

Evaluating rectal tumor staging with magnetic resonance imaging, computed tomography, and endoluminal ultrasound

A meta-analysis

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Abstract

Background: Magnetic resonance imaging (MRI), endoluminal ultrasound (EUS), and computed tomography (CT) are commonly used imaging tools to evaluate rectal tumor staging, but there was no recent meta-analysis to define the present role of the 3 tools. Here, we proposed to systematically compare the accuracy of the 3 imaging tools for rectal tumor staging.

Methods: We systematically searched diagnostic accuracy studies of MRI, CT, or EUS on rectal cancer staging, written in English or Chinese, published between January 1, 2003 and Dec 31, 2015 from database of PubMed, EMBASE, and Cochrane Library. The reference standards should be pathological findings. Hierarchical regression model was used for producing summary receiver operating characteristic (SROC) curves and calculating diagnostic accuracy data including sensitivity, specificity, and diagnostic odds ratio for the 3 imaging tools. Investigation of sample size, quality items and resolution, and magnetic field strength on heterogeneity was detected by using subgroup analysis and SROC regression.

Results: This analysis included 89 studies. MRI, CT, and EUS yielded similar diagnostic accuracy. Better performance was observed with high-resolution MRI and 3.0-T MRI (P=0.01 and 0.04, respectively). EUS showed lower diagnostic accuracy after preoperative therapies (P=0.03).

Conclusion: MRI, CT, and EUS have comparable accuracy for rectal tumor staging. High-resolution MRI and 3.0-T MRI can produce better staging results and were recommended. EUS is not suitable for rectal tumor staging for its significantly decreased accuracy.

Abbreviations: CI = confidence interval, CT = computed tomography, DOR = diagnostic odds ratio, EUS = endoluminal ultrasound, MRI = magnetic resonance imaging, SROC = summary receiver operating characteristic.

Keywords: endoluminal ultrasound, magnetic resonance imaging, rectal neoplasm, tomography, tumor staging, x-ray computed

1. Introduction

Rectal cancer is one of the leading causes of cancer-related deaths.^[1] Accurate definition of tumor stages of rectal cancer is important for assigning patients to the appropriate therapies^[2]

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and predicting the prognosis as T3/T4 tumors often showed poor survival outcomes.^[3]

Currently, the magnetic resonance imaging (MRI), computed tomography (CT), and endoluminal ultrasound (EUS) are the most commonly used noninvasive imaging tools for evaluating tumor stages before neoadjuvant therapies and/or surgery. The imaging results enable clinical practitioners to determine if a patient needs neoadjuvant therapy and how he/she responds to the treatment.^[2,4]

A meta-analysis published in 2004 by Bipat et al^[5] concluded that EUS had better accuracy in defining tumor stages than MRI and CT in rectal cancer patients. However, this study included papers published before 2002 when clinical practitioners started to apply MRI in tumor staging of rectal cancer for a short period. The low-resolution scanner which applied insufficient image matrix size and insufficient diagnostic experience of radiologists might both contribute to the poor performance of MRI.

Recently, the development of high-spatial-resolution MRI has improved its diagnostic accuracy for tumor staging because it provides precise clarification between tumor tissue and the mesorectal fascia.^[6] Meanwhile, adding multiplanar reconstructions of multidetector CT definitely improves the staging accuracy for rectal cancer with comparison of standard axial reconstructions alone.^[7] However, there remains a lack of information concerning the diagnostic accuracy of novel ultrasound techniques, and the application of EUS was limited by its inability for stenotic tumors.^[8] There has been some meta-analysis including recent literature to assess the performance of MRI for rectal tumor staging, but there is no recent meta-analysis focusing on the comparative accuracy of MRI, CT, and EUS.^[9,10] Thus, we proposed this meta-analysis to obtain the comparative accuracy of MRI, CT, and EUS in rectal cancer staging in an attempt to define their present roles in clinical practice.

2. Methods

This is a meta-analysis and included previously published studies; thus, no ethical approval and patient consent are required.

2.1. Systematic literature search

Diagnostic accuracy studies for rectal cancer staging published between January 1, 2003 and December 31, 2015 were comprehensively searched from PubMed, EMBASE database, and Cochrane Library. We used following text words "Rectal Neoplasms" and "Neoplasm Staging" OR "Muscularis Propria" and "Diagnostic Imaging" OR "Magnetic Resonance Imaging" OR "Ultrasonography" (MeSH) OR "Tomography, X-Ray Computed". To identify relevant studies, reference lists of fulltext papers were retrieved and searched manually.

2.2. Study inclusion

Studies recruited in this analysis should meet all inclusion criteria: written in English or Chinese language; no less than 20 histologically proven primary rectal cancer patients; evaluation of rectal cancer staging using MRI, EUS, or CT; histopathology used as the reference standard; sufficient diagnostic accuracy data for T-staging; patients enrolled in a single group with tumor stages unknown at enrollment. If there were duplicate data reported, the study which reported the most detailed data or had the largest sample size was chosen.

All identified studies (titles and abstracts) were reviewed to judge whether they meet the inclusion criteria or not. Two raters assessed all searched studies independently. If disagreements appeared on study inclusion, they discussed first and a third reviewer was provided for arbitration who at last made the consensus.

2.3. Data extraction

Two raters extracted study information into the data extraction form (Supplementary table 1, http://links.lww.com/MD/B385) independently. The QUADAS-2 scale^[11] was used to extract quality-related information (Supplementary table 2, http://links.lww.com/MD/B385). Then 2 raters evaluated the quality of all



Table 1

Population and study characteristics of 89 studies included in the meta-analysis.

First author	Year	Country	Language	Study design	No.*	P-R [†]
Brown	2003	United Kingdom	English	Prospective	98	Half
Matsuoka	2003	Japan	English	Unclear	21	Unclear
Fuchsjäger	2003	Austria	English	Prospective	28/39	Half
Mathur	2003	United Kingdom	English	Unclear	35	Minority
Hsieh	2003	China	English	Unclear	67	No
Bali	2004	Greece	English	Prospective	29	No
Branagan	2004	United Kingdom	English	Unclear	40	No
Akin	2004	Turkey	English	Prospective	20	No
Kim	2004	South Korea	English	Retrospective	42	No
Manger	2004	Germany	English	Prospective	330	Unclear
Kauer	2004	Germany	English	Betrospective	458	No
Chen	2005	China	English	Inclear	50	Yes
Poon	2005	United Kingdom	English	Retrospective	42	Minority
Peschaud	2005	France	English	Prospective	38	Maiority
Santoro	2005	Italy	English	Inclear	94	No
Kun	2005	China	English	Betrospective	36	Ves
Forri	2005	Italy	English	Incloar	22	No
7ammit	2005	United Kingdom	English	Prospective	117	No
Vliogon	2005	The Netherlands	English	Rotrospective	83	Minority
Kim	2005	South Koroa	English	Uncloar	25	No
NIII Dtok	2000	Gormony	English	Droppotivo	2501	No
Chup	2000	Germany South Koroo	English	Prospective	3001	NO
Unun	2006	South Korea	English	Unclear	24	INO No
Jiang	2006	China	English	Unclear	53	INO
Dnamanaskar	2006	Canada	English	Retrospective	30	Unclear
Arii	2006	Japan	English	Prospective	53	INO
Liao	2006	China	Chinese	Unclear	117	NO
Sinha	2006	United Kingdom	English	Retrospective	57	Minority
Tatli	2006	United States of America	English	Retrospective	51	Half
Maor	2006	Israel	English	Unclear	91	Minority
Kim	2007	South Korea	English	Prospective	31	No
Strassburg	2007	United Kingdom	English	Retrospective	68	Minority
Mercury Group	2007		English	Prospective	300	No
Torkzad	2007	Sweden	English	Prospective	25	Yes
Videhult	2007	Sweden	English	Retrospective	91	Half
Badger	2007	United Kingdom	English	Unclear	95	Half
Rao	2007	China	English	Prospective	67	No
Allen	2007	United Kingdom	English	Retrospective	30	Yes
Halefoglu	2008	Turkey	English	Unclear	34	No
Cui	2008	China	Chinese	Retrospective	75	No
Dinter	2008	Germany	English	Unclear	23	No
Koh	2008	United Kingdom	English	Prospective	25	Yes
Donmez	2008	Turkey	English	Prospective	25	No
Futterer	2008	The Netherlands	English	Prospective	22	No
Goertz	2008	Germany	English	Prospective	333	Minority
Kim	2008	South Korea	English	Retrospective	42	No
Rafaelsen	2008	Denmark	English	Retrospective	134	No
Kulkarni	2008	United Kinadom	English	Prospective	80	Yes
Piippo	2008	Finland	English	Unclear	37	Minority
Zhang	2008	China	English	Unclear	38	Unclear
Xu	2008	China	English	Retrospective	156	Unclear
Kim	2008	South Korea	English	Prospective	57	No
Badovanovic	2008	Serbia	English	Unclear	44	Yes
Sunniah	2009	United Kingdom	English	Betrospective	49	Yes
Barbaro	2009	Italy	English	Prospective	53	Yes
Mezzi	2000	Italy	English	Prospective	39	Yes
	2009	China	English	Inclear	78	Unclear
Zorcolo	2009	Italy	English	Prospective	54	Minority
Reer-Gahel	2000	Israel	English	Betrospective	74	Minority
Pulathis	2003	Indian	English	Prospective	44	No
Dreeen	2000	The Netherlands	English	Betrospective	67	Vec
Λίζου	2009	lanan	English	Prospective	101	No
Cho	2003	South Kores	English	Prospective	20	Vae
Wong	2003	China	English	Retrospective	00 /10	No
Ving	2010	Ullilla Dopublic of Koros	English	nelluspective Potrosportive	40	NO
NIII	2010	China	EliyiiSH English	Droopootive	109	INO No
JIIIIIIY	2010	UIIIIa	EllUIISII English	Prospective	UC	INU Light
r.dill Tomokowo	2010	Australia	ELIGIISTI Engligh	neu uspeciive Potropostivo	23 50	Hali
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Table 1

(continued).						
First author	Year	Country	Language	Study design	No.*	P-R [†]
Engelen	2010	The Netherlands	English	Prospective	79	Yes
Ahmetoglu	2011	Turkey	English	Prospective	37	Minority
Jürgensen	2011	Germany	English	Prospective + retrospective	83	No
Sani	2011	Italy	English	Unclear	30	Half
Pastor	2011	Spain	English	Prospective	235	Yes
Maronea	2011	Italy	English	Prospective	162	Half
Karatag	2012	Turkey	English	Prospective	24	No
Yimei	2012	China	English	Prospective	69/60	No
Sun	2012	China	Chinese	Retrospective	245	Minority
Wang	2012	China	English	Unclear	189	No
Halefoglu	2013	Turkey	English	Prospective	87	No
Elena	2013	Spain	English	Prospective	70	No
Alberda	2013	The Netherlands	English	Prospective	55	Yes
Dar	2013	Indian	English	Prospective	38	No
Ghieda	2014	Egypt	English	Prospective	25	No
lannicelli	2014	Italy	English	Prospective	73	No
Feng	2014	China	English	Prospective	46	No
Kocaman	2014	Turkey	English	Retrospective	50	No
Kim	2015	Republic of Korea	English	Retrospective	77	Yes
Zhan	2015	China	English	Retrospective	94	Yes
Algebally	2015	Egypt	English	Prospective	56	No
Cai	2015	China	Chinese	Retrospective	80	No

* No. of patients in analysis.

[†] Preoperative therapy.





Summary estimates of sensitivity.	specificity and DOR for MRI. EUS	and CT in the tumor staging of rectal ca	ncer.

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Imaging modality	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)
MRI	0.89 (0.86, 0.91)	0.76 (0.71, 0.80)	26 (17, 38)
EUS	0.88 (0.85, 0.90)	0.79 (0.72, 0.84)	27 (17, 43)
CT	0.89 (0.77, 0.95)	0.80 (0.72, 0.86)	34 (11, 106)

CI = confidence interval, CT = computed tomography, DOR = diagnostic odds ratio, EUS = endoluminal ultrasound, MRI = magnetic resonance imaging.

included studies independently. Studies were considered as at "low risk of bias" or "low concern regarding applicability" if all domains of bias or applicability were assessed as "low". Studies were regarded as being "at risk of bias" or as having "concerns regarding applicability" if there was "high" or "unclear" judgment in 1 or more domain.

We extracted patient-level diagnostic accuracy data on rectal cancer staging from each study and reconstructed them into 2×2 tables by defining T3 and T4 as "tumors invading through the muscularis propria" and T2 and lower stages as "tumors confined to the muscularis propria". All tabulated results were extracted. When there were diagnostic accuracy results of more than 1 rater, we selected the one with the highest sensitivity for analysis.

2.4. Statistical method

Diagnostic accuracy data including sensitivity, specificity, and diagnostic odds ratio (DOR) was calculated for the 3 index methods using hierarchical summary receiver operating characteristic (SROC) model,^[12] which provides more between- and within-study variability, allowing of test stringency and accuracy to vary across studies. SROC curves were established to summarize true- and false-positive rates.

The heterogeneity was determined by subgroup analysis and SROC regression. The methodological quality rating items and sample size were included in the heterogeneity analysis. Then, subgroup analyses compared outcomes in the patients with and without preoperative therapy; the accuracy with high-resolution MRI (defined as slice thickness \leq 4 mm and matrix \leq 0.625) and without this technique; with high field strength MRI and without high field strength MRI. A second analysis was performed on studies which evaluated index tests directly. Publication bias was evaluated by using effective sample size funnel plots.^[13]

Statistical analyses was undertaken with STATA statistical package (version 10.0, STATA, College Station, TX, USA). *P* value less than 0.05 indicated statistical significance.

3. Results

3.1. Literature search and study selection

The initial search identified 1042 abstracts, 801 articles were excluded because of diagnostic information missing. A total of 241 articles were considered relevant and acquired for full-text reading. Finally, 89 articles were included for meta-analysis (Fig. 1, Table 1, Supplementary article list, http://links.lww.com/ MD/B385).

3.2. Summary of quality assessment

The studies included in this meta-analysis had an overall of 9141 patients (range: 20–3501 patients per study). Sixty-two studies (3887 patients) provided diagnostic accuracy data for MRI, 32 studies (6659 patients) used EUS, and 9 studies (407 patients)

Sensitivity, specificity, and DOR for T-staging in a priori defined subgroups.					
Modality	Study characteristic	No. of studies	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)
MRI	Neoadjuvant therapy				
	Yes	19	0.90 (0.80, 0.96)	0.72 (0.56, 0.84)	24 (10, 58)
	No	28	0.88 (0.82, 0.93)	0.76 (0.63, 0.88)	22 (12, 40)
	Partly	8	0.85 (0.76, 0.91)	0.71 (0.57, 0.82)	15 (7, 32)
	Not specified	7	0.91 (0.81, 0.97)	0.82 (0.70, 0.91)	44 (13, 149)
	High resolution				
	Yes	21	0.93 (0.88, 0.96)	0.86 (0.76, 0.92)	68 (30, 154)
	No/not specified	41	0.86 (0.81, 0.89)	0.71 (0.65, 0.76)	15 (10, 22)
	Field strength				
	<u>≤</u> 1.5T	52	0.88 (0.84, 0.91)	0.74 (0.68, 0.79)	21 (15, 32)
	>1.5T	10	0.89 (0.84, 0.93)	0.85 (0.77, 0.90)	44 (23, 85)
EUS	Neoadjuvant therapy				
	Yes	7	0.78 (0.59, 0.90)	0.67 (0.33, 0.89)	8 (2, 33)
	No	16	0.90 (0.81, 0.94)	0.83 (0.71, 0.87)	36 (17, 76)
	Partly	2	ND [*]	ND [*]	ND*
	Not specified	7	0.91 (0.83, 0.96)	0.85 (0.73, 0.90)	54 (30, 101)
CT	Neoadjuvant therapy				
	Yes	1	ND [*]	ND [*]	ND [*]
	No	3	ND [*]	ND [*]	ND [*]
	Partly	0	ND*	ND*	ND^*
	Not specified	5	0.90 (0.76, 0.97)	0.76 (0.69, 0.87)	33 (10, 109)

CI = confidence interval, CT = computed tomography, DOR = diagnostic odds ratio, EUS = endoluminal ultrasound, MRI = magnetic resonance imaging.

* ND = not done.

Table 3







Figure 4. Summary receiver operating characteristic (SROC) curves comparing the diagnostic accuracy of high-field magnetic resonance imaging (MRI) (>1.5T) and nonhigh-field MRI (\leq 1.5T) for T-staging in rectal cancer patients. The red diamond represents the summary operating point for MRI with a field strength >1.5T. The blue diamond represents the summary operating point for MRI with a field strength \leq 1.5T. The blue diamond represents the summary operating point for MRI with a field strength \leq 1.5T. The dotted red and blue lines represent the corresponding 95% confidence intervals. Sensitivity is shown on the *y*-axis, and specificity on the *x*-axis. The solid red and blue lines represent the SROC curves.

used CT. Nine studies (439 patients) provided diagnostic accuracy data of 2 imaging tools (5 studies for MRI and EUS; 1 study for CT and EUS; and 3 studies for CT and MRI), and 2 studies provided data of MRI, CT, and EUS.

The quality assessment results are presented in Fig. 2. Six studies (6.7%) were judged at "low risk of bias", the other 83 studies (93.3%) were judged to be "at risk of bias". Forty studies (44.9%) were judged at "low concern regarding applicability", the other 49 studies (55.1%) were judged to have "concerns regarding applicability".

3.3. Diagnostic performance of MRI, CT, and EUS for Tstaging

Table 2 summarized the sensitivity, specificity, and DOR estimates of MRI, EUS, and CT.

EUS studies at "low risk of patient selection bias" produced inferior accuracy (P=0.04). MRI studies containing no less than 50 patients showed better performance than studies with small sample size (P=0.04). Neither sample size nor quality items played a role in diagnostic accuracy for CT studies.

EUS studies showed lower diagnostic accuracy in patients undergoing preoperative therapies (P = 0.03) than in patients not receiving neoadjuvant therapy. However, MRI studies presented no statistical difference between patients with and without preoperative therapies (P = 0.23) (Table 3).

Diagnostic accuracy was significantly higher in 21 studies using high-resolution MRI for T-staging than in 41 studies that did not use this technique (P=0.01; Table 2). SROC curves showing evidence of improvement in diagnostic performance using high-resolution MRI are shown in Fig. 3.



Figure 5. Summary receiver operating characteristic (SROC) curves comparing the diagnostic accuracy of the magnetic resonance imaging (MRI), computed tomography (CT), and endoluminal ultrasound (EUS) for T-staging in rectal cancer patients. The red diamond represents the summary operating point for MRI. The blue diamond represents the summary operating point for EUS. The green diamond represents the summary operating point for CT. The dotted lines represent the corresponding 95% confidence intervals. Sensitivity is shown on the *y*-axis, specificity on the *x*-axis. The solid lines represent the SROC curves.

Table 4

Comparisons of diagnostic accuracy for T-staging between 3 imaging tools.

Comparisons	Р
High resolution	
MRI vs EUS	0.06
MRI vs CT	0.24
MRI (>1.5T)	
vs EUS	0.35
vs CT	0.66
Sample >50	
MRI vs EUS	0.44
MRI vs CT	0.78
EUS vs CT	0.49
MRI vs EUS	
Without neoadjuvant therapy	0.39
With neoadjuvant therapy	0.55
Studies with low risk of patient selection bias	
MRI vs EUS	0.83
MRI vs CT	0.16
EUS vs CT	0.75

CT = computed tomography, EUS = endoluminal ultrasound, MRI = magnetic resonance imaging.

Seven studies using MRI with a field strength >1.5 T showed higher diagnostic accuracy than MRI studies where the field strength was ≤ 1.5 T (P=0.04; Table 3). SROC curves showing evidence of improvement in diagnostic performance using MRI with a field strength >1.5 T are shown in Fig. 4.

3.4. Comparative accuracy of MRI, CT, and EUS for Tstaging

The diagnostic accuracy for rectal cancer staging was similar among MRI, EUS, and CT (MRI vs EUS, P=0.58; MRI vs CT, P=0.77; EUS vs CT, P=0.89). Figure 5 presented the corresponding SROC curves.

High-resolution MRI showed similar accuracy for rectal cancer staging compared with CT (P=0.24) and EUS (P=0.06) (Table 4). High field strength MRI (>1.5 T) also yielded equivalent diagnostic performance compared with CT (P=0.66) and EUS (P=0.35) (Table 4).

There was no statistical difference between MRI and EUS for rectal cancer staging in patients with preoperative therapies (P = 0.55). MRI, CT, and EUS also showed comparable accuracy when only studies at low risk of patient selection bias were considered. Moreover, MRI, CT, and EUS studies with large sample size (\geq 50 subjects) also presented similar performance (Table 3).

There were no differences for tumor staging between either of the 2 modalities (Table 5).

3.5. Publication bias

The analysis showed that EUS studies yielded statistically significant publication bias (P=0.01), and studies with smaller sample size were inclined to yield higher diagnostic accuracy. On the contrary, there was no statistically significant publication bias in MRI and CT studies. Effective sample size funnel plots are presented in Fig. 6.

4. Discussion

In this meta-analysis, high-resolution MRI and MRI with higher field strength (>1.5 T) showed higher diagnostic accuracy for rectal cancer staging. High-resolution MRI has been increasingly used on account of its accurate spatial depiction of tumor^[6] and thus can better identify T3/4 tumors from T1/2 tumors. MRI with higher field strength produces images with increased signal-tonoise ratio,^[14] which also promote accurate judgment of muscularis propria invasion.

MRI has an obviously wider range of application than EUS which is only applicable to nonstenotic patients and is free of radiation compared with CT. Thus, MRI should be recommended as the first choice for patients with rectal cancer undergoing radiologic examinations. EUS provides a complementary method for patients with early-stage cancer which has been identified by MRI.

Lower diagnostic accuracy for rectal cancer staging was observed with MRI and EUS in patients who received neoadjuvant therapies than in patients undergoing surgery directly. However, only EUS studies showed a statistically significant decline in diagnostic accuracy for T-staging of rectal cancer. Thus, MRI should be recommended for restaging after neoadjuvant therapy. Furthermore, evaluation for tumor stages is important for assessing therapeutic efficacy, thus MRI is also the best choice for the first tumor staging in rectal cancer patients with neoadjuvant therapy.

Meanwhile, EUS studies with large sample size were inclined to be less accurate for rectal cancer staging according to the regression analysis and funnel plots. This finding suggests that high-quality diagnostic accuracy studies with large sample sizes are needed to validate the performance of EUS for tumor staging.

This meta-analysis has several limitations. Most studies reported inadequate information on patient selection, index test, reference standard, and flow and timing (as signaling questions listed in Supplementary table 1, http://links.lww.com/MD/B385), thus we cannot conduct further analysis on quality-related items. In addition, publication bias might be introduced from inclusion of studies written in English or Chinese only. Although the advantage of MRI was attributed to the use of high-resolution or >1.5-T MRI, few studies provided data on these aspects to enable direct comparison of high-resolution MRI or >1.5-T MRI with EUS or CT.

Table 5						
Direct comparison of diagnostic accuracy of MRI, EUS, and CT in T-staging.						
Pairs	No. of studies	Modality	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	
MRI vs EUS	5	MRI	0.88 (0.73-0.97)	0.75 (0.56-0.89)	23 (5–115)	
		EUS	0.88 (0.72-0.97)	0.66 (0.43-0.84)	14 (3-42)	
MRI vs CT	3	MRI	0.92 (0.71-0.99)	0.72 (0.37-0.91)	28 (4-196)	
		CT	0.89 (0.49–0.99)	0.75 (0.54–0.88)	29 (3–280)	

CI = confidence interval, CT = computed tomography, DOR = diagnostic odds ratio, EUS = endoluminal ultrasound, MRI = magnetic resonance imaging.



Figure 6. Funnel plot of the reciprocal of effective sample size plotted on the *y*-axis against the diagnostic odds ratio plotted on the *x*-axis. The regression line is used as a measure of asymmetry. The circles represent included studies. (A) Magnetic resonance imaging studies, (B) endoluminal ultrasound studies, and (C) computed tomography studies.

Our results suggest that patients with rectal cancer should initially undergo an MRI examination for tumor staging. Those with MRI-defined T1/T2 disease may be candidates for subsequent EUS examination. We also recommend using MRI instead of EUS for patients with neoadjuvant therapy. Highresolution MRI should be used routinely together with 3-T MRI if conditions allow. These techniques provide excellent discrimination between T2 and borderline T3 cancers.

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