWI. DWI,diffusion-weighted imaging.

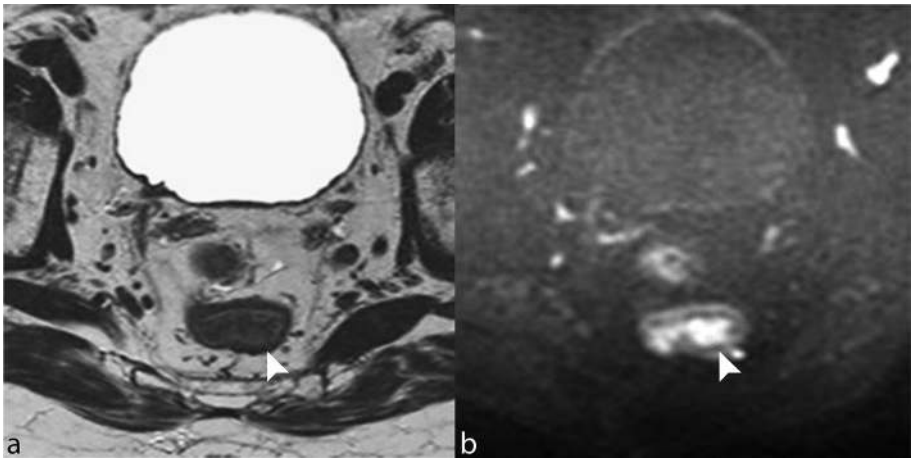
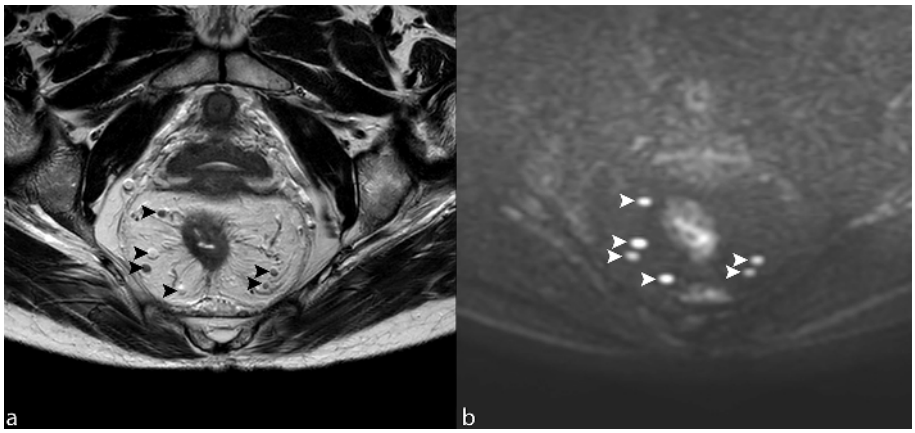


Figure 3. Pre-treatment, primary staging T_2 weighted (a) and DWI b1000 s mm^{-2} (b) images of a female patient with a spiculated tumour in the mid-rectum. Note how the various mesorectal lymph nodes (arrowheads) are very easily detectable on DWI. DWI,diffusion-weighted imaging.



The value of visual DWI evaluation for nodal characterization is less apparent. Two studies each reported a positive-predictive value of only 52% when using a high signal on DWI as a criterion for malignancy, indicating that use of DWI entails a risk for overstaging.[20,23] One study looked at the morphology of lymph nodes on DWI and found that a more heterogeneous signal on DWI was associated with malignancy,[27] an observation that has also previously been reported for nodes on T_2W-MRI[18,19] and may be less attributable to the use of DWI itself. This single-centre result has so far not been validated by other groups.

The majority of studies on DWI for characterizing rectal nodes focused on quantitatively measuring nodal ADC values.[23,28–31] An overview of these studies is presented in Table 1.

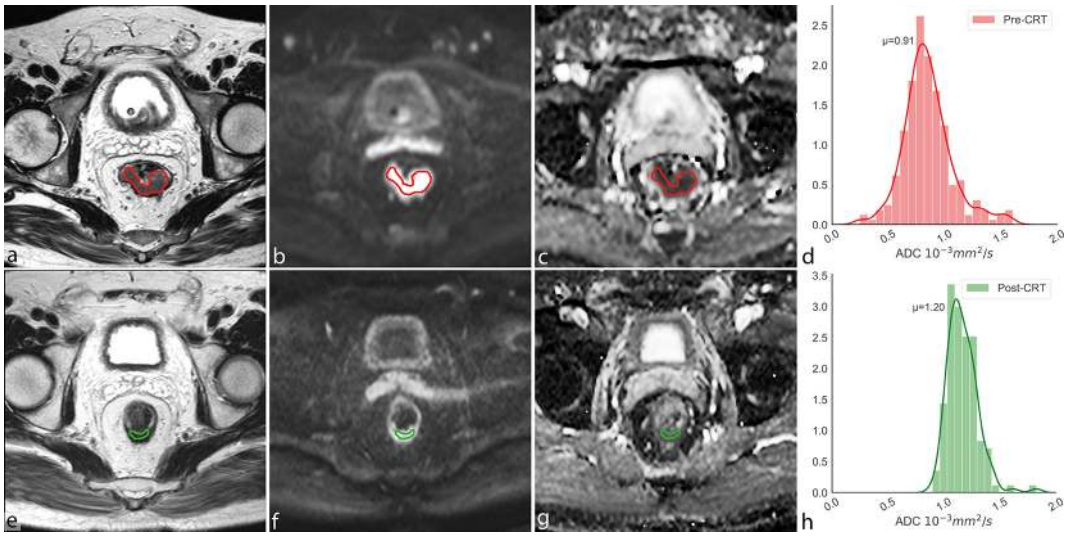
Most studies reported significantly higher ADC values (indicating a lower cellular density) for benign nodes than for malignant nodes.[28–31] Sensitivities and specificities to characterize nodes based on the ADC (using retrospectively determined threshold values) ranged from 67 to 88% and 60 to 97% respectively, which is only slightly higher than previously reported values for morphological MRI.[21,22,24,32] Moreover, reported ADC values vary across studies (using different MR vendors and protocols) and show considerable overlap between malignant and benign nodes. Also, feasibility and reproducibility of nodal ADC measurements has been reported as a potential drawback, owing to the typical small size of rectal nodes combined with the suboptimal resolution on ADC-maps, which can make it hard to delineate the nodes to measure their ADC.[24,33] Two studies specifically reported that ADC could not be measured in a subset (21–27%) of the nodes identified on DWI because they were either too small or due to local image distortions.[23,24] Along the same line, two groups omitted measurements on lymph nodes smaller than 2 mm in diameter, as delineations were technically too challenging in these nodes.[29,32]

Table 1. Overview of studies that compared the mean ADC values of benign and malignant nodes in rectal cancer, both in the primary staging setting, as well as for restaging of nodes after CRT

Author (year) (ref)	N(pt)	N(nodes)	ADC benign nodes	ADC malignant nodes	p=	Cut-off	AUC	Sens	Spec
Primary staging									
Yasui (2009)[28]	46	163	1.85 ± 0.53	1.36 ± 0.42	**0.001**	1.44	0.79	75	74
Cho (2013)[29]	34	114	1.10 ± 0.22	0.90 ± 0.15	**<0.0001**	1.00	0.73	78	67
Zhao (2014)[a30]	72	454	0.91 ± 0.19	0.77 ± 0.12	**<0.01**	–	–	88	97
Cerny (2016)[31]	24	44	1.38 ± 0.32	1.10 ± 0.19	**0.0012**	–	0.76	–	–
Heijnen (2013)[23]	21	102	1.15 ± 0.24	1.04 ± 0.22	0.1	1.07	0.64	67	60
Restaging after CRT									
Kim (2015)[32]	53	115	1.13 ± 0.23	1.36 ± 0.27	**<0.0001**	1.25	0.74	66	74
Lambregts (2011)[24]	30	115	1.19 ± 0.27	1.43 ± 0.38	**<0.001**	1.25	0.66	53	82

ADC, apparent diffusion coefficient; AUC, area under the curve;CRT, chemoradiotherapy.
NB. Statistically significant ($p < 0.05$) results are printed in bold.
[a]For Zhao (2014), results are presented on a per patient (N+ vs N0 stage) basis, all other concern node-by-node analyses.

Figure 4. Pre- (upper row) and post-CRT (bottom row) T_2 weighted (a, e), b1000 s mm^{-2} DWI (b, f) and ADC images (c, g) of a patient with a midrectal tumour that responded well to CRT (Histopathology after surgery indicated a very good response with predominant fibrosis and only rare residual tumour cells; Mandard tumour regression grade of 2). The images illustrate the different ways DWI can be used to assess response: on pre-CRT a clear high signal mass can be appreciated on DWI (b), after CRT only a small high signal remnant is visible within the fibrosis on DWI indicating a small residual tumour (f). The tumour volume on DWI decreased from 13.2 to 0.26 cm^3, while the ADC value increased from 0.91·10^{-3} to 1.20·10^{-3} mm^2 s^{-1}. Concordantly, the histograms show that the distribution of ADC values within the tumour has shifted towards more high ADC values, indicating a good response. ADC, apparent diffusion coefficient; CRT, chemo radiotherapy; DWI, diffusion-weighted imaging.



TUMOUR RESPONSE ASSESSMENT

As illustrated in Figure 1, the major focus of research in rectal DWI has been the assessment of response to neoadjuvant treatment. This specific focus follows a recent paradigm shift in the treatment of rectal cancer, based on current evidence that in patients that show a (near-)complete response to chemoradiotherapy (CRT) organ-preserving treatments such as "watch-and-wait" may be considered as safe alternatives to major surgery.[34] This shift in treatment management increases the demand for an accurate radiological response evaluation.

Different methods of response evaluation have been studied varying from visual DWI assessment to quantitative volumetric or ADC measurements, some with the addition of post-processing steps such as histogram analysis. An imaging example illustrating these various methods is provided in Figure 4.

Visual (qualitative) response assessment

Routine MRI has well-known difficulties to discern viable tumour within post-treatment fibrosis, which is reflected by its poor performance (sensitivity of only 19% in a recent meta-analysis)[35]

Table 2. Overview of studies that compared the performance of DWI and T_2W imaging to visually assess complete response to CRT

Author (year) (ref)	N (pt)	T_2W					DWI				
		AUC	Sens	Spec	PPV	NPV	AUC	Sens	Spec	PPV	NPV
Kim (2009)[a36]	40	0.67	50	78	46	80	0.85	87	83	66	94
Lambregts (2011)[a37]	120	0.67	11	94	18	82	0.79	57	93	71	89
Park (2011)[a38]	45	0.81	44	84	88	38	0.94	96	79	96	87
Song (2012)[a39]	50	–	71	67	94	25	–	88	42	92	55
Sassen (2013)[a 40]	70	0.76	25	94	64	88	0.80	55	96	72	93
Marouf (2015)[41]	19	–	60	33	–	–	–	79	80	–	–
Foti (2016)[42]	31	–	20	100	100	88	–	80	100	100	97

AUC, area under the curve; CRT, chemoradiotherapy; DWI, diffusion-weighted imaging; NPV, negative-predictive value; PPV, positive-predictive value.

NB. Presented results are the average of two readers except for,[37] who used three readers, and[41] who did not mention the number of readers.

[a]In studies,[36-40] a statistically significant improvement in results was observed for at least one of the readers after adding DWI images compared to T_2W alone for assessing complete response to CRT.

to differentiate between patients with a complete response (*i.e.* sterilized fibrosis) and patients with residual tumour. Increasing evidence suggests that DWI is better equipped to make this differentiation (overview of studies provided in Table 2). Fibrotic tissue consists of loose connective fibres resulting in relatively minor diffusion restriction. Moreover, the high collagen content in fibrosis typically has a very short T_2 relaxation time, leading to low signal on the ADC-map as well as the DW images.[43] In contrast, areas containing persistent viable tumour typically show restricted diffusion resulting in a high signal on high *b*-value DWI. Reported AUCs for DWI range between 0.70 and 0.96, compared to 0.67–0.85 for standard MRI, with a statistically significant effect in the majority of reports.[36–42] One recent study combined morphologic patterns of response on T_2W-MRI with distinct signal patterns on DWI (specific locations of focal diffusion restriction within different patterns of fibrosis). With this approach, the authors reached a sensitivity of 94% and specificity of 77% to differentiate patients with residual tumour from patients with a complete response,[44] results that remain to be validated by other groups.

Tumour restaging

Most published reports on DWI for tumour response assessment focused on the general differentiation between a favourable response (*i.e.* complete or good response) *vs* poor response. In a meta-analysis by van der Paardt et al, pooled sensitivity for predicting response (defined as either ypT0, ypT0-2 or T-downstaging compared to primary staging) was significantly higher for studies that included DWI in the MR protocol compared to studies that did not (83.6% *vs* 50.4%).[35] A second meta-analysis by Wu et al included studies focusing both on visual DWI analysis as well as studies focusing on ADC (with no subanalyses between these two groups) making it difficult to draw conclusion about the one or the other.[45] To the best of our knowledge, so far no studies exist on visual use of DWI for further yT substaging. One study recently proposed a new 3-point MR-based tumour regression grade (mrTRG) incorporating both T_2W-MRI and DWI for evaluating response after CRT. Both the accuracy for assessing response and interreader agreement improved significantly compared to the more well-known 5-point mrTRG score which uses T_2W-MRI only.[46] A single report by Park and colleagues evaluated the use of DWI in addition to T_2W-MRI to predict tumour clearance of the MRF after neoadjuvant CRT.[38] The authors reported a significantly improved performance after the addition of DWI (AUC 0.92–0.96) compared to use of only T_2W MRI (AUC 0.77–0.85).

Nodal restaging

A small number of papers reported on the diagnostic value of visual lymph node assessment using DWI in the restaging setting. Lambregts et al performed a node-by-node analysis of 157 nodes detected on DWI post-CRT and found that nodal signal intensity on DWI did not differ between yN- and yN+nodes (AUC 0.52 and 0.64 for two readers).[24] Two groups assessed the use of DWI to predict lymph node eradication (*i.e.* yN0 stage) after CRT on a patient basis.[47,48] Van Heeswijk et al reported that the visual absence of nodes on DWI after CRT was a highly reliable predictor of a negative nodal status (sensitivity 100%), but the presence of nodes on post-CRT DWI was an unspecific finding, which could indicate either the presence of benign or malignant nodes, resulting in a low specificity of only 14%, again illustrating the limited capacity of DWI to visually characterize lymph nodes.[47] Ryu et al used a confidence level score to predict lymph node eradication after CRT with and without DWI and found no improvement in diagnostic performance for DWI compared to T_2W-MRI with AUCs in the same range of 0.77–0.80.[48]

QUANTITATIVE RESPONSE ASSESSMENT

DWI tumour volumetry

Table 3 summarizes the findings of four studies that assessed the value of measuring tumour volumes on high *b*-value DW images to diagnose a complete response. Similar good results were found

Table 3. Overview of studies that have compared DWI and T_2W tumour volumetry to predict a complete response to CRT

Author (year) (ref)	N=	T_2W AUC	DWI AUC
Pre-CRT volume			
Curvo-Semedo (2011)[49]	50	0.57	0.63
Lambregts (2014)[50]	112	0.73	0.77
Post-CRT volume			
Curvo-Semedo (2011)[49]	50	0.70	0.93[a]
Lambregts (2014)[50]	112	0.82	0.92[a]
Sathyakumar (2016)[51]	64	-	0.88
ΔVolume			
Curvo-Semedo (2011)[49]	50	0.84	0.92
Lambregts (2014)[50]	112	0.78	0.86
Sathyakumar (2016)[51]	64	–	0.84
Ha (2013)[52]	100	0.79	0.91

AUC, area under the curve; CRT, chemoradiotherapy; DWI, diffusion-weighted imaging.
NB. For all studies, manual tumour segmentations were performed slice-by-slice on T_2W and DWI by experienced readers.
[a]DWI volumetry performed significantly ($p < 0.05$) better than T_2W volumetry for predicting complete response to CRT.

for the DWI tumour volume after CRT and the relative change in DWI tumour volume after CRT (Δvolume) with AUCs of 0.84–0.93.[49–52] In the three studies that compared DWI to T_2W-MRI, DWI volumetry significantly outperformed T_2W-volumetry.[49–51] Pre-treatment volumes showed only moderate performance with AUCs of 0.57–0.77 for both T_2W-MRI and DWI, indicating that volumetry is of limited value for pre-treatment response prediction.

Tumour ADC

ADC has been extensively studied as an imaging biomarker to assess and predict response. A summary of these studies, in particular the studies focusing on pre-CRT ADC, post-CRT ADC and ΔADC, is presented in Table 4. Regardless of the definition of response used in these reports (*i.e.* good or complete response), all studies reported an increase in mean tumour ADC after CRT,[36,39,42,49,51–58,60–90] which is thought to be due to radiation-induced cellular damage and necrosis.[91,92] The disruption of cell membranes reduces the diffusion restriction and therefore increases the ADC. Both the final post-CRT ADC and the relative increase in ADC (ΔADC%) were typically higher in the favourable response groups, with statistically significant results in the majority of studies.[36,42,52–55,57–70,78–80,82–84] In addition, several studies found significantly higher pre-CRT ADC values in the unfavourable response groups,[42,53–56,63–66,72–74,77,78] although a similar number of studies did not find a significant difference in pre-CRT ADC between response groups.[51,52,58,59,61,62,64,67–71,74–76,79–81,84,85,87,89] A high ADC is believed to be associated with tissue necrosis, which in turn leads to decreased tissue perfusion and hypoxia, making tumours less susceptible to CRT effects.[93,94]

In addition, six groups investigated the prognostic value of measuring changes in ADC early during CRT. The groups of Jacobs et al and Cai et al reported significant differences between good and poor responders in mean tumour ADC in week 3 and weeks 3–5, respectively.[63,66] Published results for the first 2 weeks of CRT have so far been inconsistent: some authors already found significant differences in ADC at these very early timepoints,[55,64] while others could not reproduce this.[59,66,74]

Altogether, the majority of studies that investigated ADC as a biomarker to assess or predict response to treatment found significant results at one or more time points, although a subgroup (21%) of studies could not produce any statistically significant results.[49,51,75,76,85–87,89,90] As a critical note, most study cohorts presented so far are small and single centre, and reported ADC and cut-off values show large variation and overlap between studies and have never been validated in prospective study cohorts. This stresses the need for standardization and multicentre validation studies. With this in mind, a meta-analysis by Joye et al concluded that based on current evidence the results look promising but need work with pooled sensitivities and specificities to predict complete response of 69 and 68% for pre-CRT ADC, 78 and 72% for post-CRT ADC, and 80 and 78% for ΔADC%.[95] Because of the limited number of studies and the small study sizes, no conclusions can be drawn yet with respect to the added benefit of performing ADC measurements (early) during CRT treatment.

HISTOGRAM ANALYSIS

While most studies investigated only mean tumour ADC values, some evaluated the added benefit of performing histogram analysis. With histogram analysis, the whole spectrum of ADC values within the tumour is analyzed, allowing extraction of not only mean (or median) values but also additional parameters such as the minimum and maximum, standard deviation and different percentile ranges. Based on the limited evidence available so far, these parameters do not seem to offer a clear additional benefit. Of the papers that have reported an association between ADC histogram metrics (in particular 10th–25th percentile ranges) and response,[60,84,88] the majority also reported that histogram parameters did not significantly outperform median or mean ADC values.[60,88] Two other reports by van Heeswijk et al and Chidambaram et al failed to produce any significant correlation between histogram ADC measurements and the final treatment, although these reports did not find any significant results for mean ADC values either.[96,97]

Lymph node ADC

Two of the studies included in Table 1 compared the mean ADC values of benign and malignant nodes in the restaging setting.[24,32] Both reported a significantly higher ADC for malignant nodes, and interestingly an identical optimal cut-off value of $1.25 \cdot 10^{-3}$ mm^2/s to differentiate between benign and malignant nodes. However, both groups also reported that adding ADC measurements to size-based assessment on routine T_2W-MRI yielded no statistically significant diagnostic gain, suggesting that from a clinical point of view the benefit of measuring nodal ADCs may be limited.

DWI for follow up after treatment

There is limited evidence that DWI may help diagnose locally recurrent disease during follow-up after primary treatment. Two groups assessed the value of DWI to detect pelvic recurrences post-surgery. High AUCs of 0.87–0.99 were found for MRI + DWI, though results were not significantly different compared to using only standard MRI,[98,99] except for less experienced, resident readers in one of the two reports.[99] In addition, it was reported that DWI may aid in very specific cases with multiple local recurrent sites, or for the detection of small and/or anastomotic tumours. Two other reports compared the use of MRI with and without DWI for follow up of rectal cancer patients treated with organ-preservation (local excision or wait-and-see).[100,101] Although both found no overall improvement in diagnostic performance to detect local tumour regrowths in terms of AUC, adding DWI did offer some potential benefits. In one report, adding DWI improved the sensitivity of MRI and lowered the rate of inconclusive MRI outcomes.[100] Both studies also suggested that DWI may aid in detecting recurrences earlier during follow-up.[100,101]

DWI as a prognostic marker

Over the last few years, there has been a growing interest for the use of quantitative DWI parameters as prognostic imaging

Table 4. Overview of studies evaluating mean tumour ADC to predict response to chemoradiotherapy

Author (year) (ref)	N=	Standard of reference	Pre-CRT ADC			Post-CRT ADC			ΔADC% (post *vs* pre-CRT)		
Outcome 1 – Prediction of good *vs* poor response											
			Good	**Poor**	***p***	**Good**	**Poor**	***p***	**Good**	**Poor**	***p***
Jung (2012) [53]	35	cT >ypT	0.93	1.03	**0.034**	1.29	1.18	**0.009**	+0.36a	+0.14a	**<0.0005**
Birlik (2015) [54]	43	cT >ypT	0.63	0.73	**<0.05**	1.26	0.93	**0.001**	+103%	+30%	**<0.001**
Sun (2010)[55]	37	cT >ypT	1.07	1.19	**0.013**	1.30	1.28	0.560	+23%	+10%	**<0.001**
Elmi (2013)[56]	49	cT >ypT	0.97	0.84	**0.035**	–	–	–	–	–	–
Hu (2015)[57]	56	cT >ypT	0.85	0.85	0.944	1.25	1.10	**0.001**	0.52*	0.32*	**0.015**
Iannicelli (2016)[58]	34	cT >ypT	0.92	0.90	0.268	1.34	1.15	**0.010**	0.41	0.30	0.168
Kim (2011)[59]	34	cT >ypT	0.87	0.91	0.610	–	–	–	+21%	+18%	0.430
Nougaret (2016)[60]	31	TRG3-4 *vs* TRG0-2	1.10	0.90	0.460	1.40	1.10	**0.002**	+40%	+6%	**0.004**
Lu (2017)[61]	42	TRG3-4 *vs* TRG0-2	1.21	1.25	0.503	1.93	1.82	0.282	+58%	+37%	0.181
Quaia (2016)[62]	45	RCRG1-2 *vs* RCRG3-4	0.94	0.91	0.830	1.42	1.23	**0.160**	+51%	+35%	0.250
Hu (2015)[57]	56	TRG0-1 *vs* TRG2-3	0.83	0.86	0.524	1.27	1.10	**<0.001**	0.55*	0.32*	**–0.006**
Jacobs (2016)[63]	22	TRG1-2 *vs* TRG3-5	0.94	1.11	**0.040**	1.45	1.35	**0.010**	+46%	+16%	**<0.001**
Barbaro (2012)[64]	62	TRG1-2 *vs* TRG3-5	1.50	1.20	**0.007**	–	–	–	>+23%	<+23%	**0.011**
Intven (2013)[65]	59	TRG1-2 *vs* TRG3-5	0.95	1.12	**0.001**	1.44	1.36	*NS*	+50%	+23%	**<0.001**
Cai (2013)[66]	15	TRG1-2 *vs* TRG3-5	0.66	0.89	**0.021**	–	–	–	–	–	–
Blazic (2015)[67]	58	TRG1-2 *vs* TRG3-5	0.88	0.87	0.409	1.36	1.12	**<0.001**	+55%	+30%	**<0.001**
Ippolito (2015)[68]	31	TRG1-2 *vs* TRG3-5	0.88	0.78	0.076	1.47	1.19	**0.009**	+73%	+56%	**0.008**
Ippolito (2012)[69]	30	TRG1-2 *vs* TRG3-5	0.88	0.78	0.331	1.48	1.19	**0.007**	+71%	+52%	0.113
Iannicelli (2016)[58]	34	TRG1-2 *vs* TRG3-5	0.94	0.87	0.151	1.43	1.16	**0.001**	+0.49a	+0.29a	**0.01**
Monguzzi (2013)[70]	31	TRG1-2 *vs* TRG3-5	0.83	0.82	0.273	1.43	1.25	**0.004**	+63%	+60%	0.124
Intven (2015)[65]	55	TRG1-2 *vs* TRG3-5	–	–	–	–	–	–-	+48%	+26%	**<0.001**
Kim (2011)[36]	34	TRG1-2 *vs* TRG3-5	0.89	0.91	0.530	–	–	–	+18%	+20%	0.460
Bakke (2017)[71]	27	TRG1-2 *vs* TRG3-5	0.74	0.61	>0.1	0.65	0.69	>0.1	–16%	+15%	**<0.01**
Foti (2016)[42]	31	ypCR +ypPR vs ypSD	0.83	0.91	**<0.05**	1.19	1.01	**<0.05**	+0.36a	+0.11a	**<0.020**
Kremser (2003)[72]	8	ypT0–2 *vs* ypT3	0.80	0.70	**<0.02**	-	-	-	-	-	-
Hein (2003)[73]	16	ypT0–2 *vs* ypT3	0.48	0.70	**0.012**	–	–	–	-	-	-
Lambrecht (2012)[74]	20	ypT0–2 *vs* ypT3	1.06	1.19	0.270	–	–	–	+46%	+17%	0.080

(Continued)

Table 4. (Continued)

Author (year) (ref)	N=	Standard of reference	Pre-CRT ADC			Post-CRT ADC			ΔADC% (post *vs* pre-CRT)		
Outcome 1 – Prediction of good *vs* poor response											
deVries (2003)[75]	34	ypT0–2 *vs* ypT3	0.65	0.66	0.800	–	–	–	–	–	–
Hein (2003)[76]	9	ypT0–2 *vs* ypT3	–	–	*NS*	–	–	–	–	–	–
Lambrecht (2010)[77]	22	ypT0–2 *vs* ypT3	–	–	–	–	–	–	+55%	+32%	0.320
Outcome 2– Prediction of complete *vs* incomplete response											
			Complete	**Incomplete**	***P***	**Complete**	**Incomplete**	***p***	**Complete**	**Incomplete**	***p***
Chen (2016)[78]	100	pCR *vs* non-pCR	0.86	0.90	**<0.001**	1.44	1.33	**<0.001**	+68%	+48%	**<0.001**
Intven (2013)[65]	59	" "	0.97	1.09	**0.010**	1.46	1.35	0.047	+50%	+25%	**<0.001**
Lambrecht (2012)[74]	20	" "	0.94	1.19	**0.003**	–	–	–	+88%	+26%	**0.0011**
Lambrecht (2010)[77]	22	" "	0.94	1.20	**0.002**	–	–	–	–	–	-
Blazic (2016)[79]	62	" "	0.85	0.88	0.157	1.36	1.16	**<0.001**	+61%	+33%	**<0.001**
Genovesi (2013)[80]	28	" "	1.01	1.29	0.330	1.79	1.37	**0.003**	+77%	+36%	**0.05**
Hu (2015)[57]	56	" "	0.82	0.86	0.332	1.31	1.12	**<0.001**	0.64*	0.33*	**<0.001**
Kim (2011)[81]	76	" "	0.85	0.88	0.410	1.43	1.14	**<0.0001**	+70%	+30%	**<0.0001**
Intvent (2015)[82]	55	" "	–	–	–	–	–	–	+48%	+26%	**0.012**
Lu (2017)[61]	42	" "	1.20	1.25	0.406	1.94	1.83	0.420	+63%	+48%	**0.042**
Bassaneze (2017)[83]	33	" "	–	–	–	1.53	1.16	**<0.010**	–	–	–
Choi (2016)[84]	86	" "	–	–	–	1.60	1.42	**<0.004**	–	–	–
Ha (2013)[52]	100	" "	0.59	0.49	0.484	1.33	1.13	**0.001**	–	–	–
Kim (2009)[36]	40	" "	–	–	–	1.62	1.04	**<0.0001**	–	–	–
Cho (2015)[85]	50	" "	–	–	–	1.60	1.41	**0.019**	–	–	–
Cai (2014)[86]	80	" "	–	–	–	1.65	1.52	**0.024**	–	–	–
Song (2012)[39]	50	" "	–	–	–	1.55	0.93	**<0.0001**	–	–	–
Barbaro (2012)[59]	57	" "	–	–	>0.05	–	–	–	–	–	–
De Cecco (2016)[87]	12	" "	0.93	0.85	0.818	–	–	–	–	–	–
De Felice (2017)[87]	37	" "	0.81	1.05	>0.05	1.18	1.50	0.050	–	–	–
Curvo-Semedo (2011)[49]	50	" "	1.07	1.10	0.610	1.39	1.45	0.480	+35%	+36%	0.960
Engin (2012)[88]	30	" "	0.88	0.83	0.066	1.29	1.11	0.071	–	–	–

(Continued)

Table 4. (Continued)

Author (year) (ref)	N=	Standard of reference	Pre-CRT ADC			Post-CRT ADC			ΔADC% (post *vs* pre-CRT)		
Outcome 2– Prediction of complete *vs* incomplete response											
Foti (2016)[42]	31	" "	0.78	0.87	–	1.28	1.10	–	+0.51a	+0.23a	–
Sathyakumar (2016)[51]	64	" "	0.98	1.01	*NS*	1.46	1.41	>0.05	+54%	+45%	NS
Cai (2014)[86]	65	" "	–	–	–	1.56	1.44	0.152	–	–	–

ADC, apparent diffusion coefficient; CRT, chemoradiotherapy.
Statistically significant results ($p < 0.05$) are printed in bold
Note: cT = clinical T-stage, ypT = histopathological T-stage, TRG = tumour regression grade, RCRG = rectal cancer regression grade, ypCR/pCR = pathological complete response, ypPR = pathological partial response, ypSD = pathological stable disease
Studies[53,60] used Dworak's TRG[54]; used the Wheeler's RCRG,[55] used Ryan's TRG,[56–59,61–68] used Mandard's TRG
[a]=absolute difference in ADC between pre- and post-treatment scan; *=reported as ADCratio = (ADCpost – ADCpre)/ADCpre; *NS* = not significant; " " same as above

biomarkers to predict various outcomes ranging from clinical TNM-stage, to histopathological or immunohistochemical markers, and measures of long-term outcome such as disease-free survival. Although a comprehensive discussion of the results of these studies with this wide range of outcomes is beyond the scope of this paper, a brief overview is provided in Table 5 and discussed below.

The majority of reports published so far focused on the correlation of DWI with relatively simple clinical prognostic markers (such as TN-stage) and histopathological markers such as the tumour differentiation grade, with the aim to differentiate tumours with a more or less favourable overall prognostic profile. Around half of these reports found significant correlations between DWI-derived parameters and clinical or histopathology outcomes.[96,102–111] Of those studies that found significant results, the majority reported low ADC values for the unfavourable outcome groups (*e.g.* higher TN-stage, lower differentiation grade, MRF+ stage and extranodal tumour deposits), and high ADC values for the more favourable outcome groups, suggesting that tumours with a more dense cellular structure (low ADC) tend to show a more aggressive growth pattern. As discussed in the previous section (on "Quantitative response assessment"), these low ADC tumours have also been associated with a more favourable outcome in terms of response to treatment by some groups.[42,53–56,63–66,72–74,77,78] This might suggest that the same factors that give rise to a generally more aggressive tumour profile may also render tumours more susceptible to anticancer treatment. However, given the ambiguous results published so far (with approximately 50% of studies lacking statistically significant findings), this hypothesis remains to be further tested before any definite conclusions can be drawn.

Some studies looked at more advanced DWI parameters derived from IVIM imaging (discussed in more detail in section on "Recent advances" below).[102,108] Higher IVIM perfusion related parameters were associated with poorer TN-stage, differentiation grade, lymphovascular invasion and extramural venous invasion.

In an attempt to better understand the relation between DWI-parameters and underlying tumour biology, several investigators have studied the relationship between DWI-parameters and immunochemical marker expressions related to cell proliferation/apoptosis (p21, p53, Ki-67, AgNOR), vascularization (VEGF), cell adhesion (CD44, CEA) and hypoxia (Hif1-α). So far, evidence mainly comes from single centre studies. Approximately, half of these studies found significant correlations between tumour ADC and the studied marker, which mainly consisted of either proliferation related biomarkers (Ki-67, AgNOR) or biomarkers related to perfusion (VEGF, microvessel density) and hypoxia (Hif1-α).[104,111–114]

Finally, a small subset of studies focused on the correlation between DWI-derived parameters and long-term outcome, suggesting that lower ADC values are associated with shorter disease-free survival and higher recurrence rates.[115,116] Future research is needed to confirm these findings.

Table 5. Overview of studies that investigated the relationship between DWI and prognostic outcomes

	Total number of studies [total N° of patients]	N° studies with positive outcome[a] (refs)	N° studies with negative outcome[a] (refs)
Clinical outcomes			
AJCC-stage	1 [n = 52]	–	1[102]
T-stage[b]	12 [n = 650]	5[102–106]	7[96,105,107–111]
N-stage[b]	11 [n = 609]	5[102,103,106,107,110]	6[96,104,105,108,109,111]
Mesorectal fascia involvement	6 [n = 307]	2[103,110]	4[96,102,104,109]
Extramural Venous Invasion	1 [n = 52]	1[102]	–
M-stage	3 [n = 124]	1[105]	2[96,108]
Histopathological outcomes			
Differentiation grade	8 [n = 421]	5[102,107,109–111]	3[96,104,108]
Extranodal tumour deposits	1 [n = 49]	1[104]	–
Lymphovascular invasion	5 [n = 264]	2[103,108]	3[104,109,110]
Neural invasion	2 [n = 95]	–	2[104,108]
Laboratory and immunohistochemical outcomes			
P21	1 [n = 49]	–	1[104]
P53	1 [n = 49]	–	1[104]
Her2/neu	1 [n = 49]	–	1[104]
CD44	1 [n = 49]	–	1[104]
Ki-67	4 [n = 314]	4[104,111–113]	–
AgNOR	1 [n = 49]	1[104]	–
Hif-1α	1 [n = 91]	1[111]	–
VEGF	1 [n = 91]	1[111]	–
Cell count	1 [n = 17]	–	1[113]
Total nucleic area	1 [n = 17]	–	1[113]
Average nucleic area	1 [n = 17]	–	1[113]
Microvessel density	1 [n = 17]	1[113]	–
KRAS status	1 [n = 51]	1[114]	–
CEA	4 [n = 252]	1[111]	3[102,103,110]
CA19-9	2 [n = 101]	1[104]	1[102]
Long-term outcomes			
Disease-free survival	1 [n = 61]	1[115]	–
3 year local recurrence rate	1 [n = 128]	1[116]	–
3 year distant relapse-free survival	1 [n = 128]	1[116]	–
Local or distant recurrence	2 [n = 101]	1[115]	1[109]

DWI, diffusion-weighted imaging.

Note: All presented studies included mean ADC as an input variable. References[96,102,103,105–108,113,114] additionally included more advanced parameters related to DKI,[103,105,107] IVIM,[102,108,113,114] texture[106] or histogram parameters.[96,103,106]

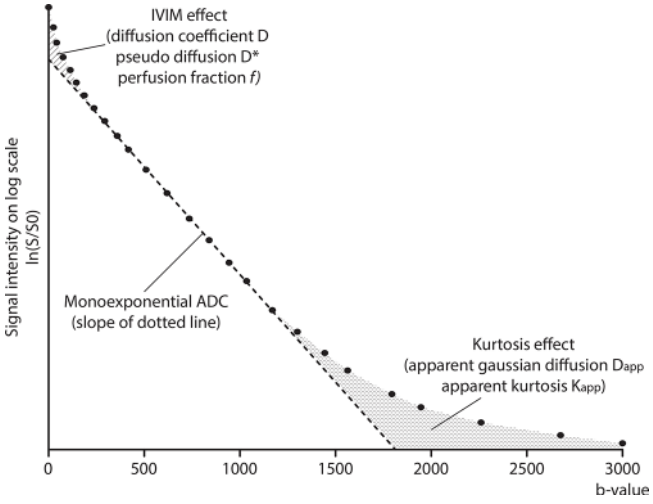
[a]Positive outcome indicates that ≥1 of the DWI parameters under investigation (*e.g.* mean ADC, ADC histogram parameters or parameters derived from, IVIM, DKI, or DWI texture) had a significant correlation with the studied outcome.

[b]All authors used pathological T- and N-stage as the outcome except for ref,[110] that used mrT- and mrN-stage.

Recent advances

Methods of DWI analysis have rapidly evolved over the years. Whereas traditionally DWI analysis was limited to visual image interpretation or "simple" ADC measurements, more complex methods of DWI acquisition, multiexponential diffusion quantification models and novel DWI post-processing tools have recently been introduced. To provide a comprehensive overview of these new methods is beyond the scope of the current paper, but a brief overview is provided below and illustrated in Figure 5:

Figure 5. Traditional DWI models use a monoexponential fit of two or more *b*-value images between *b* = 0 and 1000 to calculate the ADC value as the slope of a straight line between these points. At low *b*-values (*b* < 200) the signal decay will, however, deviate from this line as it is not only affected by tissue diffusion, but also by microperfusion effects (the IVIM effect). Another phenomena is the deviation of the signal curve when applying very high *b*-values (*b* > 1000–1500). This effect is caused by non-Gaussian diffusion as a result of complex structures (such as cell membranes, organells etc) that hinder diffusion. The degree of non-Gaussian behaviour is referred to as the kurtosis effect. Formula's to calculate the various parameters described in the Figure are as follows: Monoexponential ADC: S/S0 = exp(-b·ADC); IVIM: S/S0 = f·exp(-b(*D* + D*))+(1 f)exp(-b·D); Kurtosis: S/S0 = exp(-b·D_{app} + $b^2 \cdot D_{app}^2 \cdot K_{app}^2/6$); where *S* = signal intensity with (S) and without (S0) diffusion-weighting; *b* = b-value (s mm^{-2}) used; ADC = apparent diffusion coefficient (mm^2 s^{-1}; observed diffusion); *D* = diffusion coefficient ($mm^2 s^{-1}$; true diffusion in the tissue; depends on cell density); D*=pseudo diffusion coefficient (mm^2 s^{-1}; depends on mean capillary segment length and average blood velocity in a voxel); *f* = the perfusion fraction (indicates the fractional volume (%) of capilary blood flowing within a voxel); Dapp = apparent Gaussian diffusion coefficient (mm^2 s^{-1}; diffusion coefficient under a Gaussian assumption); Kapp = apparent kurtosis (describes how much the measured diffusion departs from the assumed Gaussian distribution; a measure for heterogeneity). ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; IVIM, intravoxel incoherent motion.



Intravoxel incoherent motion

Traditionally, ADC is calculated using a monoexponential fit of ≥2 *b*-value DWI images (typical in the range of *b* = 0 to *b* = 1000). Instead of using a monoexponential fit, the IVIM model uses a biexponential fit that separates effects of (micro-)perfusion (measurable in the low *b*-value range) and true diffusion effects (measurable at higher *b*-values). This effect is schematically illustrated in Figure 5.[117] The IVIM model separates the true diffusion coefficient *D* from two perfusion related parameters called the pseudodiffusion D^* and perfusion fraction *f*.[118] The potential benefit of IVIM is that it can provide parameters related to tissue microcirculation and perfusion in addition to cellularity, without the need for exogenous contrast agents (such as required for dynamic contrast-enhanced perfusion imaging).

Some encouraging first results have been shown for IVIM in rectal cancer to predict response,[60,61,71] for differentiating between metastatic (N+) and non-metastatic (N-) lymph nodes,[119] and to predict prognostic markers such as TNM-stage,[102,113] tumour differentiation grade,[102] lymphovascular invasion,[108] microvessel density[113] and KRAS status.[114] Potential drawbacks of the IVIM method are its test-retest reproducibility[120] and that measurements may be significantly influenced by scan parameters such as the echo time.[121] There is currently no consensus on how IVIM analysis should best be performed, as is also illustrated by the different imaging protocols used in the current literature.[60,61,71,102,108,113,114,119] Moreover, results as to whether IVIM parameters provide added benefit compared to simple mean ADC measurements have so far been conflicting.

Diffusion kurtosis imaging

In addition to the perfusion effects that can be captured by the IVIM model, DKI takes into account effects of non-Gaussian diffusion (Figure 5). In a free medium, diffusion is assumed to follow a Gaussian distribution. Since tissue contains barriers like cell membranes and vessels that influence the diffusivity, this assumption does not hold true for tissues. Especially for high *b*-values (>b1000) non-Gaussian diffusion effects can be observed. This non-Gaussian behaviour can be expressed in terms of kurtosis, which can be seen as a measure of a tissue's degree of heterogeneity.[122] The DKI model separates the signal into the apparent diffusion coefficient D_{app} (assuming a Gaussian distribution) and an apparent diffusional kurtosis K_{app} which expresses how much the measured signal departs from the assumed Gaussian distribution. A potential downside is that, similar to IVIM, DKI uses multiple model-based parameters and is therefore relatively susceptible to measurement inaccuracies.[123,124]

Evidence for DKI so far is limited. Two studies investigated a diffusion kurtosis diffusion for response prediction in rectal cancer. Although these reports were in agreement in the sense that both found significant differences in ΔD_{app}% after CRT between good and poor responders, results with respect to other studied parameters (*e.g.* pre-CRT DKI measures) were contradictory and the authors could not produce a statistically significant benefit for DKI parameters compared to routine DWI parameters (*i.e.* ADC) to predict response.[57,125] In other (preliminary) reports, the diffusion kurtosis coefficient has shown promise as a prognostic marker to predict metastases,[105] tumour differentiation grade,[103,107] T-stage,[103] N-stage,[103,107] lymphovascular invasion and involvement of the mesorectal facia.[103]

Automated DWI post-processing methods

Tumour segmentation is an important aspect of the workflow to be able to extract quantitative tumour parameters. Unfortunately, manual segmentation of rectal tumours is labour intensive, time consuming and often requires a relatively high level of experience. Given the high lesion-to-background ratio of tumours on DWI, it is a potentially suitable technique for automated (or semi-automated) segmentation methods. One study investigated

the accuracy and time needed for tumour segmentation on DWI, using a semi-automated region growing algorithm with and without manual adjustments. The semi-automated method (with some manual adjustments) had excellent agreement with full manual segmentation and resulted in a significant reduction in delineation time for the radiologist.[126] Another group investigated a deep learning segmentation approach, incorporating information from both T_2 weighted MRI and DWI to train a convolutional neural network to perform fully automated segmentation. The algorithm resulted in segmentations that were very comparable to those performed manually by expert readers with a good dice similarity index (DSI: a measure indicating the spatial overlap of voxels within the segmentations on a scale from 0 to 1) of 0.70.[127] Although these automated segmentation methods will need to be further optimized and validated, they appear promising and will likely be helpful to reduce the workload of radiologists in future research and clinics.

Conclusions and clinical recommendations

DWI in rectal cancer is an emerging topic of research and is now also increasingly finding its way to clinical practice. Over the last decade, use of DWI has evolved from qualitative visual image interpretation to increasingly advanced methods of quantitative analysis. So far the largest body of evidence exists for assessment of tumour response to neoadjuvant treatment. In this setting, particularly the benefit of DWI for visual assessment of residual tumour in post-radiation fibrosis has been established and is now increasingly adopted and highly recommended for clinical use. Promising results have also been reported for quantitative DWI analysis (mainly ADC), both for response prediction as well as for overall tumour prognostication, but protocols require standardization and results will need to be prospectively confirmed on larger scale. Until then, clinical evaluation of DWI should be limited to visual (qualitative) assessment with no role for quantification in current daily practice. The role of DWI for further clinical tumour and nodal staging is less well-defined but appears to be limited, although there could be a benefit for DWI to help detect lymph nodes. Novel methods of analysis as well as new post-processing tools are still being developed; the role of these tools remains to be established in the upcoming years.

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