RESEARCH ARTICLE

Diagnostic Value of Endorectal Ultrasound in Preoperative Assessment of Lymph Node Involvement in Colorectal Cancer: a Meta-analysis

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Abstract

Background: Nodal invasion by colorectal cancer is a critical determinant in estimating patient survival and in choosing appropriate preoperative treatment. The present meta-analysis was designed to evaluate the diagnostic value of endorectal ultrasound (EUS) in preoperative assessment of lymph node involvement in colorectal cancer. Materials and Methods: We systematically searched PubMed, Web of Science, Embase, and China National Knowledge Infrastructure (CNKI) databases for relevant studies published on or before December 10th, 2014. The sensitivity, specificity, likelihood ratios, diagnostic odds ratio (DOR) and area under the summary receiver operating characteristics curve (AUC) were assessed to estimate the diagnostic value of EUS. Subgroup analysis and meta-regression were performed to explore heterogeneity across studies. Results: Thirty-three studies covering 3,016 subjects were included. The pooled sensitivity and specificity were 0.69 (95%CI: 0.63-0.75) and 0.77 (95%CI: 0.73-0.82), respectively. The positive and negative likelihood ratios were 3.09 (95%CI: 2.52-3.78) and 0.39 (95%CI: 0.32-0.48), respectively. The DOR was 7.84 (95%CI: 5.56-11.08), and AUC was 0.80 (95%CI: 0.77-0.84). Conclusions: This meta-analysis indicated that EUS has moderate diagnostic value in preoperative assessment of lymph node involvement in colorectal cancer. Further refinements in technology and diagnostic criteria are necessary to improve the diagnostic accuracy of EUS.

Keywords: Endoscopic ultrasound - colorectal cancer - preoperative staging - lymph node - meta-analysis

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Introduction

Colorectal cancer (CRC) is the third most commonly occurring cancer and is one of the leading causes of cancer-related deaths worldwide (Jemal et al., 2010). In the US, CRC is the third most commonly diagnosed cancer in men and women and is the second leading cause of cancer deaths (Jemal et al., 2010). CRC incidence rates are comparatively lower in Africa and Asia relative to the US; however, recent studies indicate that colorectal cancer is on the rise in African and Asian countries, including China (Abdulkareem et al., 2008; Jung et al., 2010). Historically, the incidence of CRC in China has been low, but cases of CRC have been increasing in recent years due to dietary and lifestyle changes. In 2009, colorectal cancer became the third most commonly diagnosed cancer with an incidence rate of 29.44 /100000 per year, and the fifth highest cause of cancer-related deaths with a mortality rate of 14.23/100000 per year (Chen et al., 2013). The five-year survival rate of CRC has improved, but currently remains steady at approximately 60%, even in highly developed countries (Brenner et al., 2012; Majek et al., 2012). In addition to tumor size, location, and degree of differentiation, local TNM staging of colorectal cancer is an important factor in the prognosis of CRC, and depth of tumor spread beyond the rectal wall is as also an important prognostic indicator (Ramesh et al., 2006; Tokoro et al., 2009). Furthermore, development of new surgical techniques and use of neoadjuvant therapies have modified the management and improved the prognosis of colorectal cancer in recent years. For example, transanal local excision or transanal endoscopic microsurgery are suitable for colorectal cancers stage T1 or lower; total mesorectal excision is recommended for stages T2 and T3, and stage T4 patients benefit greatly from preoperative neoadjuvant therapy (Chen et al., 1994; Akasu et al., 2000; Blair and Ellenhorn, 2000). Nodal invasion in colorectal cancer constitutes locoregional spread, which plays a pivotal role in estimating survival and determining the appropriate treatment regimen, and is associated with reduced patient survival. In these patients, preoperative high-dose radiation and 5-FU-based chemotherapy improves resectability rates with possible local control as well as improved survival. The selection of suitable treatment strategies for colorectal cancer prior to surgery

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is based on preoperative lesion staging, thus accurate preoperative staging of colorectal cancer is critical. Endorectal Ultrasound (EUS) is a well-established method for imaging colorectal tumors, and is particularly useful for assessing the invasive depth of a lesion (T staging). Systematic evaluation of EUS in CRC indicates that the overall accuracy of EUS ranges from 74.0% to 94.0% for T staging (Puli et al., 2009a). Previous studies have shown, however, that the accuracy for the N staging varies widely, from 52.9% to 91.4% (Zhou et al., 2003; Halefoglu et al., 2008; Haji et al., 2012). To date, only a single meta-analysis has been conducted to evaluate the diagnostic value of EUS in assessing lymph node involvement by rectal cancers, with a pooled sensitivity of 73.2% and specificity of 75.8% (Puli et al., 2009b). The aim of the current meta-analysis is to evaluate accuracy of EUS in preoperative assessment of lymph node involvement in colorectal cancer as compared to postoperative pathological staging of the resected surgical specimen in order to assist management decisions in patients with CRC.

Materials and Methods

Literature search

A thorough search of Medline, EMBASE, Web of Science and CNKI (up to December 10th, 2014) was performed to identify eligible studies. The following search terms were employed: ("rectal cancer" OR "rectal carcinoma" OR "colon cancer" OR "colon carcinoma" OR "colorectal cancer" OR "colorectal carcinoma") AND ("endoscopic ultrasound" OR EUS OR "endosonography"), without language restrictions. The reference lists of retrieved articles were searched to identify additional relevant citations.

Selection criteria

Selection criteria were as follows: (1) endorectal ultrasound was used in preoperative lymph node staging of colorectal cancer; (2) postoperative pathologic staging of colorectal cancer was used as the reference standard; (3) results were reported as numbers of true-positive, false-positive, true-negative, and false-negative, or sufficiently detailed data were presented to derive these numbers. The following exclusion criteria were used: (1) case reports, reviews, conference, letters and editorials; (2) analysis of gastrointestinal tumors with no specific results regarding colorectal cancer; (3) sample size less than 50; (4) papers written in a non-English language. For multiple or duplicate publications that analyzed the same dataset, only the most recent or complete study was included.

Data extraction and quality assessment

Two investigators independently extracted data using a standardized form containing the following variables: first author, publication year, patients' geographical location (Western or Asian), sample size, mean age of patients, proportion of female patients, tumor types (rectal cancer, colon cancer or colorectal cancer), preoperative adjuvant therapy, and EUS probe frequency. Any disagreement between the two investigators was resolved by consensus. The methodology quality for each study was assessed using the quality assessment of diagnostic accuracy studies (QUADAS) (Whiting et al., 2003). This scoring system consists of 14 items phrased as yes/no questions, with a "yes" answer receiving a score of 1, and a "no" answer receiving a score of 0. Studies with scores of seven or greater were considered to be of high-quality.

Statistical analysis

The accuracy data from each study (true positives, false positives, true negatives and false negatives) were extracted to obtain pooled sensitivity, specificity, diagnostic odds ratio (DOR) as well as their 95% confidence intervals [95%CI]. Forrest plots were constructed to indicate the point estimates in each study relative to the summary pooled estimate. Likelihood ratios for EUS were pooled and presented graphically as scattergrams. Finally, data were pooled in summarized receiver-operating characteristic curves (sROC), where the area under the sROC (AUC) reflects test precision. Heterogeneity was evaluated using a Cochran's chi-square test and quantified by calculating the I^2 statistic to reflect the degree of variability in results across studies. To assess any potential confounding factors, including the patient's location (Western *vs* Asian), tumor types (rectal cancer *vs* colon cancer and colorectal cancer), sample size (over 100 *vs* less than 100), and preoperative adjuvant therapy (yes, partial, no or unclear), subgroup analysis and meta-regression were performed, taking into account the above factors.

In order to test for publication bias, Deek's funnel plot method was applied. Statistical analyses were performed using the Midas module in Stata software (Version 10.0), and all P-values were calculated as two-sided. The association was considered significant if the P- value was less than 0.05.

Results

Characteristics and methodological quality of include studies

The database search produced 1903 studies, of which 680 were excluded for duplication, leaving 1223 potentially relevant studies to be retrieved. Following a title and abstract search of these 1223 studies, 1066 were excluded and full-text versions of the remaining 157 were retrieved. Among these, 29 studies were excluded due to a sample size of less than 50, 3 were excluded for duplication, and 54 studies were removed due to staging only of the depth of tumor invasion (T stage). Another 38 studies were excluded for containing insufficient data needed to calculate sensitivity and specificity. In total, 33 studies were eligible for inclusion in this meta-analysis (Beynon et al., 1989; Tio et al., 1991; Lindmark et al., 1992; Glaser et al., 1993; Detry et al., 1996; Akasu et al., 1997; Osti et al., 1997; Rau et al., 1999; Spinelli et al., 1999; Hunerbein et al., 2000; Akahoshi et al., 2001; Chen WP et al., 2001; Mo et al., 2002; Stergiou et al., 2003; Zhou et al., 2003; Kulinna et al., 2004; Hurlstone et al., 2005; Knaebel et al., 2005; Zammit et al., 2005; Kim et al., 2006; Badger et al., 2007; Huh et al., 2008; Ju et al.,

2009; Wang J et al., 2009; Li JT et al., 2009; Li et al., 2010; Jurgensen et al., 2011; Marone et al., 2011; Pastor et al., 2011; Yimei et al., 2012; Fu HW, 2012; Du P et al., 2012; Zhu et al., 2013) (Figure 1); the characteristics of the included studies are detailed in Table 1.

The quality assessments of the included studies are presented in Figure 2. Of the 14 QUADAS items, items 1 (spectrum composition) and 2 (selection criteria) describe the variability of the studies, while items 8 (index test execution), 9 (reference standard execution) and 13 (uninterpretable test results) assess the quality of the reporting, the remaining QUADAS items refer to study bias. QUADAS scores of the studies ranged from 9 to 14 with a median score of 10. Most data sets suffered from selective patient sampling (90.9%), optimal description of index test (90.9%) while suboptimal description of reference test (69.7%), and poor description of selection criteria (39.4%). QUADAS item 11 (blinding for index test results) was only 18.2% fulfilled by the studies, which reflects unclear reporting. The remaining QUADAS items achieved a level of 100%, with the exception of item 7(no incorporation bias), item 10 (blinding for reference test results), item 13 (uninterpretable test results), item 14 (withdrawals explained), which were 97.0%, 97.0%, 81.8% and 90.9% fulfilled by the studies respectively.

Meta-analysis and heterogeneity

Diagnostic meta-analysis of these 33 studies containing 3,016 subjects indicated a summary sensitivity of 0.69 (95%CI: 0.63-0.75) and specificity of 0.77 (95%CI:

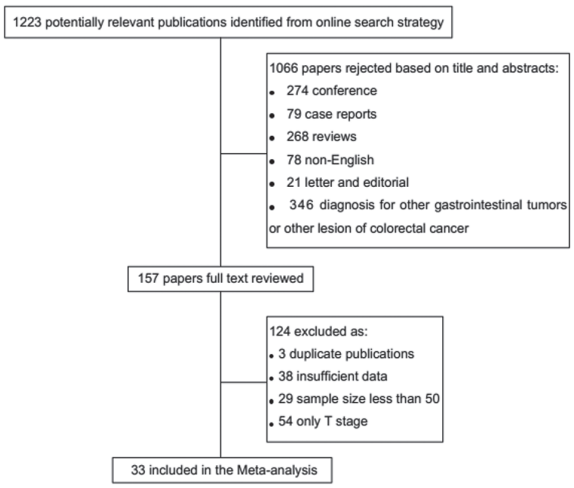

Figure 1. Study Flow Chart for the Process of selecting the Eligible Publications

Table 1. Characteristics of Studies Included in the Meta-analysis

First Author	Year	Country	Tumor	Sample Size	Mean Age	Female%	Preoperative Adjuvant Therapy	Probe Frequency (MHz)
Zhu	2013	China	rectal cancer	110	61.1	35.5	unclear	5-10
Fu	2012	China	rectal cancer	74	62.2	44.6	unclear	5-9
Yimei	2012	China	rectal cancer	60	62.0	-[a]	no	15
Du	2012	China	colorectal cancer	56	65.0	37.5	unclear	12-20
Pastor	2011	Spain	rectal cancer	235	-[a]	55.0	yes	5-20
Jürgensen	2011	Germany	rectal cancer	78	66.0	40.0	no	20
Marone	2011	Italy	rectal cancer	159	60.0	32.5	part	7.5
Li	2010	China	rectal cancer	50	67.0	28.0	no	7.5
Wang	2009	China	rectal cancer	56	60.4	30.0	unclear	5.0-7.5
Ju	2009	China	rectal cancer	78	61.0	46.2	unclear	8
LI	2009	China	rectal cancer	86	61.6	40.0	unclear	--
Huh	2008	Korea	rectal cancer	51	54.0	37.3	yes	7.5-10
Badger	2007	UK	rectal cancer	93	66.6	63.2	part	--
Kim	2006	Korea	rectal cancer	78	57.0	29.1	part	5-7.5
Knaebel	2005	Germany	rectal cancer	310	61.0	32.8	part	7-10
Zammit	2005	UK	rectal cancenr	60	70.5	5.0	no	10
Hurlstone	2005	UK	colorectal cancer	93	66.0	-[a]	unclear	12.5
Christiane	2004	Germany	rectal Cancer	63	65.0	40.2	part	7.5-10
Zhou	2003	China	colorectal cancer	75	63.0	54.7	unclear	12-20
Stergiou	2003	Germany	colonic cancer	50	68.5	24.1	unclear	12
Mo	2002	China	colonic cancer	73	-[a]	52.1	unclear	7.5
Akahoshi	2001	Japan	colorectal cancer	114	68.0	43.4	unclear	12
Chen	2001	china	colorectal cancer	50	51.0	78.6	unclear	12
Hunerbein	2000	Germany	colorectal cancer	55	62.0	44.4	unclear	12.5
Spinelli	1999	Italy	rectal cancer	71	62.0	38.0	no	7.5/12 or 7.5
Rau	1999	Germany	rectal cancer	84	-[a]	-[a]	yes	7.5-10
Osti	1997	Italy	rectal cancer	53	61.0	46.3	unclear	7
Akasu	1997	Japan	rectal cancer	164	59.0	35.4	no	7.5-12
Detry	1996	Belgium	rectal cancers	54	-[a]	-[a]	unclear	--
Glaser	1993	Germany	rectal cancer	144	-[a]	-[a]	no	7.0
Lindmark	1992	Sweden	rectal cancer	53	-[a]	-[a]	unclear	7.0
Tio	1991	Netherlands	colorectal cancer	91	65.4	35.2	unclear	7.5
Beynon	1989	UK	rectal cancer	95	67.5	44.0	unclear	5.5-7.0

*a, the information was not provided in the study

0.73-0.82) in the preoperative assessment of lymph node involvement in colorectal cancer as compared to postoperative pathological staging. Forest plots indicated the relative strength of the diagnostic accuracy of Endorectal Ultrasound (Figure 3), and graphical representation of likelihood ratios has been shown to aid clinical decision making by allowing rapid visual assessment of the usefulness of a diagnostic test. The likelihood ratios for EUS tests were pooled and are graphically presented in scattergrams (Supplementary Figure 1). The positive and negative LRs of the studies were 3.09 (95%CI: 2.52-3.78) and 0.39 (95%CI: 0.32-0.48), respectively, suggesting that EUS was insufficient to exclude or confirm lymph node metastasis in colorectal cancer. The pooled diagnostic odds ratio was 7.84 (95%CI: 5.56-11.08) (Supplementary Figure 2), and the area under the sROC was 0.80 (95%CI: 0.77-0.84), indicating moderate precision of EUS (Figure 4).

Significant heterogeneity was observed both in sensitivity (Q=150.67; p≤0.01; I^2=78.76%) and specificity (Q=159.01; p≤0.01; I^2=79.88%). To explore possible sources of this heterogeneity, subgroup analyses were conducted with respect to the patient's geographical location, sample size, tumor type, and preoperative adjuvant therapy. We observed significant heterogeneity in sensitivity and specificity in all subgroups, with the exception of the preoperative adjuvant therapy, in which heterogeneity of studies with no treatment was not statistically significant for specificity (I^2=13.68%;

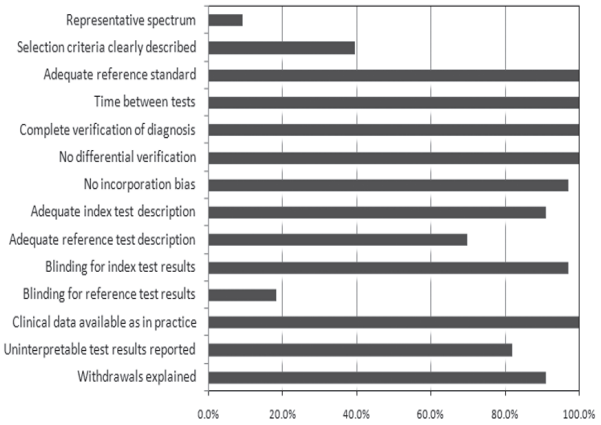

Figure 2. The Methodological Quality Assessments of Studies Included in the Meta-analysis. The vertical coordinate presents 14 QUADAS items of the quality assessment of diagnostic accuracy studies (QUADAS); the horizontal axis presents percentages of 14 QUADAS items fulfilled by studies included in the meta-analysis

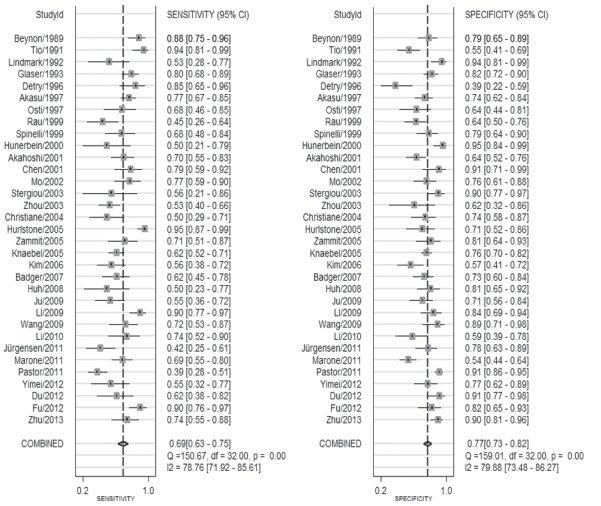

Figure 3. Forest Plots of the Pooled Sensitivity and Specificity of Endorectal Ultrasound in Preoperative Assessment of Lymph node Involvement in Colorectal cancer. The black squares in the gray squares and the horizontal lines represent the point estimate and 95% confidence interval (CI), respectively. The dotted line represents the pooled estimate, and the diamond shape represents the 95%CI of the pooled estimate

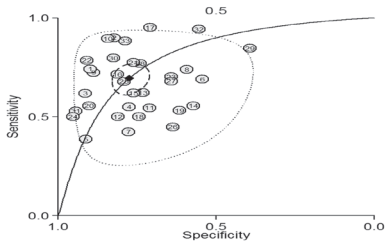

Figure 4. ROC Curve Analyses of Endorectal Ultrasound in Preoperative Assessment of Lymph node Involvement in Colorectal Cancer. AUC=0.80[0.77-0.84], sensitivity=0.69 [0.63-0.75], specificity=0.77[0.73-0.82]

Table 2. Subgroup Analysis Based on four Confounding Factors

Subgroup	Studies	SEN (95% CI)	I^2(SEN, *p* value)	SPE (95%CI)	I^2(SPE, *p* value)	AUC(95%CI)
Patient's location						
Western	18	0.68 (0.58-0.77)	83.59 (<0.01)	0.77 (0.69-0.83)	85.29 (<0.01)	0.80 (0.76-0.83)
Asian	15	0.71 (0.64-0.77)	68.01 (<0.01)	0.78 (0.71-0.83)	66.68 (<0.01)	0.81 (0.77-0.84)
Sample size						
Small[a]	26	0.70 (0.62-0.77)	77.65 (<0.01)	0.77 (0.72-0.82)	72.55 (<0.01)	0.81 (0.77-0.84)
Large[b]	7	0.68 (0.57-0.76)	84.26 (<0.01)	0.78 (0.67-0.86)	90.95 (<0.01)	0.78 (0.75-0.82)
Tumor type						
Rectal cancer	24	0.67 (0.61-0.74)	76.99 (<0.01)	0.77 (0.71-0.81)	79.93 (<0.01)	0.79 (0.75-0.82)
Others[c]	9	0.75 (0.59-0.85)	84.06 (<0.01)	0.81 (0.69-0.88)	81.08 (<0.01)	0.85 (0.81-0.88)
Therapy						
Yes or Part	8	0.56 (0.48-0.64)	59.67 (0.02)	0.74 (0.64-0.82)	87.24 (<0.01)	0.66 (0.62-0.70)
No	7	0.69 (0.59-0.77)	68.74 (<0.01)	0.77 (0.72-0.81)	13.68 (0.33)	0.78 (0.74-0.81)
Unclear	18	0.76 (0.68-0.83)	78.64 (<0.01)	0.80 (0.73-0.86)	80.88 (<0.01)	0.85 (0.82-0.88)

*SEN, sensitivity; SPE, specificity; 95% CI, 95% confidence intervals; a, the sample size <100; b, the sample size ≥100; c, colon cancer and colorectal cancer

p=0.33). However, heterogeneity was adverse in studies in which all or some patients received treatment (I^2=87.24%; p=0.02) and in studies which did not state whether or not patients received treatment (Table 2). Subsequently, meta-regression analysis was conducted based on these confounding factors in order to determine the source of heterogeneity. The meta-regression analysis indicated that preoperative adjuvant therapy was responsible for influencing heterogeneity for sensitivity (p<0.001), and patient's geographical location (p<0.01), tumor types (p=0.01), sample size (p=0.02) and preoperative adjuvant therapy were found to be sources of heterogeneity for specificity.

Lastly, funnel plots for the diagnostic value of EUS did not reveal any obvious asymmetry, with all P-values of the Egger's test greater than 0.1 (Supplementary Figure 3). Therefore, it was determined that publication bias did not have a statistically significant effect on this meta-analysis.

Discussion

EUS is the most commonly used imaging technique and is considered to be the most important modality for preoperative staging of colorectal tumor. EUS performance has been verified in clinical practice for assessing local invasion of colorectal tumors into the large bowel wall (T stage). However, published data on the accuracy of EUS in assessing lymph node involvement is inconsistent. The present meta-analysis confirms that EUS was of moderate diagnostic value in assessing lymph node involvement with respect to sensitivity (0.69, 95%CI: 0.63-0.75), specificity (0.77, 95%CI: 0.73-0.82) and AUC (0.80, 95%CI: 0.77-0.84). Our results must be interpreted with caution, as the LRs did not meet the criteria of positive LR greater than 10.0 and negative LR less than 0.1, which made it difficult for EUS to exclude or confirm lymph node metastasis in colorectal cancer.

Although this study provides a comprehensive assessment of the diagnostic value of EUS in preoperative staging of nodal invasion, several caveats should be taken into account when interpreting the results. First, the majority of studies included in this meta-analysis were either retrospective or consecutive, with a limited number of prospective studies. Second, the methodological quality varied greatly across studies. QUADAS scores of the studies ranged from 9 to 14, and QUADAS analysis of study quality indicated that the representative spectrum of patients who will receive the test in practice is fulfilled only by 9.1% of the studies included, and the selection criteria is poor described(39.4%), which indicated that the variability across studies is great. Third, the sources of observed heterogeneity were not conclusively identified, as the heterogeneity could not be fully accounted for using subgroup analysis or meta-regression analysis.

Heterogeneity was statistically significant for both EUS sensitivity and specificity. Subgroup analyses revealed that stratification of the confounding factors did not remove the heterogeneity for sensitivity. For specificity, heterogeneity was not statistically significant in studies with no preoperative adjuvant therapy (I^2=13.68%; p=0.33). However, heterogeneity was adverse in studies in which some or all patients received treatment (I^2=87.24%; p=0.02) and in studies lacking information on whether or not patients received treatment. Meta-regression analysis suggested that preoperative adjuvant therapy contributed most to the heterogeneity of sensitivity, and the patient's geographical location, tumor type, sample size and preoperative adjuvant therapy were responsible for influencing the heterogeneity of specificity, with no contribution from confounding factors. The heterogeneity among studies conducted in different geographical locations is primarily attributable to variations in EUS instruments and in the level of endoscopists' experience. More sophisticated and advanced EUS instruments are being used in developed Western countries. Ethnic differences in lifestyle, particularly in dietary patterns, which have been reported to play a significant role in CRC development, may also influence the diagnostic accuracy of EUS in assessing lymph node invasion. The heterogeneity in specificity among studies with different tumor types may also be due to morphological differences between rectal cancer and colon cancer, which can influence the diagnostic accuracy of EUS. The heterogeneity from preoperative adjuvant therapy may be due to over-staging of colorectal cancer patients who have received preoperative adjuvant therapy as radiotherapy, which is part of preoperative adjuvant therapy induced edema, inflammation, necrosis, and fibrosis of the colorectal wall. And these local changes of the colorectal wall cannot be precisely differentiated from the tumor itself by EUS, which also affects the diagnostic accuracy of EUS.

In recent years, apart from EUS, noninvasive radiologic modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have also proven their importance and are widely used diagnostic tools in the assessment of depth of cancer invasion and/or lymph node involvement. However, EUS has been reported to be superior to CT imaging in this clinical context (Kwok et al., 2000; Bipat et al., 2004). EUS and MRI are adequate and comparable techniques for T and N staging of colorectal cancer. EUS outperforms MRI in imaging of early-stage cancers, and it is possible to perform EUS-guided fine-needle aspiration (FNA), which is significantly more accurate than EUS alone in the diagnosis of recurrent rectal cancer, especially in specificity (negative result). However, unlike EUS, MRI is not influenced by tumor stenosis, it allows exclusion of distant metastasis, and is able to identify the mesorectal fascia, which is crucial for predicting tumoral involvement of the circumferential resection margin. Furthermore, the use of newer techniques including novel lymph node–specific MR imaging contrast agents (ultrasmall iron-based particles taken up by the lymphatic system) may provide a more sensitive MRI method to detect lymph node involvement (Bipat et al., 2004; Fernandez-Esparrach et al., 2011). As a result, combined use of EUS and MRI may be optimal for diagnosing lymph node involvement in colorectal cancer.

The present meta-analysis indicates that EUS had moderate diagnostic accuracy for preoperative assessment of lymph node involvement in colorectal cancer, with moderate sensitivity and specificity, and suboptimal

AUC. Verification of the diagnostic performance of EUS requires a large-scale prospective study to be conducted, and further refinements in EUS technologies and diagnostic criteria are needed to improve its diagnostic accuracy. Importantly, combined use of EUS and MRI is promising in diagnosing lymph node involvement in colorectal cancer.

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