Original Article | Gastrointestinal Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2020.1403
Korean J Radiol 2021;22(9):1451-1461

Korean Journal of Radiology
KJR

How to Combine Diffusion-Weighted and T2-Weighted Imaging for MRI Assessment of Pathologic Complete Response to Neoadjuvant Chemoradiotherapy in Patients with Rectal Cancer?

Jong Keon Jang[1*], Chul-min Lee[1*†], Seong Ho Park[1], Jong Hoon Kim[2], Jihun Kim[3], Seok-Byung Lim[4], Chang Sik Yu[4], Jin Cheon Kim[4]

Departments of [1]Radiology and Research Institute of Radiology, [2]Radiation Oncology, [3]Pathology, and [4]Division of Colon and Rectal Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Objective: Adequate methods of combining T2-weighted imaging (T2WI) and diffusion-weighted imaging (DWI) to assess complete response (CR) to chemoradiotherapy (CRT) for rectal cancer are obscure. We aimed to determine an algorithm for combining T2WI and DWI to optimally suggest CR on MRI using visual assessment.

Materials and Methods: We included 376 patients (male:female, 256:120; mean age ± standard deviation, 59.7 ± 11.1 years) who had undergone long-course CRT for rectal cancer and both pre- and post-CRT high-resolution rectal MRI during 2017–2018. Two experienced radiologists independently evaluated whether a tumor signal was absent, representing CR, on both post-CRT T2WI and DWI, and whether the pre-treatment DWI showed homogeneous hyperintensity throughout the lesion. Algorithms for combining T2WI and DWI were as follows: 'AND,' if both showed CR; 'OR,' if any one showed CR; and 'conditional OR,' if T2WI showed CR or DWI showed CR after the pre-treatment DWI showed homogeneous hyperintensity. Their efficacies for diagnosing pathologic CR (pCR) were determined in comparison with T2WI alone.

Results: Sixty-nine patients (18.4%) had pCR. AND had a lower sensitivity without statistical significance (vs. 62.3% [43/69]; 59.4% [41/69], $p = 0.500$) and a significantly higher specificity (vs. 87.0% [267/307]; 90.2% [277/307], $p = 0.002$) than those of T2WI. Both OR and conditional OR combinations resulted in a large increase in sensitivity (vs. 62.3% [43/69]; 81.2% [56/69], $p < 0.001$; and 73.9% [51/69], $p = 0.008$, respectively) and a large decrease in specificity (vs. 87.0% [267/307]; 57.0% [175/307], $p < 0.001$; and 69.1% [212/307], $p < 0.001$, respectively) as compared with T2WI, ultimately creating additional false interpretations of CR more frequently than additional identification of patients with pCR.

Conclusion: AND combination of T2WI and DWI is an appropriate strategy for suggesting CR using visual assessment of MRI after CRT for rectal cancer.

Keywords: *Rectal cancer; Adenocarcinoma; Chemoradiotherapy; Chemoradiation; Complete response; Complete remission; Magnetic resonance imaging; Diffusion-weighted imaging; DWI; T2*

INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) is the standard treatment for patients with locally advanced rectal cancer owing to its association with tumor downstaging and a lower rate of postoperative local recurrence [1-3]. Neoadjuvant CRT leads to pathologic complete response (pCR) in rectal cancer in 10–25% of patients [3,4].

Received: November 29, 2020 **Revised:** February 12, 2021 **Accepted:** March 17, 2021

*These authors contributed equally to this work.
†Current address: Department of Radiology, Hanyang University Medical Center, Seoul, Korea
Corresponding author: Seong Ho Park, MD, PhD, Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
• E-mail: parksh.radiology@gmail.com

Accurately identifying pCR to CRT is an important challenge as patients may be offered a watch-and-wait strategy instead of radical surgery [5-7], although the oncologic safety of the watch-and-wait approach has not been proven through randomized trials [8,9].

High-resolution MRI is currently the imaging modality of choice for assessing the treatment response to CRT in rectal cancer [7,10-12]. Of the various techniques of MRI, T2-weighted imaging (T2WI) for visual assessment of the treatment response, such as using the magnetic resonance tumor regression grade (TRG), is widely adopted in clinical practice; however, it has limited accuracy for diagnosing pCR [10,11,13]. Diffusion-weighted imaging (DWI) is a specialized MRI technique that maps the diffusion of water molecules in biological tissues and is used for oncologic imaging in various circumstances. The combined use of T2WI and DWI might improve the accuracy of MRI for diagnosing pCR to CRT in rectal cancer [14-17]. Nevertheless, despite the proof of theoretical feasibility, specific algorithms for combining T2WI and DWI have been obscure in published studies [10]. Furthermore, DWI studies have focused on technical parameters, such as diffusion coefficients, rather than practical visual assessments. Despite the merits of scientific investigation, quantitative analyses using diffusion coefficients are impractical and hampered by the limited reliability in obtaining the coefficients and identifying the lesion boundaries. Consequently, the optimal combination of the two imaging techniques to achieve maximal effectiveness and ready application in daily routine practice has not been established [10]. Therefore, we aimed to determine an algorithm for combining T2WI and DWI to optimally suggest complete response (CR) to CRT for rectal cancer on MRI using visual assessment.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2020-0962), which waived the need for informed patient consent.

Patients

We reviewed 391 consecutive patients who had undergone long-course CRT for rectal cancer between 2017 and 2018 at our institution (Fig. 1). According to our institutional standard of care, all patients underwent high-resolution MRI of the rectum both before (for initial staging) and after (for assessment of treatment response) CRT. Most patients had locally advanced (cT3–4 or cN+ stages as assessed by the initial rectal MRI) and mid-to-low rectal cancer, while some patients had low rectal cancer of lower stages for whom CRT was performed with the aim of the organ (sphincter and/or rectum) preservation. CRT comprised 25 fractions delivering a total dose of 45–50 Gy to the entire pelvis, followed by a booster dose of 4–6 Gy to the primary tumor. Radiation was supplemented with concurrent chemotherapy using 5-fluorouracil and leucovorin. To be eligible for this study, the ground truth of the treatment response to CRT in the primary tumor, that is, pCR vs. non-pCR had to be available (see Reference Standard section). Of the 391 patients, 10 were excluded owing to the lack of ground truth information, as they were lost to follow-up after CRT without surgery. Five additional patients were excluded as their post-CRT MRI scan was uninterpretable owing to metal artifacts caused by endoscopic clip and hip prosthesis, as independently judged by a study moderator who was not a study reader. Finally, 376 patients (male:female, 256:120; mean age ± standard deviation, 59.7 ± 11.1 years) were included (Table 1).

MRI Examination

Patients were imaged using 1.5- or 3T scanners (Magnetom Avanto and Skyra, Siemens Healthineers; Ingenia, Philips Healthcare). According to our institutional protocol, the typical timing of post-CRT MRI was 6–7 weeks after the completion of CRT, with minimal variability across patients due to differences in scheduling availability (waiting list) and patient status. The imaging techniques were compatible with the recommendations of the European Society of Gastrointestinal and Abdominal Radiology [18]. Rectal filling (using ultrasound gel) was not performed. The imaging sequences comprised high-resolution fast spin-echo T2WI with 0.5- to 0.6-mm pixel size and 3-mm slice thickness with no interslice gap in axial, coronal, sagittal, and oblique planes and axial DWI with b-factors of 0 and 1000 s/mm^2, 1.4- to 1.7-mm pixel size and 4-mm slice thickness with no interslice gap. Detailed scan parameters are listed in Supplementary Table 1.

MRI Analysis

Two board-certified abdominal radiologists experienced in rectal MRI (approximate post-CRT rectal MRI experience of 400 cases and 200 cases) performed the image analysis. The readers were provided with a pair of MRI scans (before and after CRT). They were blinded to all other patient

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Korean Journal of Radiology
KJR

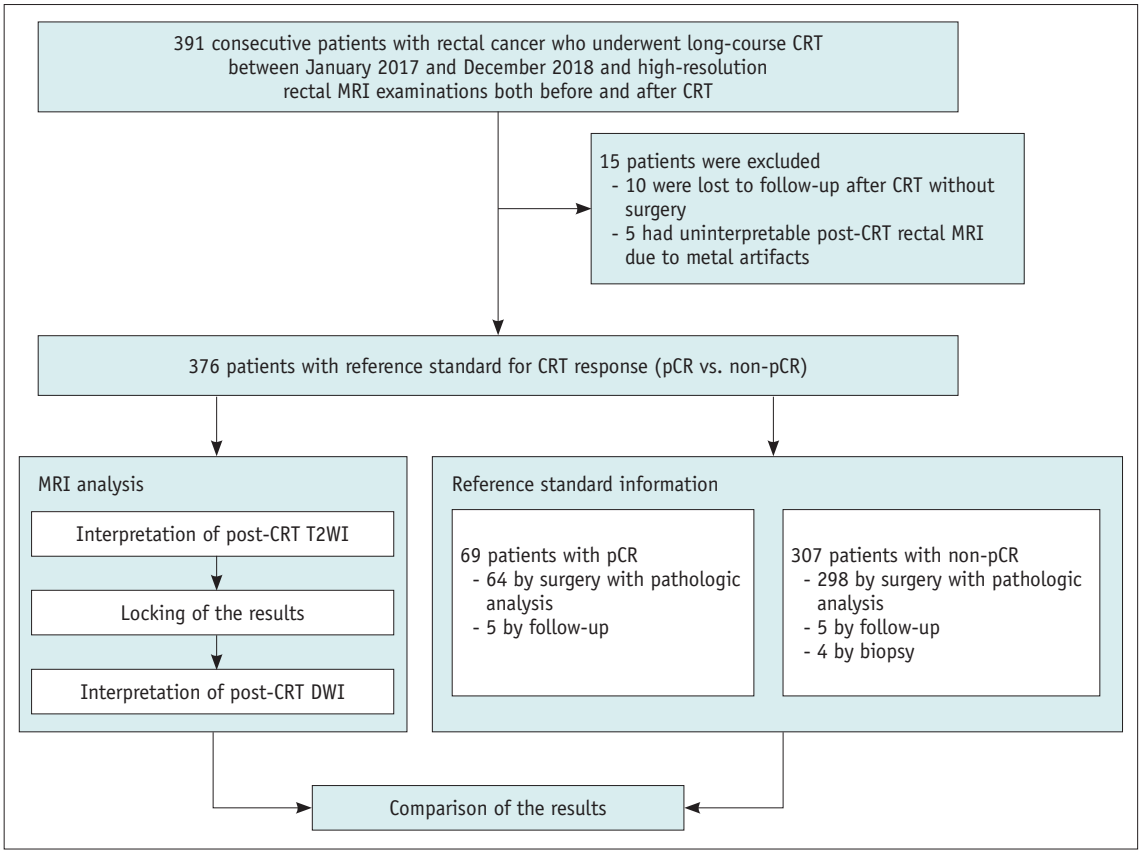

Fig. 1. Study flow diagram. CRT = chemoradiotherapy, DWI = diffusion-weighted imaging, pCR = pathologic complete response, T2WI = T2-weighed imaging

information (including the prevalence of pCR), except for the history of CRT for rectal cancer. They interpreted the findings of the primary tumor. We checked the inter-reader agreement separately before the main analysis using 50 patients randomly chosen from the entire study cohort (25 cases each randomly chosen from pCR and non-pCR patients). The case composition was to avoid overestimating the inter-reader agreement, which might occur predominantly in non-pCR cases. The readers were blinded to the composition of the cases. After confirming a high degree of inter-reader agreement (see Results section), we divided the study patients into two groups using simple randomization (197 and 179 patients), and each reader analyzed one group. T2WI was reviewed first without DWI to avoid any influence of DWI findings on the interpretation of T2WI findings. The readers determined whether a visible tumor signal was absent (CR) or present (non-CR) on post-CRT T2WI. According to recent guidelines [10,18], we considered the following findings without a mass-like or nodular intermediate signal in the tumor bed to imply the absence of a tumor signal: (near) normalization of the wall; regular, thin, hypointense scar on the luminal side with the (near) normal appearance or homogeneous intermediate signal in the underlying wall; or hypointense thickening of the wall at the former tumor location. After locking the results of the T2WI review, the readers interpreted the DWI findings in the same reading session. We did not blind DWI interpretation to T2WI as T2WI is necessary for interpreting DWI to precisely confirm the lesion location, as DWI lacks anatomical details. Likewise, DWI is typically reviewed along with T2WI in real-world clinical practice. The readers interpreted whether a residual tumor signal was absent (CR) or present (non-CR) on post-CRT DWI. DWI interpretation followed recent expert guides [10,12]. A hyperintense signal on high-b-value (1000 s/mm^2) DWI at the former tumor location, similar to the peripheral gland of the prostate in male and endometrium in female [19,20], with a low signal on the apparent diffusion coefficient map, was considered to be tumor signals. The readers carefully examined the images to avoid making false interpretations of a residual tumor based on T2 shine-through effects, a signal from a different location than the tumor site, and

 https://doi.org/10.3348/kjr.2020.1403

Table 1. Characteristics of Study Patients

Characteristic	Value*
Age (years), mean ± SD	59.7 ± 11.1
Sex	
Male	256 (68.1)
Female	120 (31.9)
cT status on pre-CRT MRI	
cT2	49 (13.0)
cT3	263 (69.9)
cT4	64 (17.0)
cN status on pre-CRT MRI	
cN (+)	326 (86.7)
cN (–)	50 (13.3)
Tumour signal on pre-CRT DWI	
Homogeneous high signal throughout the tumour	217 (57.7)
Interval from completion of CRT to post-CRT MRI (days), median (range)	42 (30–52)
Ground truth regarding CRT response	
pCR	69 (18.4)
Confirmed by surgery with pathologic analysis (pTRG1)	64 (17.0)
Confirmed by follow-up	5 (1.3)
Non-pCR	307 (81.6)
Confirmed by surgery with pathologic analysis†	298 (79.3)
pTRG2	80 (21.3)
pTRG3	170 (45.2)
pTRG4	39 (10.4)
pTRG5	1 (0.3)
Unavailable	8 (2.1)
Confirmed by biopsy	4 (1.1)
Confirmed by follow-up	5 (1.3)

*Number of patients with % in 376 patients in parentheses unless indicated otherwise. Age is at the time of the initial diagnosis, †Eight patients had a pathologic residual tumour but did not have pTRG information. CRT = chemoradiotherapy, DWI = diffusion-weighted imaging, pCR = pathologic complete response, pTRG = pathologic tumour regression grade, SD = standard deviation

artefactual signals from susceptibility artifacts [12,21]. Additionally, the readers evaluated whether the untreated tumor before CRT had a homogeneously hyperintense signal throughout the lesion on DWI (Supplementary Fig. 1) or not (Supplementary Fig. 2).

Reference Standard

Electronic medical records of patients were reviewed to obtain ground truth information regarding pCR and non-pCR after CRT. As rectal surgery was the standard of management after CRT for rectal cancer, the reference standard information was obtained through a pathologic analysis of the surgical specimen in almost all patients. The pathologic analysis of CRT response in surgical specimens was evaluated by experienced board-certified gastrointestinal pathologists using the five-point pathologic TRG (pTRG) by Mandard, ranging from pTRG1 (pCR) to pTRG5 (no regression) [22]. In a small number of patients who were followed up without surgery, biopsy results and the clinical course after CRT were reviewed. Patients who had no clinical evidence of residual cancer in the rectum after CRT according to post-CRT MRI and endoscopic examination with biopsy and did not subsequently develop tumor recurrence/regrowth for a minimum of 2 years were regarded as having achieved pCR.

Statistical Analysis

Inter-reader agreement in the MRI interpretation was assessed using kappa statistics with a 95% confidence interval (CI). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MRI for diagnosing pCR were calculated for T2WI, DWI, and three different methods of combining T2WI and DWI, as explained below. As the target state to diagnose was pCR, the sensitivity and specificity were defined as the number of patients interpreted as having CR (absence of visible tumor signal) and non-CR (presence of visible tumor signal) on MRI, respectively, divided by the number of patients with pCR and non-pCR, according to the ground truth.

Regarding the combination of T2WI and DWI results, we analyzed three algorithms: 'AND,' if both results were CR; 'OR,' if anyone result was CR; and 'conditional OR,' if T2WI showed CR or DWI showed CR after pre-treatment DWI showed homogeneous hyperintense signal throughout the lesion. We considered the conditional OR method for the following reasons. The limited accuracy of DWI for revealing residual tumors after CRT is known [10]. Therefore, blindly interpreting the absence of a hyperintense DWI signal after CRT as CR (the OR method) may be inadequate. It may be more appropriate to make CR interpretations using DWI with high confidence. The conditional OR method was based on our hypothesis that one might be more confident about the absence of residual tumor when the homogeneous hyperintense DWI signal throughout the tumor before CRT completely disappears after CRT. In contrast, if the untreated lesion shows a heterogeneous or weak DWI signal, one may not confidently refute that the absence of a hyperintense DWI signal after CRT is merely due to the intrinsic DWI signal characteristics of the tumor.

https://doi.org/10.3348/kjr.2020.1403

Korean Journal of Radiology
KJR

The sensitivity and specificity of the three combination algorithms were compared with those of T2WI using the McNemar test. A p value < 0.017 was considered statistically significant after Bonferroni adjustment for multiple comparisons. The number of true- (CR on MRI in patients with pCR) and false-positive (CR on MRI in patients with non-pCR) MRI interpretations of CR were calculated. Additionally, using the sensitivity and specificity of MRI for diagnosing pCR obtained in our study, we calculated the predicted numbers of true- and false-positive MRI interpretations of CR in 1000 imaginary patients with 10% and 25% prevalence of pCR, respectively. We chose pCR rates of 10% and 25% for this prediction according to the lower and upper limits of the reported pCR rates [4]. MedCalc version 18.11 (MedCalc software) was used for statistical analyses.

RESULTS

Patient Characteristics

The characteristics of the 376 patients are shown in Table 1. The patients underwent post-CRT MRI 30–52 days (median, 42 days) after completion of CRT. The reference standard information regarding pCR and non-pCR was obtained based on surgery with a pathologic analysis in 362 patients (96.3%), follow-up in 10 patients (2.7%), and biopsy in four patients (1.1%). In the 362 patients who underwent surgery, the interval from post-CRT MRI to surgery was 1 day–12 months (median 11 days), with 93.6% (339 of 362) of patients within 1 month, and the remaining patients in variably longer time. Sixty-nine patients (18.4%) had pCR, with 64 patients confirmed through surgery performed at 1 day–3 months (median 10 days) from post-CRT MRI and five patients confirmed through follow-ups, that is, under the watch-and-wait management without tumor recurrence/regrowth for 24–38 months after the clinical judgment of no evidence of residual cancer.

Regarding the DWI findings of initial untreated rectal cancer on pre-CRT MRI, 217 patients (57.7%) showed homogeneously hyperintense signals throughout the tumor.

Interobserver Agreement

The 50 patients consisted of 25 patients with pCR and 25 patients without pCR (six patients with pTRG2, 15 patients with pTRG3, and four patients with pTRG4). The kappa value for inter-reader agreements in interpreting CR (absence of visible residual tumor) and non-CR (presence of visible residual tumor) on MRI was 0.83 (95% CI, 0.67–0.99) for T2WI and 0.80 (95% CI, 0.64–0.96) for DWI. Further details are provided in Supplementary Table 2.

Accuracy of MRI for Diagnosing pCR

The sensitivity, specificity, PPV, and NPV of T2WI, DWI, and the three different algorithms combining T2WI and DWI for diagnosing pCR are shown in Table 2. Additionally, the sensitivity and specificity of DWI in the 217 patients whose untreated tumors showed homogeneously hyperintense signals throughout the lesion on pre-CRT DWI were 78.0% (32/41) and 59.7% (105/176), respectively, which were similar to the results for all 376 patients. The cross-tabulation of T2WI and DWI interpretations in the 69 patients with pCR is shown in Table 3.

With the AND combination, the sensitivity decreased without statistical significance (62.3% [43/69] vs. 59.4%

Table 3. T2WI and DWI Interpretations in the 69 pCR Patients

	T2WI		
	CR	Non-CR	Total
DWI			
CR	41	13	54
Non-CR	2	13	15
Total	43	26	69

CR = complete response, DWI = diffusion-weighted imaging, pCR = pathologic CR, T2WI = T2-weighted imaging

Table 2. Accuracy of T2WI, DWI, and Different Algorithms of Combining T2WI and DWI Results for Diagnosing pCR

	T2WI Alone	DWI Alone	Combination of T2WI and DWI					
			AND		OR		Conditional OR	
			Result	*P**	Result	*P**	Result	*P**
Sensitivity, %	62.3 (43/69)	78.3 (54/69)	59.4 (41/69)	0.500	81.2 (56/69)	< 0.001	73.9 (51/69)	0.008
Specificity, %	87.0 (267/307)	60.3 (185/307)	90.2 (277/307)	0.002	57.0 (175/307)	< 0.001	69.1 (212/307)	< 0.001
PPV, %	51.8 (43/83)	30.7 (54/176)	57.8 (41/71)		29.8 (56/188)		34.9 (51/146)	
NPV, %	91.1 (267/293)	92.5 (185/200)	90.8 (277/305)		93.1 (175/188)		92.2 (212/230)	

Values in parentheses are the number of patients. *Comparison with T2WI alone A p value < 0.017 was considered statistically significant, i.e., Bonferroni adjustment for multiple comparisons. DWI = diffusion-weighted imaging, NPV = negative predictive value, pCR = pathologic complete response, PPV = positive predictive value, T2WI = T2-weighted imaging

https://doi.org/10.3348/kjr.2020.1403

[41/69], p = 0.500), while the specificity increased significantly (87.0% [267/307] vs. 90.2% [277/307], p = 0.002). Both OR and conditional OR combinations resulted in large increases in sensitivity and large decreases in specificity, both of which were statistically significant. When analyzed for each reader separately, the two readers' results showed a similar pattern (Supplementary Tables 3, 4).

The number of true- and false-positive MRI interpretations of CR according to different methods of combining T2WI and DWI is summarized in Table 4 and Figure 2. Compared to T2WI alone, the AND combination reduced a lot more false-positive MRI interpretations of CR (Fig. 3), a reduction by 10 patients from 40 to 30 patients, than it lost true-positive interpretations of CR (Fig. 4), a loss of two patients from 43 to 41 patients (Fig. 2A). In the two pCR patients whose DWI findings were non-CR despite CR results on T2WI, pathologic examination of surgical specimens obtained at 7 and 13 days after post-CRT MRI did not reveal unique findings to explain a small nodular hyperintense signal on DWI that mimicked a residual tumor (Fig. 4). In contrast, both OR and conditional OR methods increased false-positive MRI interpretations of CR by far greater numbers than they increased true-positive MRI interpretations of CR (Fig. 2A). Similar predicted results were obtained when calculated for a total of 1000 imaginary patients with 10% and 25% prevalence of pCR (Fig. 2B, C).

DISCUSSION

Previous studies suggested that the combined use of T2WI and DWI could be beneficial for diagnosing pCR after CRT for rectal cancer compared to using T2WI alone, although the specific algorithm for combining the results from the two MRI techniques has not been established [14-17]. The current study adds to the previous studies and shows that adding DWI to T2WI in the AND combination (CR if both T2WI and DWI results are CR) is an appropriate strategy, when using visual assessment, to capitalize

Table 4. Number of True- and False-Positive Diagnosis of CR on MRI with Different Algorithms of Combining T2WI and DWI Results

	T2WI Alone	Combination of T2WI and DWI		
		AND	OR	Conditional OR
Observed results in the 376 study patients				
Prevalence = 18.4%				
TP CR	43	41	56	51
FP CR	40	30	132	95
Predicted results for a total of 1000 imaginary patients				
Prevalence = 10%				
TP CR	62	59	81	74
FP CR	117	88	387	278
Prevalence = 25%				
TP CR	156	149	203	185
FP CR	98	74	323	232

CR = complete response, DWI = diffusion-weighted imaging, FP = false-positive, TP = true-positive, T2WI = T2-weighted imaging

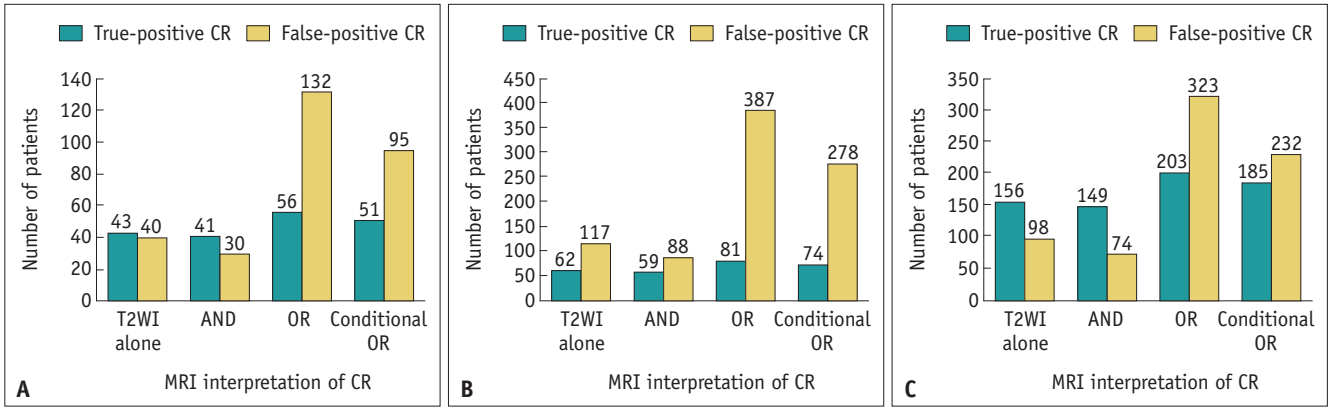

Fig. 2. Histograms of true- and false-positive MRI interpretations of CR in 376 study patients (A) and 1000 imaginary patients with 10% (B) and 25% (C) of pathologic CR prevalence. CR = complete response, T2WI = T2-weighed imaging

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Korean Journal of Radiology
KJR

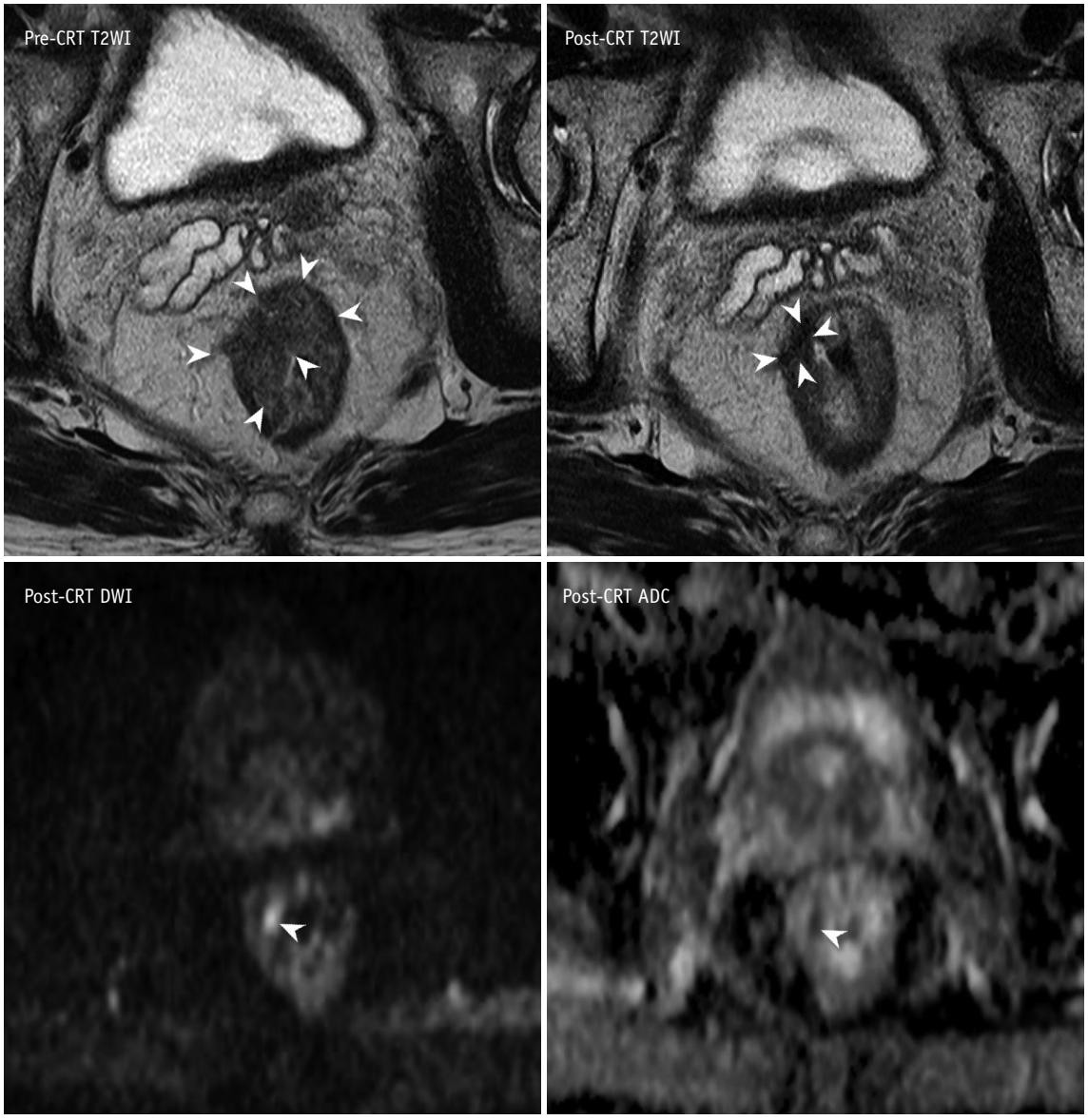

Fig. 3. An example of DWI demonstration of non-pathologic complete response undetected by T2WI in a 67-year-old male. Post-CRT T2WI shows a remarkable decrease in the tumor (arrowheads in the upper left and right) with the remaining hypointense thickening of the wall without visible tumor signal, whereas DWI shows residual tumor signal (arrowheads in the lower left and right). Pathological analysis revealed pTRG3. ADC = apparent diffusion coefficient map, CRT = chemoradiotherapy, DWI = diffusion-weighted imaging, T2WI = T2-weighed imaging

on the characteristics of the two MRI techniques. This approach slightly decreased the sensitivity of MRI for the diagnosis of pCR. However, the resultant loss in true-positive MRI interpretations of CR (CR by MRI in patients with pCR) was minor and was exceeded by the much greater reduction in false-positive MRI interpretations of CR (CR by MRI in patients with non-pCR). In contrast, both OR and conditional OR combinations were unfavorable, as the large decrease in specificity created a large number of false-positive MRI interpretations of CR, which eclipsed the much lesser increase in true-positive MRI interpretations of CR.

The AND combination of multiple tests, that is, the simple intersection of test results, generally has a potential pitfall in making the diagnostic criteria too stringent. Therefore, before the study, we were concerned that introducing DWI with the AND combination might make the MRI diagnosis so strict that it might deprive an opportunity for less invasive management in many patients who achieved pCR. Therefore, one finding that is noteworthy and enabled the AND combination to work well is that of the 43 patients who

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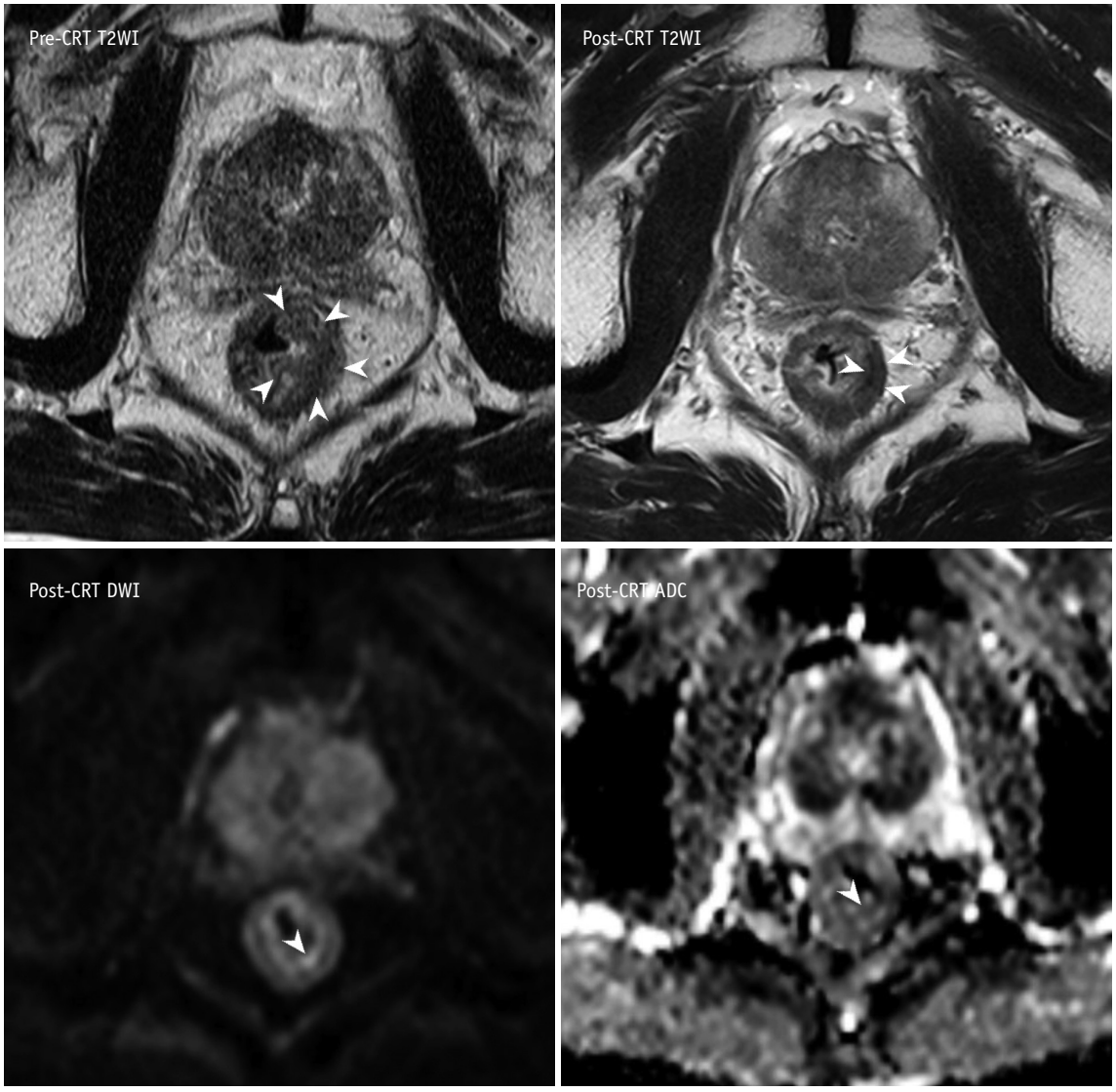

Fig. 4. An example of false DWI signal in a 72-year-old male with pCR. Post-CRT T2WI shows a resolution of the tumor (arrowheads in the upper left and right) with the remaining thin, hypointense scar on the luminal side and homogeneous intermediate signal in the underlying wall without visible tumor signal. DWI shows a nodular diffusion restriction (arrowheads in the lower left and right). However, surgery and pathologic analysis performed 13 days after post-CRT MRI revealed pCR. ADC = apparent diffusion coefficient map, CRT = chemoradiotherapy, DWI = diffusion-weighted imaging, pCR = pathologic complete response, T2WI = T2-weighed imaging

had pCR and whose T2WI rendered correct interpretations of CR, DWI also yielded correct interpretations of CR in 41 patients (95.3%); alternatively, there was a 95.3% sensitivity of DWI for diagnosing pCR in this particular subgroup of patients without visible residual tumors on T2WI. This value is much higher than the overall sensitivity of DWI for diagnosing pCR in all relevant patients post-CRT, that is, 78.3% in our study and 86% in a meta-analysis [10]. To the best of our knowledge, the sensitivity of DWI for diagnosing pCR according to T2WI findings has not been investigated separately. Our study showed that the probability of a spurious DWI signal to mimic a residual tumor is likely quite low once the patient has been cleared of residual tumors through T2WI. We conjecture that the low rate of the spurious DWI signal in this subgroup is likely due to a more homogenous and rather normalized architecture of the tumor site after CRT as manifested on T2WI. It should also be noted that incorrect interpretations of DWI are at times due to mistaking artefactual signals, such as T2 shine-through effects, a signal from a different location than the former tumor site, and artefactual signals from susceptibility artifacts, for residual tumors [12,21], which we specifically tried to avoid in this study. Therefore, the reader's experience is also important [21]. Further

https://doi.org/10.3348/kjr.2020.1403

Korean Journal of Radiology
KJR

investigation on the reason behind the spurious DWI signals mimicking a residual tumor would be worthwhile. According to a few related studies published to date, severe fibrosis and inflammation induced by CRT are also associated with a high signal on post-CRT DWI [23,24].

Considering all study findings, DWI may play a role as a supplementary tool to T2WI rather than an alternate imaging method for evaluating pCR after CRT. Alternatively, DWI may be used to further exclude patients with remaining tumors after they have initially been screened with T2WI, instead of being used alone to suggest the diagnosis of CR. This conservative approach would also be sensible if the watch-and-wait management is considered for patients interpreted as CR on MRI after CRT, considering that the oncologic safety of the watch-and-wait management is still under debate and is currently being investigated [9]. Regression of rectal cancer after CRT occurs through fragmentation and shrinkage of the tumor and typically leaves microscopic tumor fragments below the resolution of MRI examinations [25]. Consequently, the PPV of rectal MRI for pCR is not high, even with the AND combination. Therefore, the absence of a residual tumor signal on post-CRT rectal MRI should be interpreted with caution. It is particularly the case for DWI as DWI has a lower spatial resolution, lower signal-to-noise ratio, and lack of anatomical details than T2WI [26]. Our study additionally revealed that this caution should be applied regardless of the initial untreated tumor showing a homogeneous hyperintense DWI signal throughout the lesion.

This study had some limitations. First, as this study was a retrospective analysis of data accumulated through clinical practice, there was some variability in the timing of MRI after CRT and that of surgery after post-CRT MRI. In addition, the timing of MRI was slightly earlier in some patients than the timing discussed in a recent expert consensus, although the best timing is an issue of ongoing debate [18]. Considering the association of the timing of MRI and that of surgery with the accuracy of MRI and the rate of pCR, respectively, as reported in some published studies [27-30], a more homogeneous timing through prospective research would have been ideal. Second, while we investigated the CRT response of the primary tumor alone, the clinical decision of CR requires holistic evaluation of the primary tumor and other tumor spread, particularly lymph node metastasis. However, unlike the primary tumor, the role of DWI seems less relevant in evaluating lymph nodes. As diagnosing negative lymph node metastasis on post-CRT MRI is even more challenging [11,31], some authorities have proposed a simple size-based categorization of a short-axis diameter < 5 mm and ≥ 5 mm for reporting the absence and presence, respectively, of nodal metastasis on post-CRT MRI [18].

In conclusion, adding DWI to T2WI in the AND combination (CR if both T2WI and DWI results are CR) is an appropriate strategy for MRI interpretation of CR using visual assessment, as the combination mostly corrected false diagnoses of CR on T2WI while nullifying only a few correct diagnoses of CR on T2WI. DWI may play a role as a supplementary tool to T2WI instead of being used alone to further exclude patients with remaining tumors after they have initially been screened using T2WI.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2020.1403.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jong Keon Jang, Chul-min Lee, Seong Ho Park. Formal analysis: Seong Ho Park. Investigation: Jong Keon Jang, Chul-min Lee. Methodology: Jong Keon Jang, Chul-min Lee, Seong Ho Park. Project administration: Seong Ho Park. Resources: Jong Hoon Kim, Jihun Kim, Seok-Byung Lim, Chang Sik Yu, Jin, Cheon Kim. Supervision: Seong Ho Park, Jong Hoon Kim, Jihun Kim, Seok-Byung Lim, Chang Sik Yu, Jin Cheon Kim. Visualization: Jong Keon Jang, Chul-min Lee. Writing—original draft: Jong Keon Jang, Chul-min Lee. Writing—review & editing: Seong Ho Park, Jong Hoon Kim, Jihun Kim, Seok-Byung Lim, Chang Sik Yu, Jin Cheon Kim.

ORCID iDs

Jong Keon Jang
https://orcid.org/0000-0002-2938-6635
Chul-min Lee
https://orcid.org/0000-0001-7621-3377
Seong Ho Park
https://orcid.org/0000-0002-1257-8315
Jong Hoon Kim
https://orcid.org/0000-0001-9002-1195

Jihun Kim
https://orcid.org/0000-0002-8694-4365
Seok-Byung Lim
https://orcid.org/0000-0001-8824-4808
Chang Sik Yu
https://orcid.org/0000-0001-9401-9981
Jin Cheon Kim
https://orcid.org/0000-0003-4823-8619

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