

EUS versus magnetic resonance imaging in staging rectal adenocarcinoma: a diagnostic test accuracy meta-analysis CME



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Background and Aims: EUS and magnetic resonance imaging (MRI) are both used for locoregional staging of rectal cancer, which determines treatment options. There is a lack of consensus on the best modality for locoregional staging, with studies supporting both EUS and MRI. In this study, we performed the first diagnostic test accuracy meta-analysis to compare the diagnostic accuracy, sensitivity, and specificity of EUS and MRI in the staging of rectal cancer.

Methods: A comprehensive electronic literature search up to June 2018 was performed to identify prospective cohort studies directly comparing the accuracy of EUS with MRI in staging nonmetastatic rectal cancer with surgical pathology as the reference standard. Quality of the included studies was measured by using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. A bivariate hierarchical model was used to perform the meta-analysis of diagnostic test accuracy according to the Cochrane approved methodology. Summary receiver operating characteristics were developed, and the area under the curve was calculated for overall and individual T and N staging, for EUS, MRI, and head-to-head comparison.

Results: Six of 2475 studies including 234 patients were eligible. Pooled sensitivity and specificity in T staging were .79 (95% confidence interval [CI], .72-.85) and .89 (95% CI, .84-.93) for EUS and .79 (95% CI, .72-.85) and .85 (95% CI, .79-.90) for MRI, respectively. Pooled sensitivity and specificity in N staging were .81 (95% CI, .71-.89) and .88 (95% CI, .80-.94) for EUS and .83 (95% CI, .73-.90), and .90 (95% CI, .82-.95) for MRI, respectively. In area under the curve head-to-head analysis, EUS was superior to MRI in overall T staging ($P < .05$). EUS outperformed MRI in overall T, overall N, T1, and T3 staging ($P < .01$), after excluding studies using an endorectal coil for MRI. MRI was superior to EUS in T2 staging ($P = .01$) in both analyses.

Conclusions: EUS and MRI both provide reasonable diagnostic accuracy in the staging of nonmetastatic rectal cancer. EUS was superior to MRI in overall T staging and overall T and N staging after adjusting for MRI technology. Practitioners should be aware of advantages and disadvantages of both modalities and choose appropriate methods while considering diagnostic accuracy of each test and institutional practices and limitations. (Gastrointest Endosc 2019;90:196-203.)

Abbreviations: AUC, area under the curve; CI, confidence interval; DOR, diagnostic odds ratio; MRI, magnetic resonance imaging.

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Colorectal cancer is the most common gastroenterologic malignancy and the third leading cause of cancer-related death in Western countries.^{1,2} Rectal cancer is diagnosed in approximately 40,000 Americans and 125,000 Europeans annually.^{1,2}

Treatment of rectal cancer depends on staging, based on local invasion, involvement of lymph nodes, and distant metastasis. Patients with early tumors with maximum invasion depth into the submucosa may be candidates for transanal endoscopic microsurgery, whereas identification of locally invasive rectal tumors prompts the use of neoadjuvant therapy. Although CT is useful for distant metastases, EUS or magnetic resonance imaging (MRI) is typically used to determine depth of tumor invasion and metastatic lymph nodes. One conventional meta-analysis, with proper methodology, assessed the accuracy of EUS and MRI in staging of rectal cancer without head-to-head comparison.³ To our knowledge, no study has directly compared EUS and MRI in the same patient population with surgical pathology as the reference standard. A previous meta-analysis determined that EUS was most accurate for determination of local invasion compared with MRI,⁴ whereas a systematic review showed EUS and MRI were equivalent, but MRI with rectal coil was most accurate.⁵ In contrast, a meta-analysis from 2015 showed that MRI, EUS, and CT could not provide reliable evaluation for lymph node metastasis.⁶ None of these studies used the methodology by the Cochrane Collaboration⁷ to perform a diagnostic test accuracy meta-analysis to compare the diagnostic accuracy, specificity, and sensitivity of these 2 modalities.

Meta-analysis of diagnostic test accuracy was specifically designed by the Cochrane Collaboration group to analyze and compare the accuracy, sensitivity, and specificity of a diagnostic test compared with a reference standard.⁷ It differs from a conventional meta-analysis in the quality assessment of articles and statistical analysis. The present study aims to determine the diagnostic test accuracy of EUS and MRI in head-to-head comparative studies in the staging of rectal cancer compared with the reference standard.

METHODS

Registration

The study protocol was registered (CRD42017069308) with the International Prospective Register of Systematic Reviews.

Study selection

Studies directly comparing the accuracy of EUS and MRI in staging rectal cancer with surgical pathology as the reference standard were included. No restrictions were placed on US frequency or type of EUS used or on the field strength or type of coil used for MRI.

Studies using nonendoscopic US, such as rigid endorectal sonography, were excluded. Studies with insufficient

data, abstracts, pediatric studies, case-control studies, duplicate publications, lack of diagnostic test accuracy data, postradiation studies, and studies with no reference standards were excluded. Studies on patients who received radiation therapy before imaging were excluded. No restriction was imposed in terms of language, location, or quality of studies.

Electronic search methods for identification of studies

Two individual investigators completed a comprehensive literature search using OVID MEDLINE, EMBASE, Web of Science, Cochrane Library, and Google Scholar databases up to June 2018. The following search terms were used: colorectal and rectal-neoplasm, cancer, adenocarcinoma, malignancy and tumour, EUS, endoscopic ultrasound, endosonography, MRI, magnetic resonance imaging. No restriction was applied in terms of language, location, or quality of the studies during the literature search. Recursive searches and cross-referencing were carried out by using a "similar articles" function. References of articles identified after initial search were manually reviewed.

Data collection and analysis

Study selection. Two authors (B.P.H.C. and R.P.) independently screened references and selected studies for inclusion. There were no differences in study selection between authors based on full-text article assessments. A third author (M.Y.) was involved if there was conflict.

Data extraction and management. Two authors (B.P.H.C. and R.P.) independently extracted data from each included study. A third author (M.Y.) was involved in the event of a conflict. True-positive, true-negative, false-negative, and false-positive values were determined for T and N staging for EUS and MRI, as composites and individual T and N staging. Overstaging was defined as the reported stage by a test that was higher than the one reported by the reference standard. Understaging was defined as the reported stage by a test that was lower than the one reported by the reference standard.

Assessment of methodologic quality. Study quality and risk of bias was assessed using the QUADAS-2 assessment tool according to the recommendation by the Cochrane Collaboration.⁷ The 2 main categories are risk of bias and applicability. Each category has its own set of assessment domains. Studies with "low risk of bias" in all domains were considered to have high methodologic quality.

Outcome measure. The main outcome of interest was the diagnostic test accuracy of EUS and MRI in the staging of rectal cancer. Secondary objectives were to compare sensitivity and specificity of EUS and MRI in T and N staging, as a composite and individual stages.

Statistical analysis and data synthesis

Sensitivity was defined as the probability that the index test result will be positive in a diseased case. Specificity

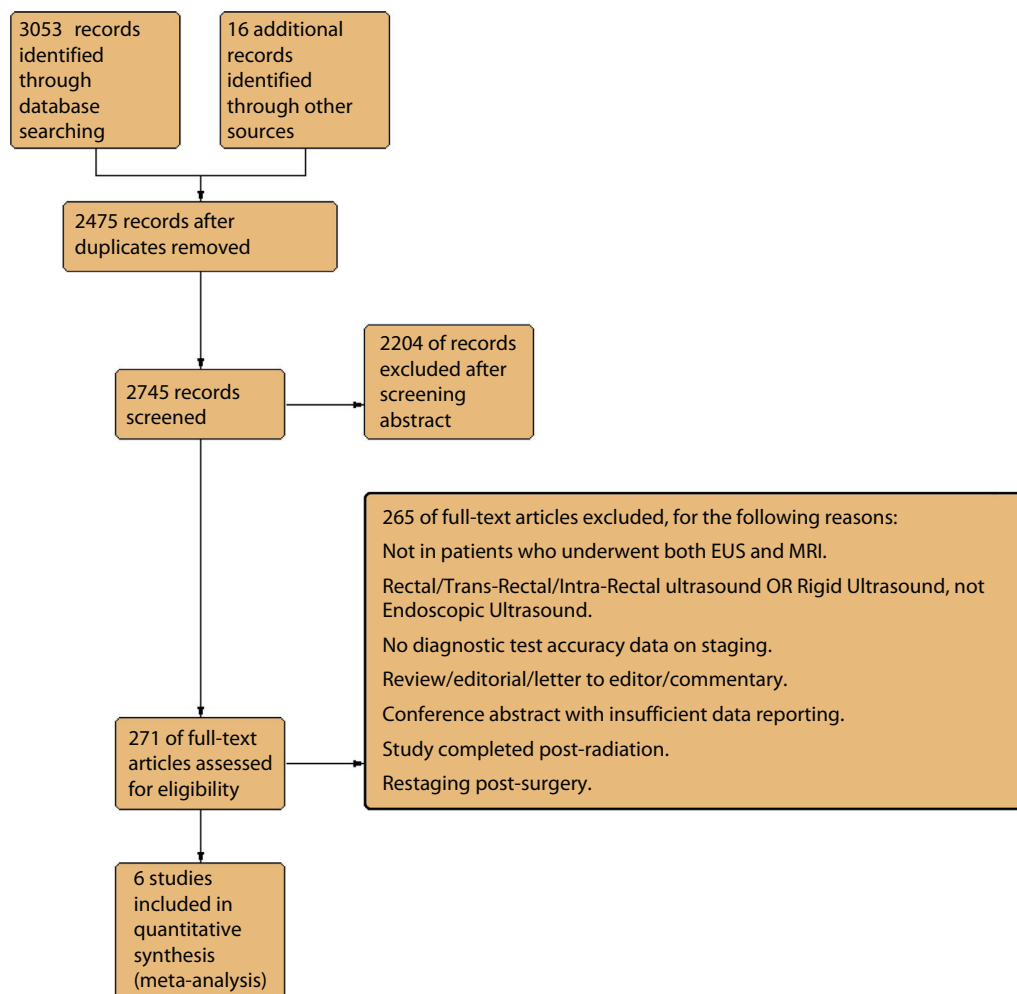


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study identification, inclusion, and reasons for exclusion. *MRI*, Magnetic resonance imaging.

was defined as the probability that the index test result will be negative in a nondiseased case. Diagnostic odds ratio (DOR) was defined as a single number that describes how many times higher the odds are of obtaining a test positive result in a diseased rather than a nondiseased person and summarizes the diagnostic accuracy of the index test. DerSimonian-Laird methods were used to estimate the overall DOR and hence to determine the best-fitting receiver operating characteristic curve. This allowed us to calculate summary receiver operating characteristics and area under curve (AUC) for each test. A perfect test has an AUC close to 1, and poor tests have AUCs close to .5.

In Stata version 12 (Stata Corp, College Station, Tex, USA), we used the *roccomp* command to test for equality of receiver operating characteristic areas for EUS and MRI, the *diagt* command to derive summary statistics, and the *mcc* command to compare sensitivities and specificities. DORs were compared using the approach recommended by Altman and Bland⁸ via WinPEPI software.⁹

Published data were transformed into datasets using the reported true-positive, true-negative, false-negative, and false-positive values for each staging. RevMan version 5.3 (The Nordic Cochrane Centre; Copenhagen) was used to create Forrest plots and risk of bias graphs. We assessed the risk of publication bias by using a Funnel plot and planned to conduct a meta-regression using the Moses-Shapiro-Littenberg approach if the number of included studies was more than 10. Studies performed after 2000 were assessed as a separate group to investigate any difference in diagnostic accuracy because of changes in MRI technology, because studies before 2001 all used an endorectal coil for MRI. A jackknife analysis was performed to determine if the results of our meta-analysis were influenced by any single study, using the methodology described by Efron and Stein.¹⁰ We reported pooled sensitivities and specificities, DORs, and AUCs, alongside 95% confidence intervals (CIs) and *P* values where appropriate. Comparative AUC graphs are shown.

TABLE 1. Characteristics of included studies

Study	Publication year	No. of patients	Enrollment	Study type	Reference standard	EUS	MRI	Blinded
Meyenberger et al ¹⁸	1995	21	Consecutive	Prospective	Histopathology	Radial 7.5 MHz	1.5 T endorectal coil	Yes
Zagoria et al ¹⁹	1997	10	Consecutive	Prospective	Histopathology	Radial 7.5 MHz	1.5 T endorectal coil	Yes
Maldjian et al ¹¹	2000	14	Consecutive	Prospective	Histopathology	Radial 7.5 MHz or 12 MHz	1.5 T endorectal (12) body (2) coil	Yes
Bianchi et al ²⁰	2005	49	Consecutive	Prospective	Histopathology	7.5 MHz	1 T body coil	Yes
Fernández-Esparrach et al ²¹	2011	90	Consecutive	Prospective	Histopathology	Radial	1.5 T or 3 T	Yes
Kocaman et al ²²	2014	50	N/A	Retrospective	Histopathology	Radial 7.5 MHz or 10 MHz	1.5 T phased array coil	Yes

MRI, Magnetic resonance imaging; N/A, not available.

RESULTS

Literature Search

Six of 2475 studies were included in the diagnostic test accuracy meta-analysis. Figure 1 depicts the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for the detail of study selection and Table 1 the characteristics of included studies. Quality of included studies and risk of bias using the QUADAS-2 tool are represented in Figure 2.

Comparison of EUS and MRI

In overall T staging, EUS was significantly superior with an AUC of .87 (95% CI, .83-.90) as compared with .82 (95% CI, .78-.86) for MRI ($P = .0001$). In overall N staging, there was no difference between groups with AUC of .90 (95% CI, .85-.94) for EUS as compared with .86 (95% CI, .81-.92) for MRI ($P = .11$) (Fig. 3). In pooled individual staging, EUS outperformed MRI in T3 staging (EUS: .94; 95% CI, .90-.98; MRI: .83; 95% CI, .77-.89; $P < .01$), whereas MRI was superior to EUS in T2 staging (EUS: .82; 95% CI, .74-.90; MRI: .92; 95% CI, .87-.97; $P = .005$). There were no differences between the groups in pooled AUC otherwise for individual T or N staging.

Subgroup and sensitivity analyses

In subgroup analysis after excluding studies using an endorectal coil, EUS was significantly superior to MRI in overall T, T1, T3, and N staging ($P < .01$ for all) (Table 2). However, MRI remained superior to EUS in T2 staging ($P = .01$).

Jackknife analysis

In the jackknife analysis, EUS remained significantly superior to MRI in overall T staging. In overall N staging, EUS was found to be significantly superior to MRI using the exclusion of Maldjian et al¹¹. Otherwise, with the exclusion of other studies, there was no difference between EUS and MRI in overall N staging (Supplementary Table 1, available online at www.giejournal.org).

Pooled sensitivity and specificity of EUS

EUS demonstrated pooled sensitivity and specificity of .79 (95% CI, .72-.85) and .89 (95% CI, .84-.93), respectively, for T staging with a DOR of 31.6 (95% CI, 17.6-56.6). The pooled sensitivity and specificity of EUS for N staging was .81 (95% CI, .71-.89) and .88 (95% CI, .80-.94). DOR of EUS for N staging was 30.7 (95% CI, 13.7-68.8).

Pooled sensitivity and specificity of MRI

Pooled sensitivity and specificity of MRI for T staging was .79 (95% CI, .72-.85) and .85 (95% CI, .79-.90), respectively, with a DOR of 21.7 (95% CI, 12.7-37.1), which was not significantly different from EUS ($P = .35$). Pooled sensitivity and specificity of MRI for N staging was .83 (95% CI, .73-.90) and .90 (95% CI, .82-.95), respectively. DOR was 40.7 (95% CI, 17.1-96.6), which was not significantly different from EUS ($P = .64$). Additional summary estimates and diagnostic accuracy data of individual staging are depicted in Figure 4.

DISCUSSION

To our knowledge, this is the first diagnostic test accuracy meta-analysis comparing EUS and MRI in staging rectal cancer as compared with surgical pathology as the reference standard, in a head-to-head comparison, using appropriate methodology by the Cochrane Collaboration.⁷ Although both EUS and MRI showed reasonable diagnostic accuracy, EUS significantly outperformed MRI in overall T staging of rectal cancer in head-to-head analysis. After adjusting for technology and removing studies that used the older technology of an endorectal coil in MRI, EUS significantly outperformed MRI in overall T, N, T1, and T3 staging.

The accuracy of EUS in detecting early-stage rectal cancer might have clinical applicability because a T1 rectal cancer can be treated by endoscopic means such as EMR or endoscopic submucosal dissection as well as by transanal excision. Tumors with T3 or T4 invasion or any nodal

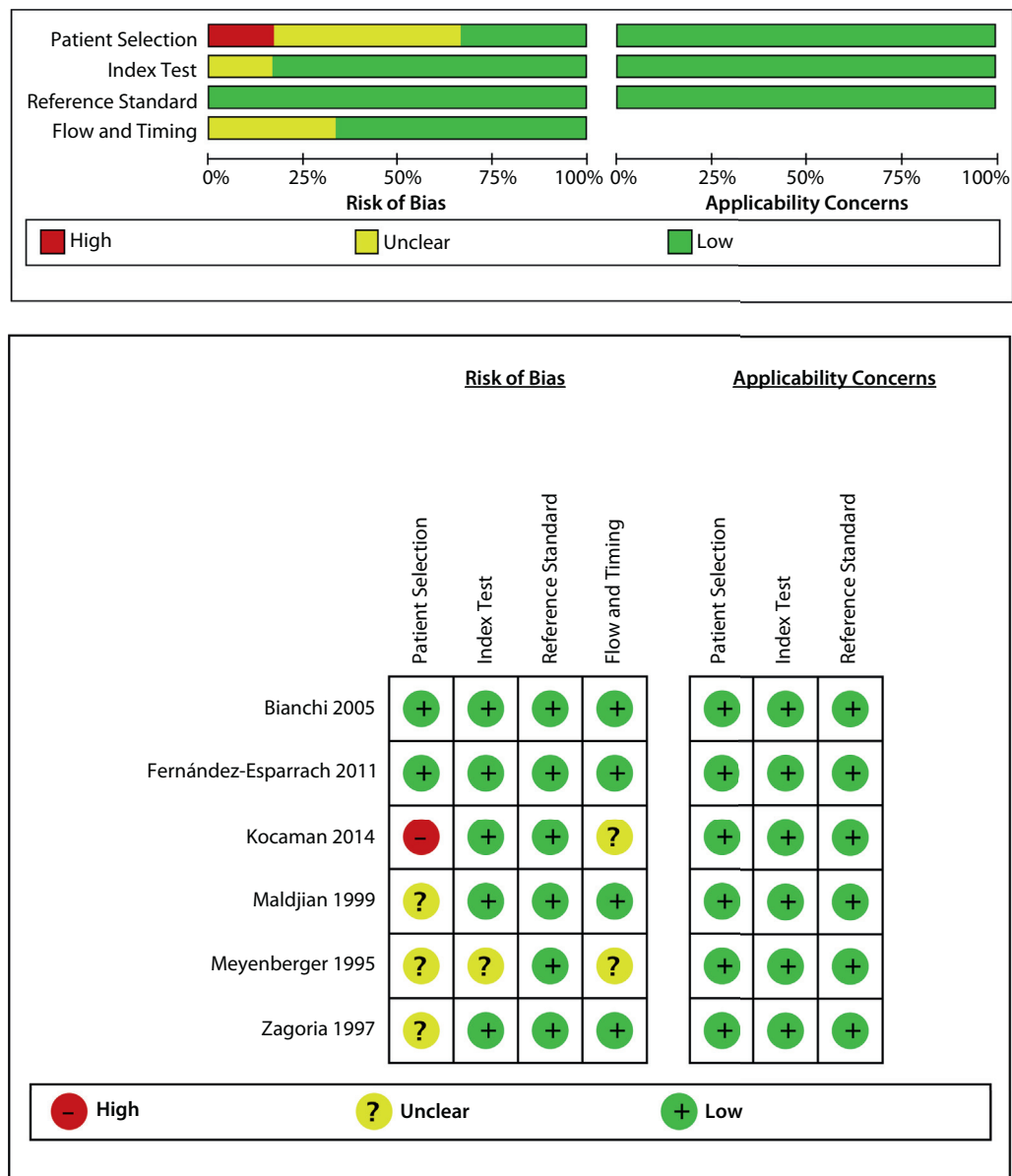


Figure 2. QUADAS-2 analysis, recommended by the Cochrane Collaboration for the assessment of risk of bias in included studies.

involvement may qualify for neoadjuvant therapy. Therefore, accurate and reliable staging techniques are crucial for early cancers to avoid unnecessary measures and adverse events.

In our study, EUS was found to be superior to MRI in T1 and T3 lesions, whereas MRI was better in detecting T2 lesions. One might assume this represents a discrepancy; however, all differences were statistically significant and remained robust after excluding studies using MRI endorectal coil. These results might be because of a higher sensitivity of EUS in detecting smaller lesions. The submucosa and serosa are thinner than the muscularis propria in the colorectal wall. Therefore, MRI might better detect invasion to the muscularis propria (T2 lesions) than EUS. Muscularis propria appears dark and isoechoic compared

with most adenocarcinomas in EUS view and thus might decrease the sensitivity of EUS in detecting invasion to muscularis propria (T2 lesions), as compared with submucosa (T1 lesions) or serosa (T3 lesions), which is usually brighter than the tumor tissue.

Our study also showed EUS to be superior to MRI in N staging, after exclusion of studies that used an endorectal coil in MRI. However, no significant difference was found in subgroups of N0 or N1/2 tumors. It is likely that a study with more patients might provide a more precise comparison and a more robust conclusion because the number of patients in these subgroups was small. Our finding that EUS is superior to MRI in overall N staging is important in clinical practice, because EUS is traditionally considered less accurate than other imaging modalities such as CT and

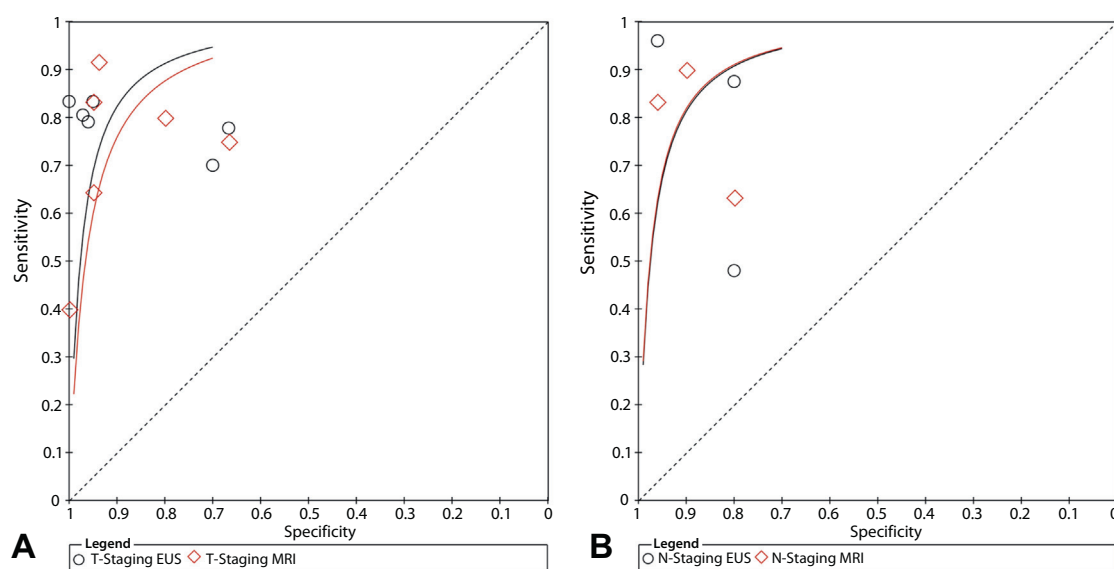


Figure 3. **A**, Summary receiving operating characteristic curve, comparing the diagnostic accuracy of EUS with MRI in overall T staging ($\chi^2 = 15.03$, $df = 1$, $P < .01$). **B**, Summary receiving operating characteristic curve, comparing the diagnostic accuracy of EUS with MRI in overall N staging ($\chi^2 = 2.57$, $df = 1$, $P = .11$). *MRI*, Magnetic resonance imaging.

TABLE 2. Area under the curve for EUS and MRI in overall and individual T and N staging for all studies and adjusted for technology

	Stage	All studies			Studies using MRI endorectal coil excluded		
		EUS	MRI	P value	EUS	MRI	P value
T staging	Overall	.87	.82	<.01	.88	.82	<.01
	1	.93	.77	.06	1.00	.96	<.01
	2	.82	.92	<.01	.83	.94	.01
	3	.94	.83	<.01	.96	.84	<.01
	4	.76	.72	.46	.76	.72	.48
N staging	Overall	.90	.86	.11	.92	.85	<.01
	0	.95	.91	.32	.95	.91	.32
	1/2	.92	.93	.71	.95	.89	.07

MRI, Magnetic resonance imaging.

MRI in detecting nodal involvement. In addition to EUS characteristics, which may help in differentiating a malignant node from a benign node, the endosonographer has the ability to perform FNA or biopsy sampling to obtain a tissue sample. This can confirm the nature of a suspected lymph node, whereas a separate procedure would need to be arranged to obtain a tissue sample for suspected lesions using MRI or CT.

The authors of previous meta-analyses and systematic reviews have attempted to compare EUS and MRI. In a systematic review, MRI, CT, and endorectal US for preoperative staging of rectal cancer using pathology as the reference standard were compared.⁵ The authors included 83 studies, comprising 4879 patients, in a non-head-to-head study and showed that EUS was better than MRI in T staging, whereas MRI was the most accurate in N staging. They did not do a head-to-head analysis and included patients who received preoperative radiation

therapy. A meta-analysis from 2004 compared MRI, CT, and endoluminal US for local staging and assessment of lymph nodes in rectal cancer, with pathology as the reference standard.⁴ The authors included 90 studies and showed that EUS outperformed MRI in T staging, whereas all 3 modalities were equivalent in N staging. There was an overlap of 45 articles between these 2 meta-analyses. In both studies, no head-to-head comparisons were made, and the authors simply calculated the accuracy of EUS and MRI from different studies and compared the numerical results in an indirect comparison. Based on this methodology, the authors could have compared the result of the EUS in 1 patient with the result of MRI in a different patient. Therefore, the level of evidence derived from the results of these 2 studies are likely less than the level based on our head-to-head analysis. In addition, use of rigid endorectal US was not excluded, and therefore the results could not be generalized to

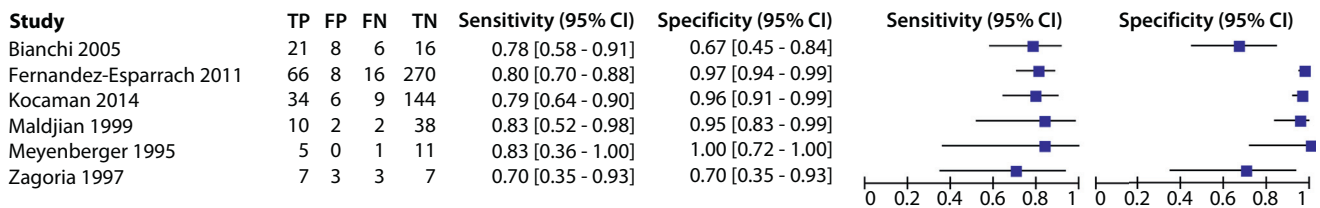
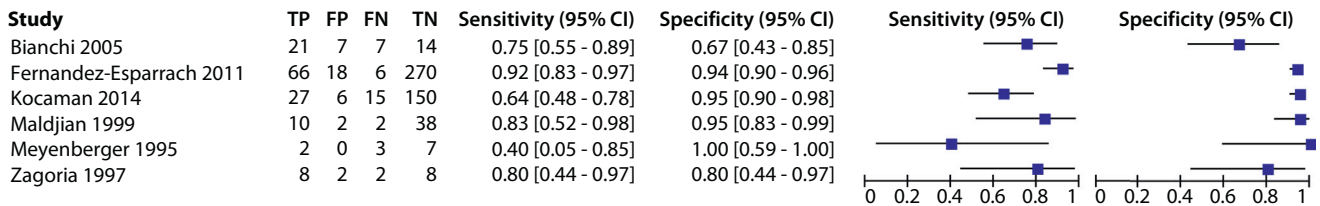
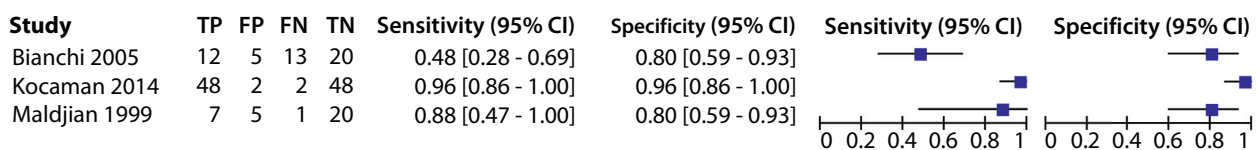
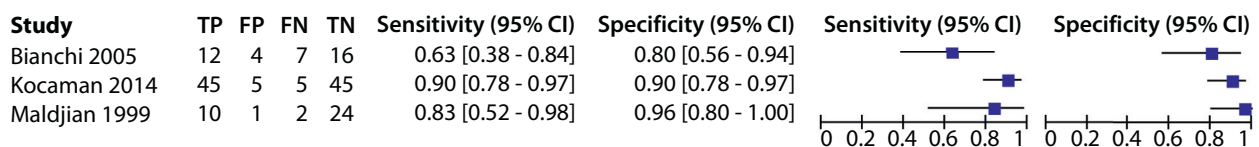
T- Staging EUS**T- Staging MRI****N- Staging EUS****N- Staging MRI**

Figure 4. Forrest plots of included studies for overall T and N staging of rectal cancer. *MRI*, Magnetic resonance imaging; *CI*, confidence interval; *TP*, true positive; *TN*, true negative; *FN*, false negative; *FP*, false positive.

patients undergoing EUS. Our meta-analysis differs in that only true EUS was included and all studies were head-to-head EUS and MRI, using surgical pathology as the reference standard.

A lack of consensus remains regarding the best staging modality among guidelines provided by different professional associations. The American Society for Gastrointestinal Endoscopy recommends the use of EUS for locoregional staging of colorectal cancer to guide therapy.¹² The European Society of Medical Oncology suggests the use of EUS or MRI in early T staging, and MRI is preferential in N staging, with EUS being a less-optimal modality.¹ The National Comprehensive Cancer Network lists both MRI and EUS for clinical staging, although MRI is preferred.¹³ Given the reasonable operating characteristics of EUS and MRI and lack of consensus in guidelines, clinical decisions may ultimately be determined by access to resources, local expertise, and institutional policy, which is often influenced by cost-effectiveness. Only 1 study has looked at cost-effectiveness of EUS compared with MRI in the evaluation of rectal cancer.¹⁴ Abdominal and pelvic CT was compared

with CT plus EUS and CT plus MRI. For nonmetastatic proximal rectal tumors, CT plus EUS was the most cost-effective approach. The measure of effectiveness was a recurrence-free rate and not survival. Additional cost-effectiveness and economic analyses are required to aid in policy development.

Sensitivity analysis was performed by removing studies that used an endorectal coil, which represented studies from 2000 and earlier. This analysis showed that EUS outperformed MRI in overall T, T1, T3, and N staging. Endorectal coils provide higher resolution of the rectal wall but are not widely used because of a limited field of view, patient, and cost factors.^{15,16} Consensus guidelines from the European Society of Gastrointestinal and Abdominal Radiology group support the use of a surface coil, whereas endorectal coils are not recommended.¹⁷ There was no consensus on the optimal MRI field strength (1.5 T vs 3 T). EUS was recommended as the preferred technique for differentiation and staging of T1 tumors. Similarly, the European Society of Medical Oncology supports the use of EUS for early tumors but considers pelvic MRI as the most accurate test for locoregional staging.¹ As MRI and

EUS technologies continue to improve, additional studies will need to be completed to compare the 2 modalities.

The results of our meta-analysis should be interpreted with caution given the limitations in conducting a meta-analysis. Our meta-analysis included 6 studies comprising 234 patients. More studies and a higher number of patients would likely provide a more accurate estimate and comparison of results. The number of patients reflects the lack of head-to-head studies comparing EUS and MRI in staging, which is likely because of extensive resources required to perform such studies. There are many studies looking at EUS alone or MRI alone in staging of rectal cancer compared with surgical pathology. However, head-to-head analysis provides the most accurate comparison between the 2 modalities. It should be noted that both EUS and MRI are operator-dependent, and the interpretation of findings is subject to bias. Therefore, the results of included studies may not be generalizable to all centers, based on local expertise in EUS and MRI. Likewise, the conclusions of our meta-analysis are predicated on availability of local expertise. Of the included studies, there was heterogeneity in the type of coil used as well as the field strength, which must be taken into account when interpreting our results. As EUS and MRI technology changes and improves, this will also affect our conclusions. Furthermore, although surgical pathology is highly accurate in staging rectal cancer, the assumption of 100% accuracy in a reference standard does not hold true in clinical practice, including our case of staging rectal cancer.

In conclusion, both EUS and MRI provide reasonable diagnostic accuracy in staging nonmetastatic rectal cancer with EUS significantly more accurate than MRI in determining overall T staging. We recommend both modalities be considered for the staging of rectal cancer based on local availability and expertise.

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SUPPLEMENTARY TABLE 1. AUC for overall T and N staging with individual studies excluded

Study removed	Publication year	AUC overall T staging			AUC overall N staging		
		EUS	MRI	<i>P</i> value	EUS	MRI	<i>P</i> value
None		.87	.82	<.01	.90	.86	.11
Meyenberger et al ¹⁸	1995	.87	.82	<.01			
Zagoria et al ¹⁹	1997	.88	.82	<.01			
Maldjian et al ¹¹	2000	.87	.81	<.01	.92	.85	<.01
Bianchi et al ²⁰	2005	.88	.81	<.01	.93	.91	.44
Fernández-Esparrach et al ²¹	2011	.83	.78	.02			
Kocaman et al ²²	2014	.88	.84	.01	.80	.80	1.00

AUC, Area under the curve; *MRI*, magnetic resonance imaging.