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MRI Assessment of Complete Response to Preoperative Chemoradiation Therapy for Rectal Cancer: 2020 Guide for Practice from the Korean Society of Abdominal Radiology

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Objective: To provide an evidence-based guide for the MRI interpretation of complete tumor response after neoadjuvant chemoradiation therapy (CRT) for rectal cancer using visual assessment on T2-weighted imaging (T2) and diffusion-weighted imaging (DWI).
Materials and Methods: PubMed MEDLINE, EMBASE, and Cochrane Library were searched on November 28, 2019 to identify articles on the following issues: 1) sensitivity and specificity of T2 or DWI for diagnosing pathologic complete response (pCR) and the criteria for MRI diagnosis; 2) MRI alone vs. MRI combined with other test(s) in sensitivity and specificity for pCR; and 3) tests to select patients for the watch-and-wait management. Eligible articles were selected according to meticulous criteria and were synthesized.
Results: Of 1615 article candidates, 55 eligible articles (for all three issues combined) were identified. Combined T2 and DWI performed better than T2 alone, with a meta-analytic summary sensitivity of 0.62 (95% confidence interval [CI], 0.43–0.77; I^2 = 80.60) and summary specificity of 0.89 (95% CI, 0.80–0.94; I^2 = 92.61) for diagnosing pCR. The criteria for the complete response on T2 in most studies had the commonality of remarkable tumor decrease to the absence of mass-like or nodular intermediate signal, although somewhat varied, as follows: (near) normalization of the wall; regular, thin, hypointense scar in the luminal side with (near) normal-appearance or homogeneous intermediate signal in the underlying wall; and hypointense thickening of the wall. The criteria on DWI were the absence of a hyperintense signal at high b-value ($\geq$ 800 sec/mm^2) in most studies. The specific algorithm to combine T2 and DWI was obscure in half of the studies. MRI combined with endoscopy was the most utilized means to select patients for the watch-and-wait management despite a lack of strong evidence to guide and support a multi-test approach.
Conclusion: This systematic review and meta-analysis provide an evidence-based practical guide for MRI assessment of complete tumor response after CRT for rectal cancer.
Keywords: *Rectal cancer; Adenocarcinoma; Chemoradiotherapy; Chemoradiation; Response; Remission; Regression; CR; Magnetic resonance imaging; Watch and wait; Wait and see; Organ preservation; Surveillance; Evidence; Guideline; Recommendation*

INTRODUCTION

Preoperative neoadjuvant chemoradiation therapy (CRT) is now a standard treatment for rectal cancers with a high risk of recurrence after surgery (1). CRT typically takes 5–6 weeks (long-course therapy), and surgery is generally performed a few months later (1). Within the published literature, 10–25% of patients achieve pathologic complete response (pCR) after CRT, i.e., no residual tumor on pathologic examination (1, 2). Evidence from observational studies suggests that patients who are considered to have achieved pCR after CRT could be managed with careful regular surveillance, referred to as the watch-and-wait approach as an alternative to surgery (3-7). This watch-and-wait approach may provide an opportunity to avoid surgical complications, perioperative morbidity and mortality, and the need for a permanent stoma. It is critical to carefully determine patients with no clinically apparent residual tumor with a thorough assessment of the treatment response to CRT, as the safety of the watch-and-wait approach is yet uncertain.

Magnetic resonance imaging (MRI) is the imaging of choice in patients with rectal cancer to evaluate the response to CRT, as well as for the initial pretreatment evaluation (7-9). Unlike well-established guidelines on the pretreatment MRI evaluation of rectal cancers (10-15), there is a relative scarcity of guidance for the MRI evaluation of CRT response. Therefore, this study aimed to provide an evidence-based guide from the Korean Society of Abdominal Radiology (KSAR) for the MRI assessment of complete tumor response after CRT for rectal cancer. There is a variety of MRI techniques used for this purpose. Of those, this study addresses visual assessment using T2-weighted imaging (T2) and diffusion-weighted imaging (DWI) because these are the imaging methods that are widely used in the real-world practice at present. Other techniques—including radiomics, texture analysis, modeling using artificial intelligence (such as machine learning or deep learning), quantitative lesion metrics (such as volumetry or sum of the areas by drawing the lesion boundary), quantitative diffusion analysis (such as apparent diffusion coefficient, kurtosis coefficient, and intravoxel incoherent motion parameters), and perfusion analysis by dynamic-contrast enhanced imaging—were not considered as these are mostly still in research territory due to limitations in generalizability, reproducibility, and practicality (16, 17). Additionally, this study focuses on the evaluation of the primary tumor site and does not cover other types of tumor spread, such as nodal metastasis and tumor deposits.

MATERIALS AND METHODS

Literature Database Search

PubMed MEDLINE, EMBASE, and Cochrane Library were searched to identify articles related to any of the three issues as follows:
- Issue 1: sensitivity and specificity of MRI (T2 or DWI) for diagnosing pCR and the criteria for the MRI diagnosis
- Issue 2: comparison of MRI alone (T2 with or without DWI) and MRI combined with other test(s) regarding sensitivity and specificity for pCR
- Issue 3: tests used to select patients for the watch-and-wait management.

This study developed the search queries according to the PICO method (18) as much as applicable and jointly used hand-searching to enable an exhaustive literature search, as shown in Table 1. Besides the basic search terms, this study also included extra terms that frequently appeared in the relevant articles in the search query in 'OR' combination to expand the search (i.e., additional terms regarding P, I, and C as shown in Table 1). The last update of the literature database search was on November 28, 2019. The literature database search covered both print publications and electronic publications ahead of print.

A total of 1615 articles were screened for eligibility, after deleting overlaps between the three databases (Fig. 1). The general criteria for article exclusion were as follows: 1) duplicated publications; 2) articles not within the topics of interest of this study; 3) not an original research or study protocol (for issue 3), such as case reports, review articles, editorials, letters, or comments; 4) articles without the full text available, such as conference abstract/proceedings; and 5) articles written in other languages than English. Articles that had any of these characteristics were excluded. Then, each issue-specific eligibility criteria were applied to further select relevant articles, as explained later in the corresponding sections. The article screening and selection were performed by one of eight authors. In any case, where there was an ambiguity, another reviewer was invited to jointly review the article and arrive at a consensus. The nine authors also performed data extraction from eligible articles for meta-analysis and systematic review in the same manner, i.e., data extraction by one of the eight authors and double-checked by the remaining author to make a

Table 1. Query for Literature Database Search

PICO	Query for Issues 1 and 2		Query for Issue 3	
	Search Concept	Search Term	Search Concept	Search Term
P: A AND B AND C	A. Patient with rectal cancer: #1 OR #2	#1: "Rectal Neoplasms"[Mesh] #2: (Colorectal[TW] OR Rectal[TW] OR rectum[TW] OR Anus[TW]) AND (Neoplasm*[TW] OR neoplasia[TW] OR cancer*[TW] OR tumor*[TW] OR tumour*[TW] OR Carcinoma*[TW] OR Malignan*[TW])	A. Patient with rectal cancer: #1 OR #2	#1: "Rectal Neoplasms"[Mesh] #2: (Colorectal[TW] OR Rectal[TW] OR rectum[TW] OR Anus[TW]) AND (Neoplasm*[TW] OR neoplasia[TW] OR cancer*[TW] OR tumor*[TW] OR tumour*[TW] OR Carcinoma*[TW] OR Malignan*[TW])
	B. Undergoing chemoradiation therapy: #3 OR #4 OR #5 OR #6	#3: "Chemoradiotherapy"[Mesh] #4: chemoradiotherap*[TW] OR chemoradiation*[TW] OR radiochemotherap*[TW] OR chemo-rad*[TW] OR Radio-Chemo*[TW] OR "CCRT"[TW] OR "CCRTx"[TW] #5: chemotherap*[TW] AND (radiation therap*[TW] OR Radiotherap*[TW]) #6: "Neoadjuvant Therapy"[Mesh] OR neoadjuvant*[TW]	B. Undergoing chemoradiation therapy: #3 OR #4 OR #5 OR #6	#3: "Chemoradiotherapy"[Mesh] #4: chemoradiotherap*[TW] OR chemoradiation*[TW] OR radiochemotherap*[TW] OR chemo-rad*[TW] OR Radio-Chemo*[TW] OR "CCRT"[TW] OR "CCRTx"[TW] #5: chemotherap*[TW] AND (radiation therap*[TW] OR Radiotherap*[TW]) #6: "Neoadjuvant Therapy"[Mesh] OR neoadjuvant*[TW]
	C. Pathologic complete response to therapy: #7 OR #8	#7: Basic terms: complete respon*[TW] OR complete remission*[TW] #8: Additional terms to expand the search: completed respon*[TW] OR pathologic respon*[TW] OR Clinical respon*[TW] OR "tumour regression grade"[TW] OR "tumor regression grade"[TW] OR "tumour regression grades"[TW] OR "tumor regression grades"[TW] OR viable[TW]	C. Managed by watch and wait approach after therapy: #14	#14: "Watchful Waiting"[Mesh] OR "Watch and wait"[TW] OR "Wait-and-see"[TW] OR "Watch & Wait"[TW]
I and C	MRI or other typical tests (endoscopy, endorectal ultrasound, CT, or PET): #9 OR #10 OR #11 OR #12 OR #13	#9: Basic terms: Magnetic Resonance Imaging[Mesh] OR Magnetic Resonanc*[TW] OR MRI[TW] OR MRIs[TW] OR MR[TW] #10: Additional terms to expand the search: "diffusion-weighted"[TW] OR "DWI"[TW] OR "T2-weighted"[TW] #11: "Colonoscopy"[Mesh] OR colonoscop*[TW] OR Endoscop*[TW] OR Ultrasound*[TW] OR ultrasonograp*[TW] OR EUS[TW] OR Endosonography[Mesh] OR Endosonograp*[TW] #12: "Tomography, X-Ray Computed"[Mesh] OR CT[TI] OR Computed tomograp*[TW] OR computer assisted tomograp*[TW] OR computerised tomograp*[TW] #13: "Positron-Emission Tomography"[Mesh] OR "Positron-Emission"[TW] OR PET[TW]	Not applicable	
O	Not applied, i.e., hand search of relevant articles		Not applicable	
Others	Written in English	#15: English[Lang]	Written in English	#15: English[Lang]
Final search query	P AND (I and C) AND Others		P AND Others	

Table shows search query for PubMed MEDLINE. Search in EMBASE and Cochrane Library was performed using same search queries except for minor modifications related to differences in design of three databases. We additionally limited EMBASE search to article, article in press, and review by adding "AND ('article'/it OR 'article in press'/it OR 'review'/it)" to query for more effective search as EMBASE includes a lot more conference abstracts/proceedings than PubMed MEDLINE. We could not use language restriction to English (#15) for Cochrane Library as it did not have this functionality. CT = computed tomography, PET = positron-emission tomography
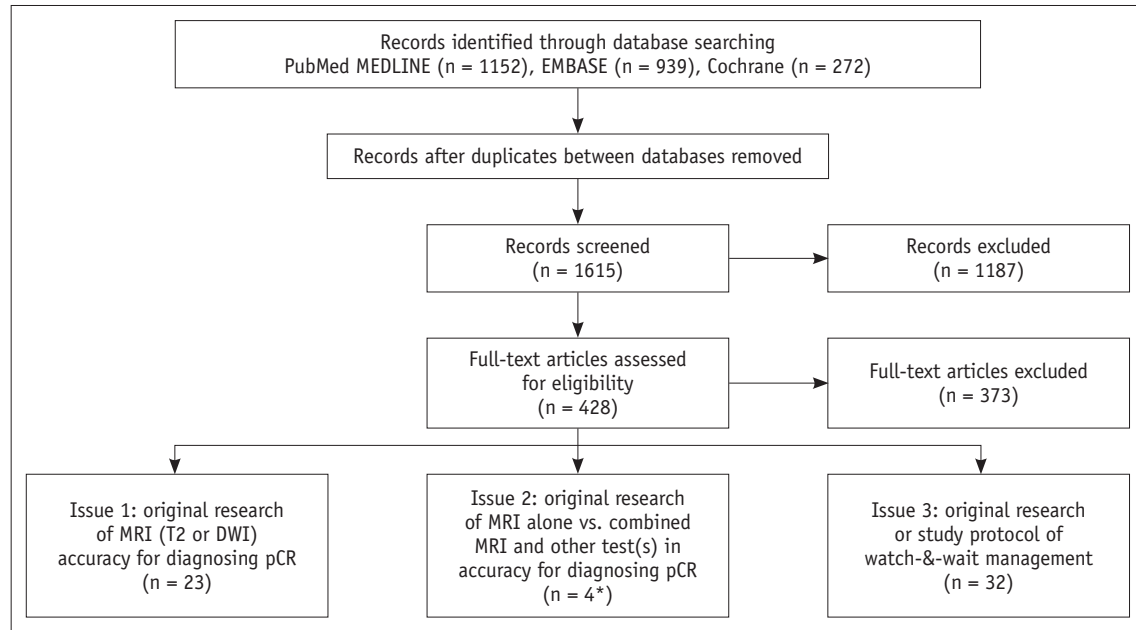
Fig. 1. Flow diagram of literature search. Four articles selected for issue 2 (asterisk) are also included in 23 articles selected for issue 1. DWI = diffusion-weighted imaging, MRI = magnetic resonance imaging, pCR = pathologic complete response, T2 = T2-weighted imaging

consensus for any ambiguities. All the nine people who participated in the literature review were board-certified radiologists with expertise in the subject matters as well as in the systematic review of the literature.

Issue 1: Sensitivity and Specificity of MRI (T2 or DWI) for Diagnosing pCR and the Criteria for the MRI Diagnosis

For this analysis, eligible articles were selected by further applying the following issue-specific criteria: 1) accurate, sufficient details to construct a diagnostic 2-by-2 table of visual interpretation of T2 or DWI and the reference standard findings for pCR (Fig. 2); 2) at least ten patients for both patients with pCR and those without pCR; 3) technical requirement for MRI according to the 2016 recommendation from the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), including use of an external surface coil on a 1.5T or 3T systems and, in case of DWI, use of a high b-value of ≥ 800 sec/mm^2 (16); and 4) MRI obtained after the completion of CRT. Articles not fulfilling any of these criteria were excluded. As shown in Figure 2, pCR instead of residual cancer was considered as the target condition to diagnose, and the sensitivity and specificity were defined accordingly. Studies that reported receiver operating characteristic (ROC) analysis alone without presenting any specific cutoff to use for the binary diagnosis were excluded. The exclusion was

Fig. 2. Diagnostic 2-by-2 table for pCR.

because ROC analysis alone, unaccompanied by a suggestion of a specific cutoff, can only show a theoretical diagnostic performance over the entire range of possible cutoff values. Therefore, it cannot be directly translated into daily practice.

Meta-Analysis of the Sensitivity and Specificity of T2, DWI, and Combined T2 and DWI for Diagnosing pCR

One article may contain more than one set of the 2-by-2 results (Fig. 2). Then, the data for meta-analysis were chosen as follows: the main result was considered when both the main result for the entire subjects and result(s) for the subgroup(s) were present; if one article presents parallel results for > 1 independent patient groups, each was considered as a separate study; and in case of a multi-reader study or a study suggesting > 1 discrete diagnostic

criterion, the result of the reader or the diagnostic criterion that yielded the highest Youden index value was considered.

The presence of heterogeneity between studies concerning sensitivity and specificity was assessed using Higgins I^2 statistics (19, 20). Heterogeneity by threshold effect was analyzed primarily by visual assessment of the coupled forest plots of sensitivity and specificity. It was further tested using the Spearman correlation coefficient between sensitivity and 1-specificity (20, 21). The summary sensitivity and specificity and their 95% confidence intervals (CIs) were obtained using a bivariate random-effects model (20, 22). These analyses were performed separately for T2, DWI, and combined T2 and DWI.

Of the eligible studies, a subgroup of studies that reported sensitivity and specificity for pCR both for T2 and for combined T2 and DWI in the same group of patients were identified. T2 and combined T2 and DWI were compared regarding the sensitivity and specificity for pCR in this subgroup of studies using a joint-model bivariate meta-regression.

The statistical analyses were conducted using Stata version 15.1 (StataCorp LLC, College Station, TX, USA), with $p < 0.05$ considered statistically significant.

Systematic Review of the Criteria for the MRI Diagnosis of Complete Tumor Response

The criteria for diagnosing complete tumor response on either T2 or DWI described in the studies identified were categorized, and the number of articles for each category was counted. The methods of combining the results of the two imaging methods were recorded for studies reporting the sensitivity and specificity of combined T2 and DWI.

Issue 2: Comparison of MRI alone (T2 with or without DWI) and MRI Combined with Other Test(s) Regarding Sensitivity and Specificity for pCR

We considered endoscopy, endorectal ultrasound, and positron-emission tomography (PET, including PET, PET-CT, and PET-MR) as other tests used in combination with MRI. Reports of studies that evaluated the sensitivity and specificity for diagnosing pCR both for MRI alone and for MRI combined with any of these other tests in the same group of patients were identified. Otherwise, the article selection criteria were the same as those explained earlier in issue 1. MRI alone and MRI combined with other test(s) were compared regarding sensitivity and specificity for pCR using a joint-model bivariate meta-regression. Stata version

15.1 was used, with $p < 0.05$ considered statistically significant.

Issue 3: Tests Used to Select Patients for the Watch-and-Wait Management

Articles that collected patients to offer the watch-and-wait management after CRT for rectal cancer and mentioned the use of specific test(s) for the patient selection, for example, a clear mention of MRI, endoscopy, etc., instead of a vague description of "various imaging modalities," besides basic physician assessment and physical examination (such as digital rectal examination), were collected. Both original research studies and research protocols describing a plan for such a study were identified. The two types of articles were checked regarding any overlap, i.e., a publication of research that corresponds to a previously published protocol. Specific tests that were used to select patients for the watch-and-wait management, as described in the published articles, were summarized.
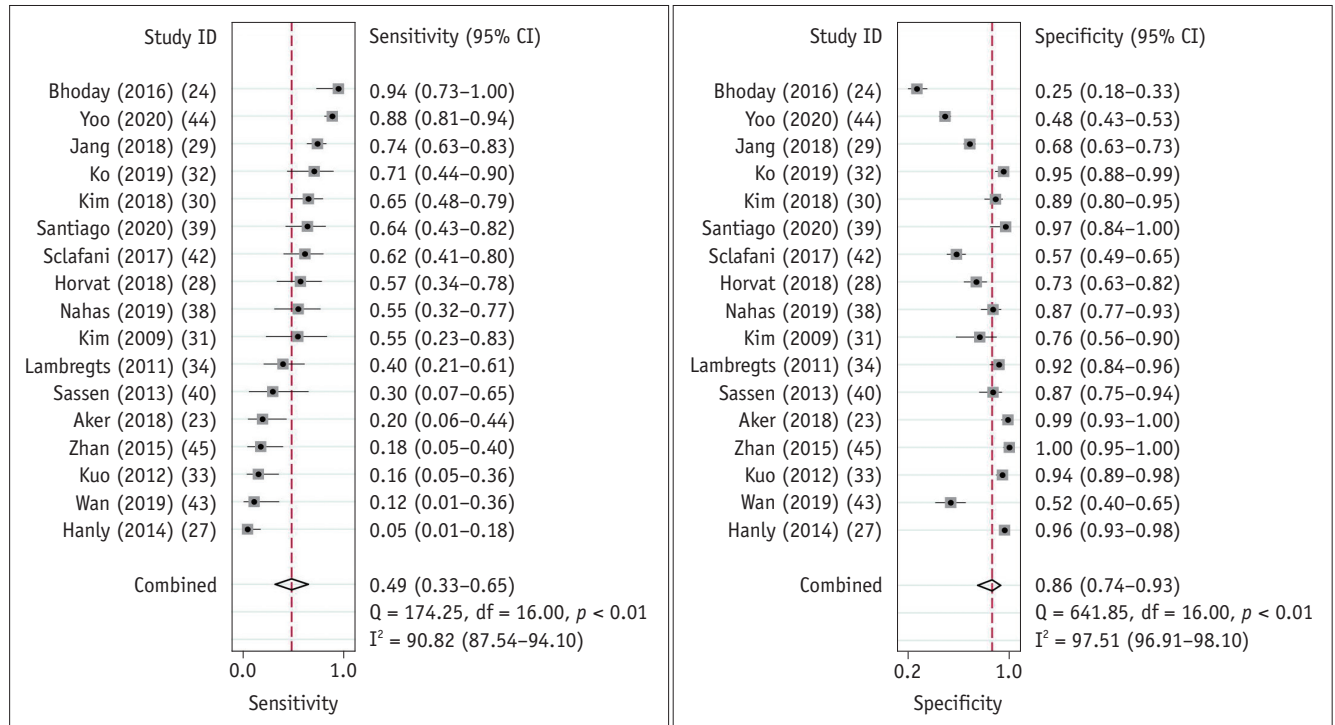
RESULTS

Article Selection

The article screening and selection processes are summarized in Figure 1. A total of 23 articles (23-45) were identified regarding issues 1 and 2, and a total of 32 articles were identified for issue 3 (6, 46-76).

Issue 1: Sensitivity and Specificity of MRI (T2 or DWI) for Diagnosing pCR and the Criteria for the MRI Diagnosis

Of the 23 eligible articles (23-45), 20 were reports of retrospective research studies, and three were prospective studies. They included a total of 40–514 patients (median, 103 patients); with 10–103 patients with pCR (median, 21 patients) and 29–411 patients (median, 83 patients) without pCR (i.e., residual tumor). There were 17 studies, five studies (a study by Cai et al. (25) was counted twice as it had separate results for two independent patient groups, each of which was considered separately for the meta-analysis), and eight studies that reported the sensitivity and specificity for diagnosing pCR for T2, DWI, and combined T2 and DWI, respectively.

Meta-Analysis of the Sensitivity and Specificity of T2, DWI, and Combined T2 and DWI for Diagnosing pCR

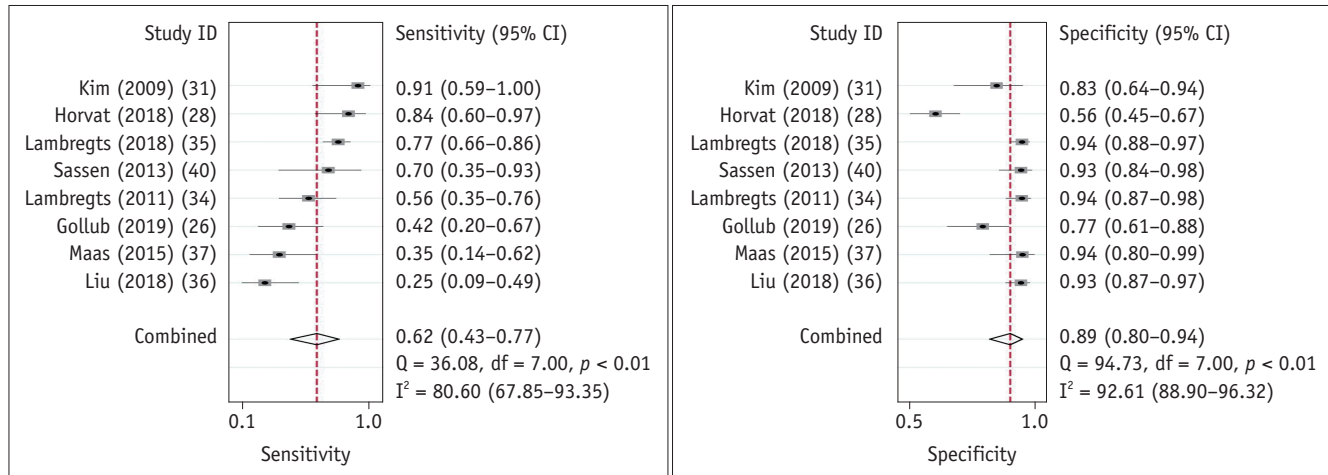The meta-analytic results of the 17 studies reporting the
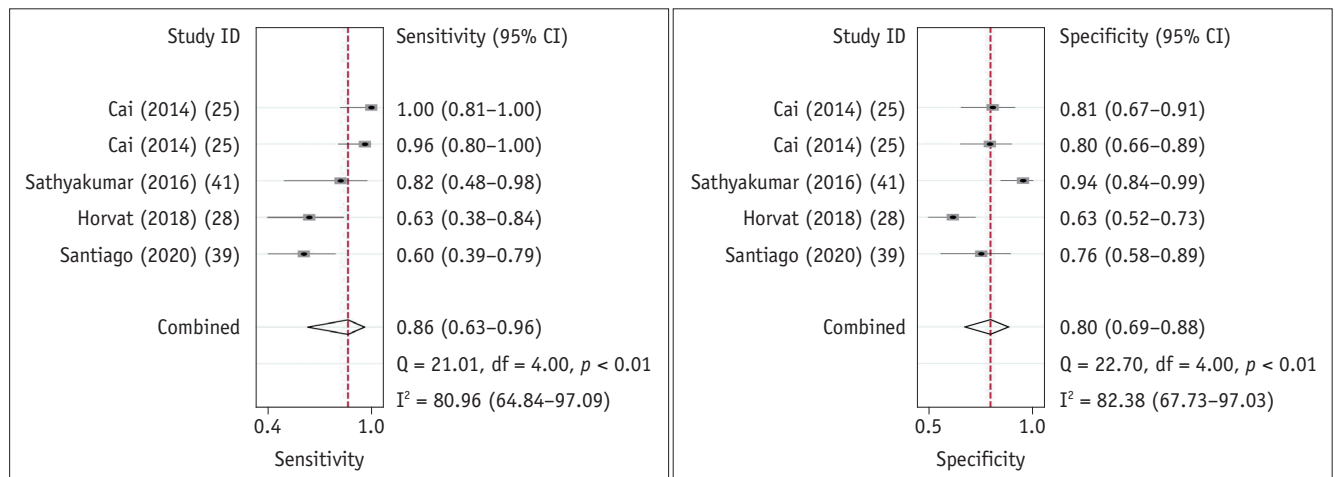
Fig. 3. Coupled forest plots of sensitivity and specificity of MRI for diagnosing pCR.
A. T2. **B.** DWI. Cai (2014) (25) is included twice as it contains separate results for two independent patient groups, each of which was considered separately for meta-analysis. CI = confidence interval

sensitivity and specificity of T2 for diagnosing pCR (23, 24, 27-34, 38-40, 42-45) are summarized in Figure 3A as coupled forest plots. There was a large study heterogeneity both for the sensitivity and the specificity ($I^2 = 90.82$ [95% CI, 87.54–94.10] for sensitivity and $I^2 = 97.51$ [95% CI, 96.91–98.10] for specificity). The coupled forest plots revealed a mild inverse relationship between sensitivity and specificity, although the Spearman's rho between sensitivity and 1-specificity was not statistically significant (0.472,

$p = 0.056$). The summary sensitivity and specificity were 0.49 (95% CI, 0.33–0.65) and 0.86 (95% CI, 0.74–0.93), respectively.

The meta-analytic results of the five studies reporting the sensitivity and specificity of DWI for diagnosing pCR (25, 28, 39, 41) are summarized in Figure 3B as coupled forest plots. There was a large study heterogeneity both for the sensitivity and the specificity ($I^2 = 80.96$ [95% CI, 64.84–97.09] for sensitivity and $I^2 = 82.38$ [95% CI, 67.73–97.03]

C

Fig. 3. Coupled forest plots of sensitivity and specificity of MRI for diagnosing pCR.
C. Combined T2 and DWI. CI = confidence interval

for specificity). The threshold effect was not apparent (Spearman's rho between sensitivity and 1-specificity = -0.600, p = 0.285). The summary sensitivity and specificity were 0.86 (95% CI, 0.63–0.96) and 0.80 (95% CI, 0.69–0.88), respectively.

The meta-analytic results of the eight studies reporting the sensitivity and specificity of combined T2 and DWI for diagnosing pCR (26, 28, 31, 34-37, 40) are summarized in Figure 3C as coupled forest plots. There was a large study heterogeneity both for the sensitivity and the specificity (I^2 = 80.60 [95% CI, 67.85–93.35] for sensitivity and I^2 = 92.61 [95% CI, 88.90–96.32] for specificity). The threshold effect was not apparent (Spearman's rho between sensitivity and 1-specificity = 0.333, p = 0.420). The summary sensitivity and specificity were 0.62 (95% CI, 0.43–0.77) and 0.89 (95% CI, 0.80–0.94), respectively.

Four studies reported the sensitivity and specificity for pCR both for T2 and for combined T2 and DWI in the same group of patients (28, 31, 34, 40). The details are provided in Table 2. None of the individual studies explicitly reported statistical comparisons regarding sensitivity and specificity between T2 and combined T2 and DWI. The meta-analytic comparison revealed a significant difference between the two imaging techniques (p = 0.01). According to the sample values alone reported in the individual studies (i.e., without regard to statistical comparison), three studies reported an increase in both sensitivity and specificity with combined T2 and DWI compared with T2 alone (31, 34, 40).

Systematic Review of the Criteria for the MRI Diagnosis of Complete Tumor Response

The criteria for diagnosing complete tumor response on either T2 or DWI and the methods of combining the results of T2 and DWI, as reported in the 23 eligible articles (23-45), are summarized in Table 3. For the T2, most studies used the absence of visible tumor signal as the criteria. Meanwhile, the exact definitions and strictness for the absence of visible tumor varied among studies, ranging from complete normalization to hypointense thickening (i.e., dense fibrosis) of the wall in the tumor bed. For DWI, most articles adopted the absence of a hyperintense signal on high b-value ($\geq$ 800 sec/mm^2) DWI in the former tumor location. The methods of combining the results of T2 and DWI were obscure in half of the studies. Those studies that specifically reported the rules to combine T2 and DWI considered the absence of residual tumor on both T2 and DWI as complete tumor response or primarily followed T2 findings and referred to DWI when T2 findings were equivocal.

Issue 2: Comparison of MRI Alone (T2 with or without DWI) and MRI Combined with Other Test(s) Regarding Sensitivity and Specificity for pCR

Four studies reported the sensitivity and specificity for pCR both for MRI alone and for MRI combined with other test(s) in the same group of patients (32, 33, 36, 37). The details are provided in Table 4. The meta-analytic comparison revealed a significant difference between MRI alone and MRI combined with other test(s) (p = 0.02). According to the sample values alone reported in the individual studies,

Table 2. Studies Reporting Sensitivity and Specificity for Diagnosing pCR both for T2 and for Combined T2 and DWI in Same Group of Patients

First Author (Year)	Study Type	MR Method	Sensitivity, %*	Specificity, %*	Comparative Result	Method to Combine T2 and DWI Results
Kim (2009) (31)	Retrospective	T2	54.5 (6/11)	75.9 (22/29)	Significantly higher overall accuracy for combined T2 and DWI compared with T2 (p = 0.0313 by McNemar test)	T2 findings as primary results, with DWI to override T2 when T2 findings are equivocal or to increase reader confidence if T2 and DWI findings are consistent
		Combined T2 and DWI	90.9 (10/11)	82.8 (24/29)		
Lambregts (2011) (34)	Retrospective	T2	40.0 (10/25)	91.6 (87/95)	No statistical comparisons regarding binary interpretations. Area under ROC curve was 0.8 for combined T2 and DWI and 0.76 for T2 (p = 0.39)	Obscure
		Combined T2 and DWI	56.0 (14/25)	93.7 (89/95)		
Sassen (2013) (40)	Retrospective	T2	30.0 (3/10)	86.7 (52/60)	No statistical comparisons regarding binary interpretations. Area under ROC curve was 0.89 for combined T2 and DWI and 0.77 for T2 (p = 0.005)	Obscure
		Combined T2 and DWI	70.0 (7/10)	93.3 (56/60)		
Horvat (2018) (28)	Retrospective	T2	57.1 (12/21)	73.1 (68/93)	No statistical comparisons	Obscure[†]
		Combined T2 and DWI	84.2 (16/19)	56.3 (49/87)		
Meta-analytic summary	NA	T2	47 (95% CI, 30–63)	84 (95% CI, 72–95)	p = 0.01 from joint-model bivariate meta-regression analysis	NA
		Combined T2 and DWI	74 (95% CI, 60–88)	85 (95% CI, 74–96)		

*Numbers in parentheses are number of patients unless specified otherwise, [†]Article states complete tumor response on MRI when both T2 and DWI were negative for residual tumor. However, reported results are more compatible with combined MRI result of complete tumor response when T2 or DWI was negative for residual tumor. CI = confidence interval, DWI = diffusion-weighted imaging, MR = magnetic resonance, NA = not applicable, pCR = pathologic complete response, ROC = receiver operating characteristic, T2 = T2-weighted imaging

three studies showed higher specificity but lower sensitivity for pCR when MRI was combined with other test(s) (32, 33, 36), whereas one study reported an increase in both sensitivity and specificity when endoscopy and digital rectal examination were also used combined with MRI (37).

Issue 3: Tests Used to Select Patients for the Watch-and-Wait Management

Twenty-nine original research articles (6, 48-65, 67-76) and three reports of research protocols (46, 47, 66) were eligible. There was no overlap between them. The details are summarized in Table 5. Almost all studies adopted MRI and endoscopy as the tests to select patients for the watch-and-wait management despite some small variations among studies.

DISCUSSION: KSAR GUIDE

Sensitivity and Specificity of MRI for Diagnosing pCR

There is a limitation in interpreting the meta-analytic summary sensitivity and specificity of T2 or DWI for diagnosing pCR due to the large heterogeneity in the published results. Study heterogeneity is common for systematic review and meta-analysis of diagnostic test accuracy (77). Determining the specific causes for the heterogeneity is difficult because, in general, various factors are intertwined. Within the limitations, MRI using visual assessment of T2 overall had low sensitivity and moderately high specificity for diagnosing pCR after CRT for rectal cancer. Adding DWI to T2 seems beneficial as it increased the diagnostic performance to some extent.

Table 3. Criteria for MRI Diagnosis of Complete Tumor Response

MR Method	Criterion	Number of Articles*
T2	Visible tumor signal is absent.	
	- Normalization of wall in tumor bed; no detectable mass, nodular intermediate signal, or wall thickening (with individual layers of wall identified again)	4
	- mrTRG1[†]: linear/crescentic thin scar in mucosa/submucosa or apparent normalization of wall in tumor bed	5
	- Regular, hypointense scar in inner layer without bulging or breach by intermediate signal and homogeneous intermediate signal in underlying layer of wall in tumor bed	1
	- Normalization of wall or hypointense wall (with thickening) without intermediate signal in tumor bed	5
	- mrTRG1–2[†]: mrTRG1 or dense fibrosis with no obvious residual tumor	4
	Visible tumor signal may be present in small amount.	
	- mrTRG1–3[†]: mrTRG1–2 or > 50% fibrosis or mucin and visible residual intermediate tumor signal	1
	- Residual intermediate tumor signal in ≤ 25% of tumor bed	1
	Obscure	3
DWI	No hyperintense signal on high b-value (≥ 800 sec/mm^2) DWI in tumor bed	8
	Hyperintense signal in ≤ 25% in tumor bed	1
	Obscure	2
Combined T2 and DWI[‡]	When both T2 and DWI are negative for residual tumor	1
	When both T2 and DWI are negative for residual tumor, with DWI being decisive if T2 findings are equivocal	2
	T2 findings as primary results, with DWI to override T2 when T2 findings are equivocal or DWI to increase reader confidence if T2 and DWI findings are consistent	1
	Obscure	4

*One article may present more than one criterion, [†]mrTRG is magnetic resonance tumor regression grade system proposed by MERCURY study group (24). Descriptions for mrTRG categories are according to most recent relevant papers (9, 24, 29), [‡]Rules to combine T2 and DWI results.

The diagnostic performance of MRI was moderate despite the combined use of T2 and DWI, and the lack of visible residual tumor on these imaging examinations does not necessarily mean pCR. This is primarily because of the pathologic nature of the tumor response to CRT (Fig. 4) (78). Rectal cancer is known to respond to CRT through fragmentation and shrinkage (78). Besides, a small minority of originally non-mucinous rectal cancers may develop mucin lakes (8, 78). This mucinous transformation is considered a good prognostic sign, like fibrosis, and should be distinguished from the primarily mucinous subtype that tends to show a poor response to CRT (8). Fragmentation, i.e., the destruction of the main tumor mass and formation of small nests of tumor cells, is reported to occur in about 40–80% of relevant cases and typically leaves microscopic tumor fragments that are below the resolution of imaging examinations (Figs. 5, 6) (78, 79). Consequently, if patients without visible residual tumor on MRI after CRT for rectal cancer are offered the watch-and-wait management, a careful regular surveillance for tumor regrowth is crucial.

Interpretation of Complete Tumor Response on T2

A noteworthy finding is the somewhat heterogeneous criteria adopted by studies to diagnose complete tumor response on T2. Despite mild diversity, most of them have the commonality of a remarkable decrease of the tumor to the absence of mass-like or nodular intermediate signals (which would be perceived on T2 as residual tumor areas) in the tumor bed. Post-CRT changes in rectal cancer, as seen on T2, as well as pathologically are more complex than the simple characterization of normalization, fibrosis (hypointense signal on T2), and residual tumor (intermediate signal on T2) (8, 80). Complete normalization of the wall on MRI in the former tumor location is rare (8). Additionally, post-CRT changes without a residual tumor tissue can create an intermediate signal that can mimic the intermediate signal of a residual tumor (80). Therefore, the heterogeneous criteria adopted by the published studies list the varied T2 appearances of post-CRT state without apparent residual cancer (Fig. 7, Supplementary Materials). The findings of (near) normalization of the wall and regular, thin, hypointense scaring in the luminal side with (near)

Table 4. Studies Reporting Sensitivity and Specificity for Diagnosing pCR both for MRI Alone and for MRI Combined with Other Test(s) in Same Group of Patients

First Author (Year)	Study Type	Method	Sensitivity, %*	Specificity, %*	Comparative Result	Method to Combine Results of MRI and Other Test(s)
Kuo (2012) (33)	Retrospective	MRI (T2)	16.0 (4/25)	94.3 (133/141)	No meaningful statistical comparisons due to low statistical power	Complete tumor response if both MRI and other tests are negative for residual tumor
		MRI combined with endoscopy and routine superficial re-biopsy	8.0 (2/25)	100 (141/141)		
Maas (2015) (37)	Prospective	MRI (combined T2 and DWI)	35.3 (6/17)	93.9 (31/33)	No statistical comparisons	Obscure
		MRI combined with endoscopy and digital rectal examination	70.6 (12/17)	97.0 (32/33)		
Liu (2018) (36)	Prospective	MRI (combined T2 and DWI)	25.0 (5/20)	93.3 (97/104)	No statistical comparisons	Obscure
		MRI combined with endoscopy	10.0 (2/20)	100 (104/104)		
Ko (2019) (32)	Retrospective	MRI (T2)	70.6 (12/17)	95.3 (81/85)	No significant difference in sensitivity (p = 0.250) and specificity (p = 1.000)	Obscure
		MRI combined with endoscopy	52.9 (9/17)	96.5 (82/85)		
Meta-analytic summary	NA	MRI	34 (95% CI, 7–62)	94 (95% CI, 91–97)	p = 0.02 from joint-model bivariate meta-regression analysis	NA
		MRI combined with other test(s)	29 (95% CI, 3–55)	99 (95% CI, 98–100)		

*Numbers in parentheses are number of patients unless specified otherwise.

normal-appearance or homogeneous intermediate signal in the underlying wall are reported to be less likely to harbor occult residual cancer compared to the finding of hypointense thickening of the wall (39, 81). Considering these factors, it would be desirable for the clinical reading of a post-CRT MRI to describe not only the absence vs. presence of visible residual tumor but also the specifics of the MRI findings interpreted as the lack of visible residual tumor.

Interpretation of Complete Tumor Response on DWI

The interpretation of complete tumor response on DWI was more uniform in the published studies as the absence of a hyperintense signal on high b-value DWI in the former tumor location. Nevertheless, the lack of anatomical details and the greater vulnerability to artifacts of DWI can introduce inaccuracy and variability in interpreting DWI according to the level of experience of the readers (8, 82). The readers should be particularly careful to avoid making

false interpretations for T2 shine-through effects, a signal from a different location than the former tumor site, and artefactual signals from susceptibility artifacts (8, 82).

Combining T2 and DWI

Published studies suggest that combined use of T2 and DWI is better than using T2 alone to diagnose pCR. Nonetheless, the exact algorithm to combine the results of T2 and DWI was a bit obscure. If one places more emphasis on the oncologic outcome of the patients, it is reasonable to use DWI to exclude patients suspicious of remaining tumor after it was initially ruled out on T2. However, it is yet uncertain if a simple intersection of the two results in this manner, i.e., complete tumor response on MRI when both T2 and DWI are negative for residual tumor, is ideal as it would increase the specificity probably at the cost of some decrease in sensitivity for pCR (i.e., increased likelihood of sending patients with pCR for radical surgery). The studies that reported both increased sensitivity and

Table 5. Tests Used to Select Patients for Watch-and-Wait Management

First Author (Year)	Article Type	Test Used* (+ = Used)						
		MRI	Endoscopy	EUS	CT	CEA	PET	EUA
Habr-Gama (1998) (50)	Original research		+	+	+	+		
Lambregts (2011) (59)	Original research	+	+	+				
Maas (2011) (62)	Original research	+	+					
Dalton (2012) (48)	Original research	+						+
Habr-Gama (2013) (52)	Original research	+	+	+			+	
Habr-Gama (2014) (51)	Original research	+	+	+	+			
Li (2015) (60)	Original research	+	+	+	+			
Smith (2015) (71)	Original research	+	+			+		
Lai (2016) (58)	Original research	+	+	+	+			
Martens (2016) (63)	Original research	+	+					
Renehan (2016) (6)	Original research	+	+					
Rupinski (2016) (67)	Original research	+	+					
Sanchez Loria (2016) (68)	Original research	+	+					
Habr-Gama (2017) (54)	Original research	+	+					
Hupkens (2017) (57)	Original research	+	+					
Hupkens (2018) (56)	Original research	+	+					
Lin (2018) (61)	Original research	+	+		+		+	
Oh (2018) (65)	Original research	+	+	+	+	+	+	
São Julião (2018) (69)	Original research	+	+	+		+		
Sposato (2018) (74)	Original research	+	+					
Habr-Gama (2019) (53)	Original research	+	+					
Habr-Gama (2019) (55)	Original research	+	+	+	+	+		
Nasir (2019) (64)	Original research	+	+					
São Julião (2019) (70)	Original research	+	+	+		+		
Smith (2019) (72)	Original research		+					
Spiegel (2019) (73)	Original research	+	+		+			
Strode (2019) (75)	Original research	+	+	+	+			
Yeom (2019) (76)	Original research	+						
Dizdarevic (2020) (49)	Original research	+	+					
Barina (2017) (46)	Study protocol†	+	+		+	+		
Battersby (2017) (47)	Study protocol†	+						
Rombouts (2017) (66)	Study protocol†	+	+					

*Evaluations that belong to basic physician assessment and physical examination such as digital rectal examination are not included. PET includes PET, PET-CT, and PET-MR, †Corresponding research results have not been published yet. CEA = carcinoembryonic antigen, EUA = examination under anesthesia, EUS = endorectal ultrasound

increased specificity for diagnosing pCR with the addition of DWI suggest that improved diagnostic performance without sacrificing any of both parameters is achievable (31, 34, 40), likely by combining the two results in some obscure tailored manners. Therefore, further studies are needed to explicitly determine the optimal algorithms to combine T2 and DWI. Hence, all readers can use the two imaging methods together more reliably and more effectively.

Combining MRI and other Tests

One approach to deal with the limited accuracy of MRI in diagnosing pCR would be to combine it with other tests.

This systematic review shows that the combination of MRI and endoscopy is the approach that is most favored by the experts in the field. This is consistent with the statistics collected by the International Watch and Wait Database Consortium from 47 participating institutions in 15 countries (7). Published studies show that false diagnosis of pCR in patients who had a residual tumor could be reduced by combining MRI with other tests. However, it was at the cost of reduced sensitivity for pCR. These results are expected with the approach of deciding a complete tumor response if both MRI and other tests are all negative for the residual tumor. This approach would be appropriate if
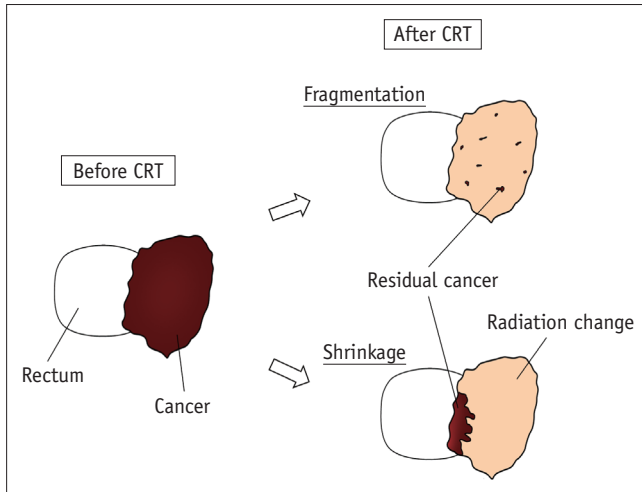
Fig. 4. Schematic representation of patterns of rectal cancer response to CRT. Fragmentation is destruction of main tumor mass and formation of small nests of tumor cells, whereas shrinkage is tumor reduction in direction of mucosa. CRT = chemoradiation therapy
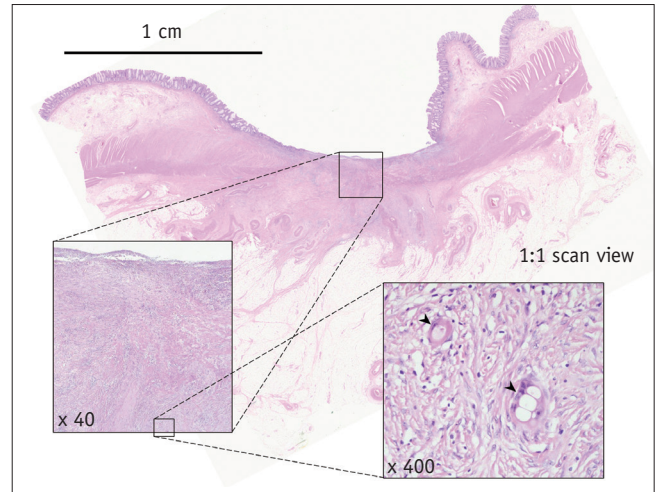

Fig. 5. Microscopic size of residual tumor in case of near total regression after CRT for rectal cancer. Tiny nests of residual cancer cells are marked by arrowheads in most magnified (x 400) view. H&E stain (Courtesy of Dr. Hee Sang Hwang in Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea). H&E = hematoxylin and eosin
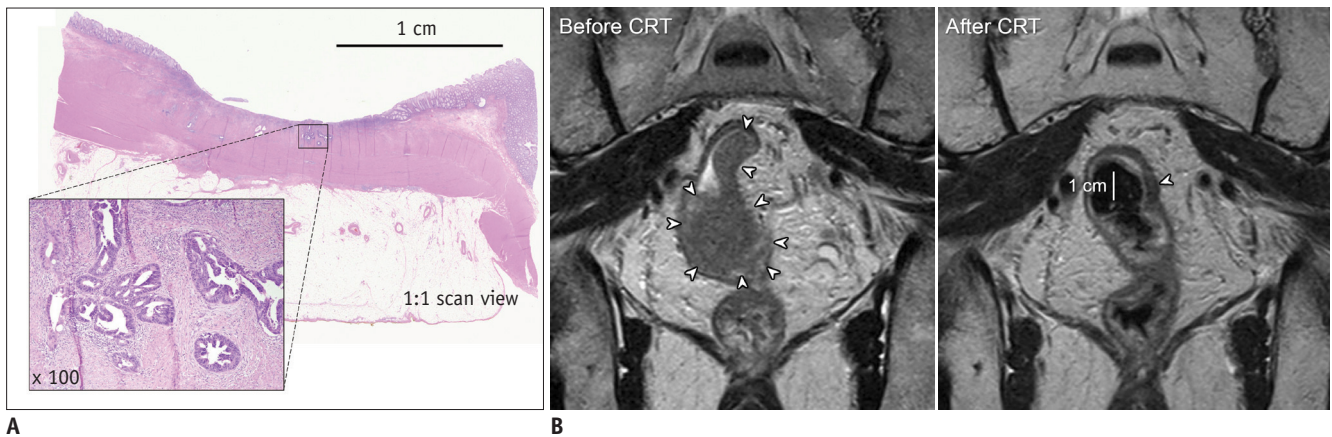

Fig. 6. Microscopic size of residual tumor in case of moderate regression after CRT for rectal cancer.
A. Small glands of residual cancer cells are noted in tumor bed. H&E stain (Courtesy of Dr. Hee Sang Hwang in Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea). **B.** Residual tumor is still too small to be seen on MRI, albeit larger than that of near total regression as shown in Figure. 5. Therefore, wall in tumor bed (arrowheads) appears essentially normal on MRI after CRT.

oncologic outcome and safety are the concern. However, compared with the use of a single test, this approach would deprive an opportunity for less invasive management in more patients who have achieved pCR. There are yet limited data to confirm if and how a multi-test approach could increase the performance for diagnosing pCR and avoid sacrificing the sensitivity or the specificity. Therefore, further investigations are needed to determine the most effective strategy to combine different tests to select patients for the watch-and-wait management.

Issues Uncovered

Although this guide focuses on the interpretation of

complete tumor response on MRI with respect to the primary tumor, the entire clinical decision of complete tumor response requires the same evaluation for nodal metastasis and tumor deposits. To our knowledge, there is not enough data in the literature to draw an evidence synthesis on the evaluation for nodal metastasis and tumor deposits. Nevertheless, ESGAR has recently proposed as an expert consensus opinion that all nodes with a short-axis diameter < 5 mm and ≥ 5 mm on post-CRT MRI should be considered benign and suspicious, respectively (16).

Summary

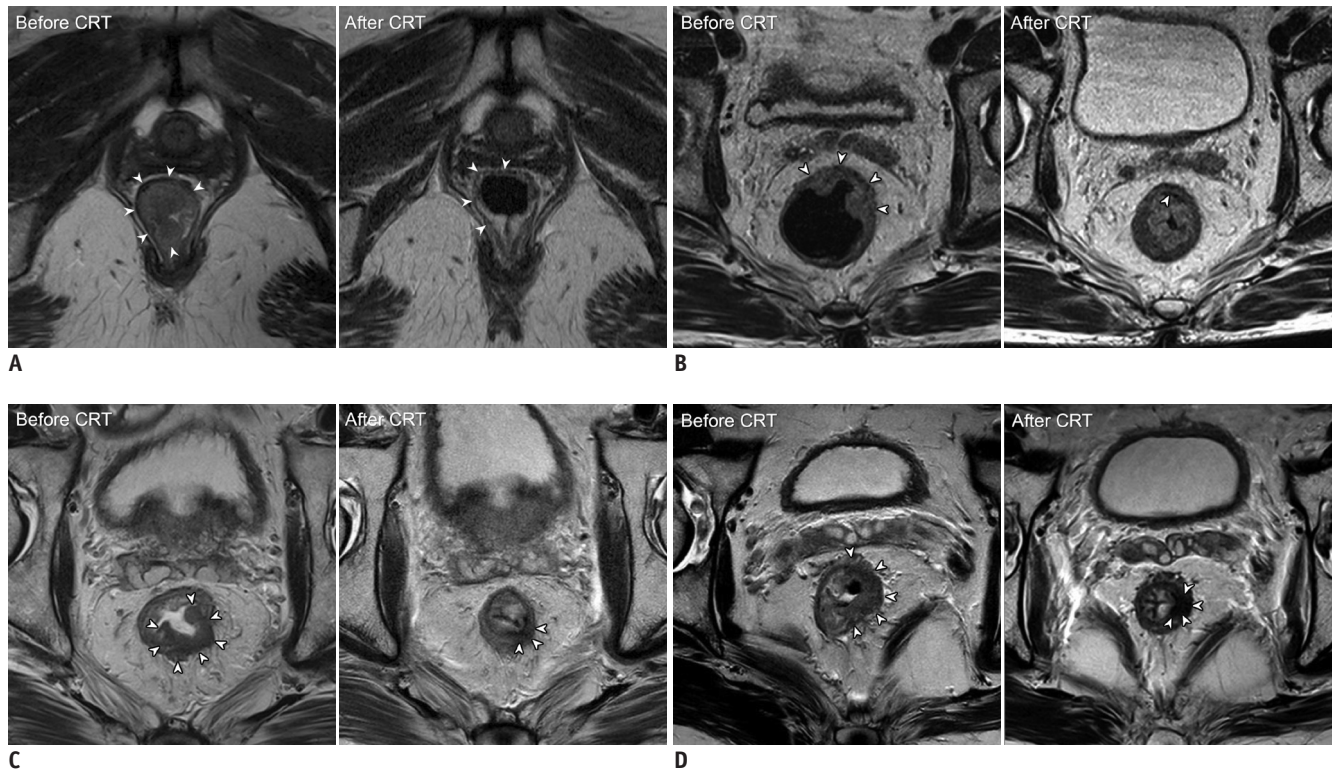This systematic review and meta-analysis provide an

Fig. 7. Exemplary cases of complete tumor response, i.e., no visible residual tumor on T2 after CRT.
A. Complete normalization of wall in tumor bed (arrowheads) after CRT. Pathology was total regression. **B.** Regular, thin, hypointense scar in luminal side and normalization of underlying wall in tumor bed (arrowheads) after CRT. Pathology was total regression. **C.** Regular, thin, hypointense scar in luminal side and a homogeneous, intermediate signal of underlying wall with mild thickening in tumor bed (arrowheads) after CRT. Pathology was total regression. **D.** Dense, hypointense thickening of wall in tumor bed (arrowheads) after CRT. Pathology was total regression.

evidence-based practical guide for MRI assessment of complete tumor response after CRT for rectal cancer. Within the limitation of considerable heterogeneity in the published results, with visual assessment, combined T2 and DWI seems more favorable than T2 alone in diagnosing pCR after CRT for rectal cancer and showed modest summary sensitivity and moderately high summary specificity. The criteria for complete tumor response on T2 may include (near) normalization of the wall; regular, thin, hypointense scar in the luminal side with (near) normal-appearance or homogeneous intermediate signal in the underlying wall; and hypointense thickening of the wall in the former tumor location. The criterion for complete tumor response on DWI should be the absence of a hyperintense signal on high b-value DWI in the former tumor location. The optimal algorithms to combine the results of T2 and DWI have yet to be defined more explicitly. The use of MRI and endoscopy was the most utilized means to select patients for the watch-and-wait management. However, the evidence is yet scarce regarding if a multi-test approach is beneficial and what combinations of the tests are most effective.

Supplementary Materials

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