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ORIGINAL ARTICLE

Estimation of invasion depth of early colorectal cancer using EUS and NBI-ME: a meta-analysis

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Abstract

Background Endoscopic ultrasonography (EUS) and narrow band imaging-magnifying endoscopy (NBI-ME) are often used as diagnostic tools to estimate the depth of invasion in early colorectal cancer (CRC). The aim of this study was to compare NBI-ME with EUS in distinguishing between slight submucosal invasion (invasion depth < 1000 μm) and massive submucosal invasion in patients with early CRC, since slight submucosal invasion is currently considered as an indication for endoscopic resection.

Methods For this meta-analysis, relevant studies were identified from PubMed, Embase, Web of Science, Scopus and the Cochrane Library databases between January 1997 and September 2016. Data on the yield of tumors were extracted, pooled, and analyzed by stata12.0 software. The sensitivity, specificity, positive likelihood ratio and negative likelihood ratio in differentiating slight submucosal invasion from massive submucosal invasion were calculated for both diagnostic modalities.

Results Sixteen studies involving 2197 lesions were included: nine were studies on EUS and 7 were studies on NBI-ME. The pooled sensitivity of EUS was 0.902 (95% CI 0.863–0.930), the specificity was 0.877 (95% CI 0.810–0.922), the positive likelihood ratio was 7.314 (95% CI 4.551–11.755) and the negative likelihood ratio was 0.112 (95% CI 0.076–0.164). The pooled sensitivity and specificity of NBI-ME were 0.981 (95% CI 0.949–0.993) and 0.651 (95% CI 0.600–0.699), respectively, the positive likelihood ratio was 2.815 (95% CI 2.432–3.258) and the negative likelihood ratio was 0.029 (95% CI 0.010–0.080).

Conclusions The sensitivity tended to be higher in ME-NBI than EUS for early CRC with slight submucosal invasion, whereas the specificity was significantly lower in NBI-ME than in EUS.

Keywords Invasion depth · Endoscopic ultrasonography · Narrow band imaging-magnifying endoscopy · Early colorectal cancer

Introduction:

Colorectal cancer (CRC) is the third most common malignancy and the third leading cause of cancer-related deaths in the world [1]. It is a devastating disease with a significant impact on patients' lives and on healthcare systems throughout the world. Early diagnosis and treatment could greatly improve the prognosis [2].

Surgery is the traditional treatment, but it is in old patients in poor general health surgery is associated with high mortality and morbidity [3]. In these situations, endoscopic treatments, such as endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD), may offer alternatives to surgery for early CRC [4]. It should be noted that the selection of a treatment method for early CRC, especially determination of the indication for endoscopic treatment, is very important in clinical practice.

Mucosal cancer (M) and CRC with slight submucosal invasion (SM_s, invasion depth < 1000 μm) are currently considered as an indication for endoscopic resection because lymph node metastasis is rare [5, 6]. In contrast, cancers with massive submucosal invasion (SM_D; 1000 μm or

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deeper) have a 10–15% risk of metastasis and must be surgically treated by colectomy with lymph node dissection [5].

Therefore, the most important step in choosing the therapeutic strategy for early CRC is to determine the invasion depth before treatment. Endoscopic ultrasonography (EUS) and narrow band imaging-magnifying endoscopy (NBI-ME) have often been used as diagnostic tools to determine the invasion depth of early CRC.

EUS can produce axial images of the tumors, which could help to objectively diagnose the depth of tumor invasion by detecting the invasion of the normal layered structure of the colorectal wall [7]. The normal colonic wall has a five-layer structure in the images of EUS. The first and second layers are the mucosal layers, the third layer corresponds to the submucosal layer, the fourth layer is the muscularis propria, and the fifth layer is the serosa [8]. NBI is an optical image enhancement technology: the band of an optical filter in a frame-sequential type video endoscope is narrowed, shifted to the short wavelength side, and the penetration depth of the observation light is localized to the mucosal surface layer. Three short wavelength light beams of 500, 445, and 415 nm are used, and each has a bandwidth of 30 nm [9, 10]. Further combining the NBI system and ME brings a simple and clear visualization of capillary vessels and their fine structure in the surface layer [11, 12].

Compare NBI-ME with EUS for predicting the depth of tumor invasion in patients with early CRC.

Materials and methods

Search strategy

An electronic search was performed using PubMed Embase, Web of Science, Scopus and the Cochrane Library databases (January 1997–September 2016). The search terms ''colorectal''(or ''colon''), ''Narrow-Band Imaging'' (or ''NBI''), ''Endoscopic ultrasonography'' (or ''EUS''), ''invasion'' (or ''invasive'') and ''depth'' (or ''deep'') were used in combination with the Boolean operator AND or OR. Only studies on humans and in the English language were considered for inclusion. We did not restrict the search by patients' age and also manually searched the reference lists of eligible studies and textbooks. Furthermore, the reference lists of all the retrieved articles were examined to identify any additional articles missed during the initial search.

Study selection

Two investigators (GC and FY) read the abstracts and used a standardized data extraction form to identify potentially eligible articles. Then, they read the full text versions of these articles to determine whether they were eligible for inclusion in our study. Disagreements were resolved by discussion with a third investigator (TL).

The inclusion criteria were as follows:

1. Studies that used NBI-ME or EUS in measuring the invasion depth of early CRC.
2. Studies that compared NBI-ME or EUS with histopathology as the gold standard.
3. Studies with available data for constructing contingency tables for true positive, false positive, false negative and true negative.
4. Studies that were published as a full article.
5. Without age or gender restrictions.
6. More than ten patients included in the study.

The exclusion criteria were as follows:

1. Data without histological confirmation of lesions.
2. Studies with incomplete data.
3. Studies that overlapped the studies selected.
4. Articles about NBI not using the Hiroshima classification (Table 1).
5. Letters, editorials and expert opinions, review without original data, case reports or studies with fewer than ten cases.
6. Low quality of research according to the quality evaluation.

Table 1 Hiroshima classification

A type	Microvessel intensity is vague or invisible None or isolated lacy vessels may be present coursing across the lesion, Brown or black dots, star shaped or round surrounded by white
B type	Regular surface pattern of the increased microvessel intensity around the pits and image enhancement or regular meshed microvessel network pattern is observed
C type	
1	Irregular surface pattern of the increased microvessel intensity around the pits and image enhancement Thickness and distribution of vessels are homogenous
2	More irregular surface pattern of the increased microvessel intensity around the pits and image enhancement Thickness and distribution of vessels are heterogenous
3	Surface pattern is completely unclear Thickness and distribution or vessels are heterogenous. Avascular area (AVA) and scattered microvessel fragments are observed

Data extraction and assessment of study quality

Two investigators (GC and FY) independently extracted relevant data about the design and results of each study according to a standardized form. Observers were not blinded to the journal name, the authors' names, the authors' affiliations, or the year of publication since blinding to these study characteristics has been shown to be unnecessary [13]. To resolve disagreement between reviewers, another reviewer (WG) assessed all discrepancies and chose the majority opinion used for the analysis. Methodological quality of included studies was assessed independently by two observers (SZ) with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) used [14], which is a quality assessment tool specifically developed for systematic reviews of diagnostic accuracy studies. This scoring system consists of 14 items phrased as questions, with "yes", "no", or "unclear" as answer options. The questions are based on the reported study methodology and results. All questions answered are scored as 1 point. A score of 7 or more is seen as high-quality study.

To perform validity analyses, we extracted the following items from each study: (a) the first author; (b) publication year; (c) the study design (prospective, retrospective, or unknown); (d) the treatment.

Statistical analysis

We performed data analysis by STATA12.0 software. True positive, false positive, false negative and true negative were extracted. We constructed 2×2 tables that contained the number of early CRC cases. We then calculated sensitivity specificity and the diagnostic odds ratio (OR) as the ratio between true positive and false positives divided by the ration between true negative and false negative. Ninety-five percent confidence intervals for sensitivity, specificity, predictive values, the positive likelihood ratio and negative likelihood ratio were also calculated. The positive likelihood ratio is a measure of how well the test identified the disease, and the negative likelihood ratio assesses how well the same test performs in excluding the disease [15]. Values of the diagnostic OR, Q statistic, and area under the receiver operating curve (ROC) (AUC) [16] were used to analyze the diagnostic precision of NBI-ME or EUS. A higher diagnostic OR suggests a greater diagnostic precision [17]. Heterogeneity in meta-analysis refers to a high degree of variability in study results, which is a fairly common finding in diagnostic meta-analyses. Heterogeneity was explored by the Chi-square test and likelihood ratio (LR) I^2. If $p > 0.05$, while values of I^2 to 25% may be considered to represent low heterogeneity. We also introduced Deeks' funnel plot [18, 19] to investigate publication bias. When $p > 0.05$, no statistical publication bias was considered to be present.

Results

Literature search and study selection

The detailed procedure of study selection in the meta-analysis is shown in Fig. 1. The literature search identified 16 eligible studies published between 1997 and 2016. One hundred and forty-two initial studies were searched from all the databases. After reading the titles and abstracts, meetings, reviews, letters and other types of articles were excluded, and we reviewed 85 studies in detail. Sixty-nine were excluded altogether because (a) the contents of the articles were not about the invasion depth of NBI or EUS for the early CRC ($n = 26$); (b) insufficient data were reported to construct or calculate true-positive, false-positive, true-negative, and false-negative results ($n = 24$); (c) researchers in the articles did not use histopathology analysis as the gold standard ($n = 3$); (d) articles about NBI did not use the Hiroshima classification ($n = 14$); (e) there were fewer than 10 patients in the study ($n = 2$). Sixteen articles fulfilled all the inclusion criteria and were selected for data extraction and data analysis. We obtained all the full texts for the 16 eligible studies.

Study design characteristics

Table 2 shows the principal characteristics of the 16 studies, with a total of 2197 lesions that were included in this meta-analysis. One study was conducted in the UK [32], all the others were performed in Japan. Meanwhile, the majority of the selected studies had a retrospective design (12 out of 16). In the selected 16 studies, 7 studies were performed with NBI-ME [20–26] and all of these studies diagnosed colorectal tumors using the Hiroshima classification (Table 1),

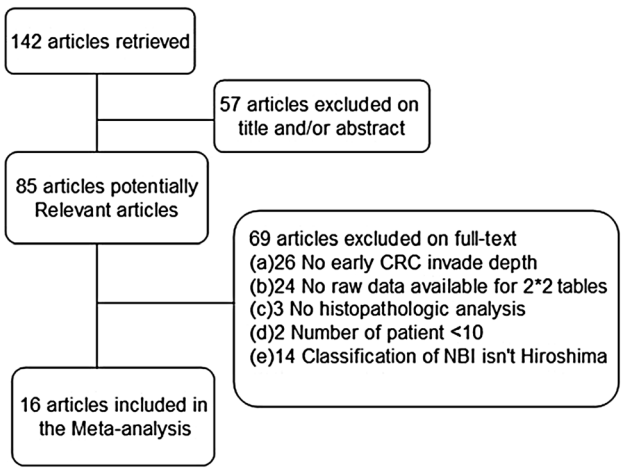


Fig. 1 Flow chart of the systematic literature search

9 studies with EUS [27–35]. The gold standard was histopathology analysis in these 16 studies. The principal characteristics of the 16 studies included in our meta-analysis are summarized in Table 2.

Quality assessment

We used the QUADAS quality assessment tool to evaluate each selected study. All studies included in the meta-analysis were of high quality, although none of the studies satisfied all items of the quality checklist. Five studies satisfied 8 items of the 14 standard items, 5 studies satisfied 9 items, 2 studies satisfied 10 items, 2 studies satisfied 11 items, 1 study satisfied 7 items, 1 study satisfied 12 items., The score of the eligible studies was 7 or more in the 14 questions, indicating good quality.

Summary estimates of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, AUC and diagnostic OR

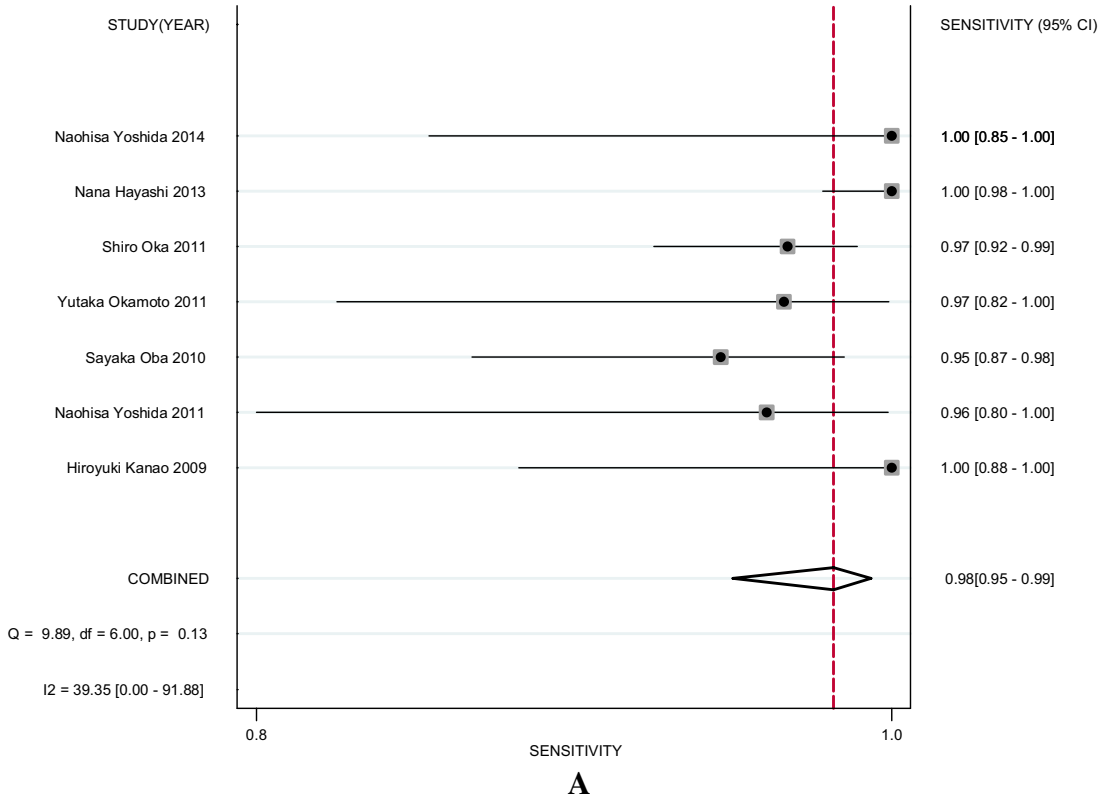
Sixteen studies involving 2197 lesions were enrolled, which includes 9 studies performing EUS and 7 studies with NBI-ME. The pooled sensitivity estimate for EUS was 0.902

Table 2 Main features of the 15 eligible studies included in the meta-analysis

Author	Year	Period	Country	Histopathology
Hiroyuki Kanao [20]	2009	2004.1–2007.7	Japan	Endoscopic resection or surgery
Naohisa Yoshida [21]	2011	2008.8–2010.4	Japan	Biopsy or EMR or ESD or surgery
Sayaka Oba [22]	2010	2004.1–2009.1	Japan	Endoscopic resection or surgery
Yutaka Okamoto [23]	2011	2007.8–2009.3	Japan	Endoscopic resection or surgery
Shiro Oka [24]	2011	2005.3–2010.9	Japan	Endoscopic resection or surgery
Nana Hayashi [25]	2013	2005.3–2011.8	Japan	Endoscopic resection or surgery
Naohisa Yoshida [26]	2014	2011.8–2012.3	Japan	EMR or ESD or surgery
Shiro Miyazak [27]	1998	1994.7–1995.11	Japan	Endoscopic resection or surgery
Osamu Tsuruta [28]	1998	1994.4–1997.10	Japan	EMR or surgery
N. Harada [29]	2001	1994.1–1998.9	Japan	EMR or surgery
Takayuki Matsumoto [30]	2002	1995.8–2001.4	Japan	Endoscopic resection or surgery
Kiyonori Kobayashi [31]	2003	1989–2002	Japan	Endoscopic resection or surgery
D P Hurlstone [32]	2005	2003.1–2005.3	UK	EMR or surgery
Takaya Shimura [33]	2014	2011.2–2012.11	Japan	EMR or ESD or surgery
Miyuki Mukae [34]	2015	1989.1–2012.8	Japan	Endoscopic resection or surgery
Tomonori Yamada [35]	2015	2011.2–2012.12	Japan	Endoscopic resection or surgery

Tp	Fp	Fn	Tn	Study design	Tool
29	17	0	30	Retrospective	ME-NBI
24	4	1	7	Prospective	ME-NBI
69	28	4	51	Unknown	ME-NBI
28	3	1	8	Retrospective	ME-NBI
145	37	5	65	Unknown	ME-NBI
165	38	0	84	Unknown	ME-NBI
23	5	0	3	Unknown	ME-NBI
8	0	3	11	Prospective	EUS 20 MHz
21	0	3	21	Prospective	EUS 20 MHz
7	3	2	23	Prospective	EUS 15 MHz
20	2	2	25	Unknown	EUS 12, 20 MHz
225	17	18	104	Unknown	EUS 7.5, 20 MHz
12	2	0	38	Prospective	EUS 12.5, 20 MHz
31	5	4	26	Prospective	EUS 20 MHz
373	27	41	183	Retrospective	EUS 7.5, 20, 12.5 MHz
27	11	8	20	Prospective	EUS 20 MHz

tp true positive, *fp* false positive, *fn* false negative, *tn* true negative, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *EUS* endoscopic ultrasonography



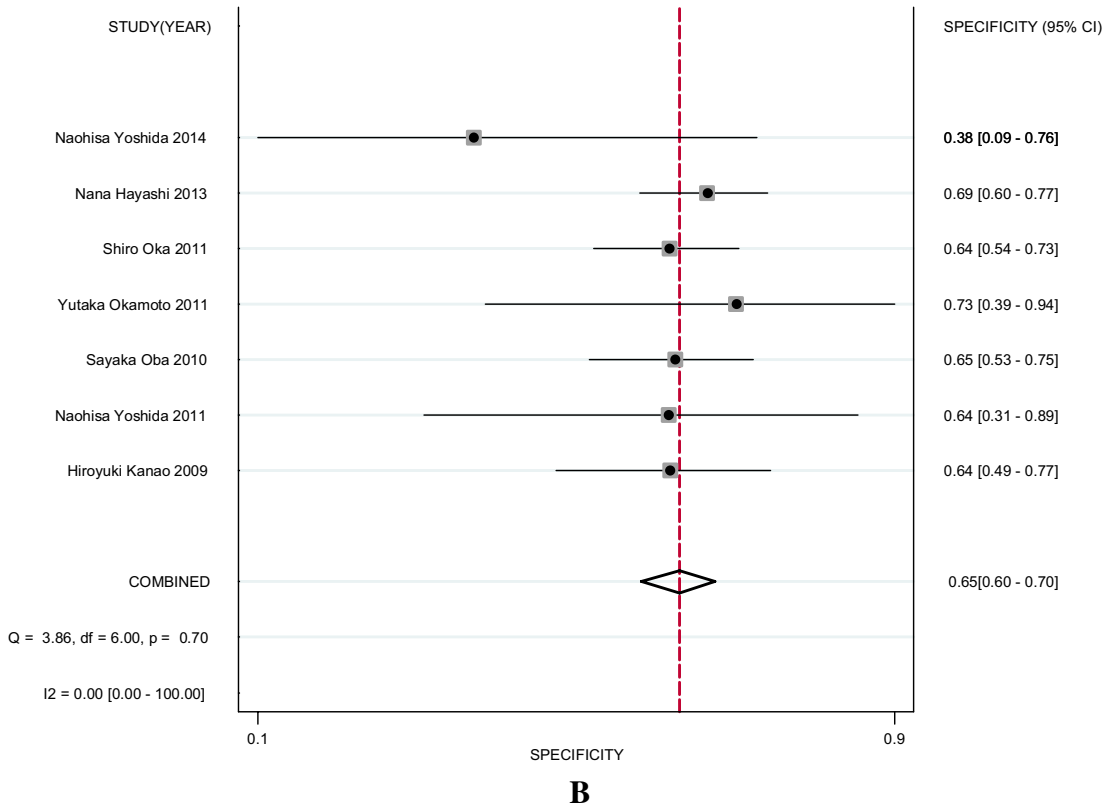
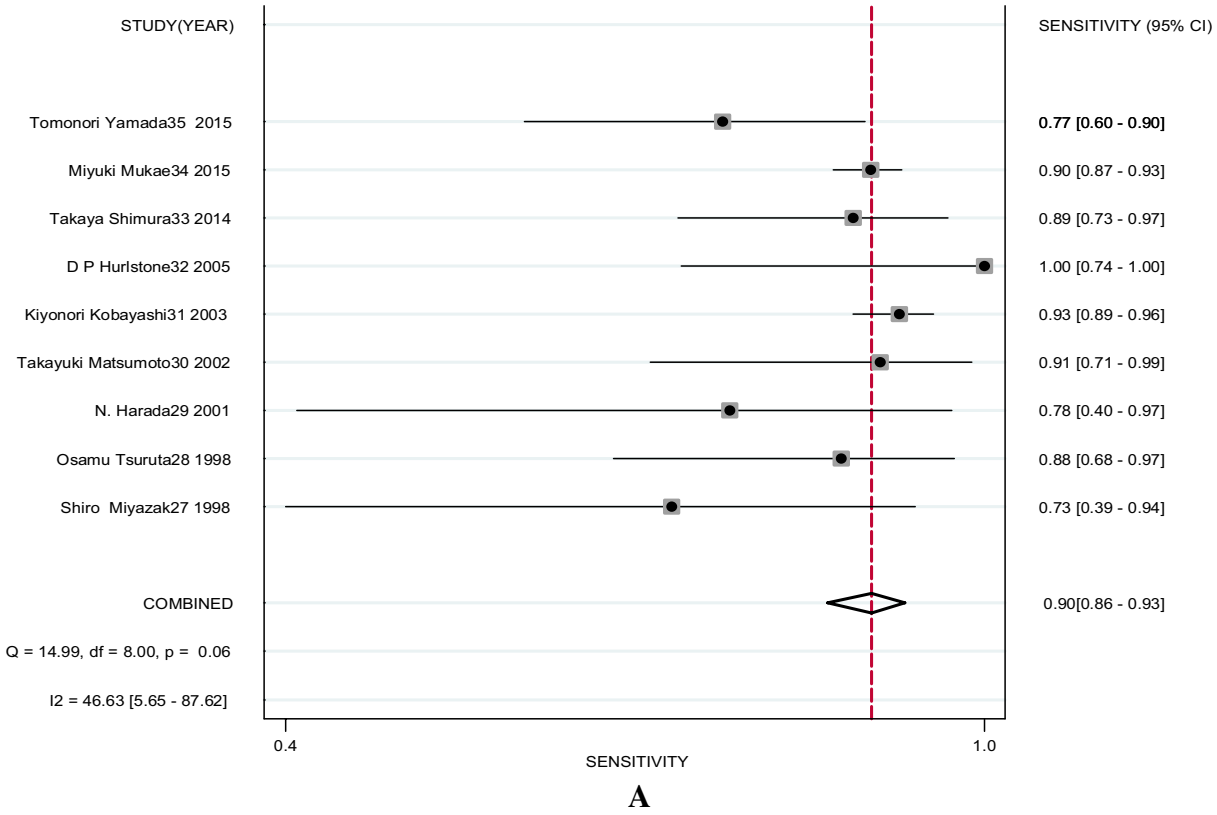
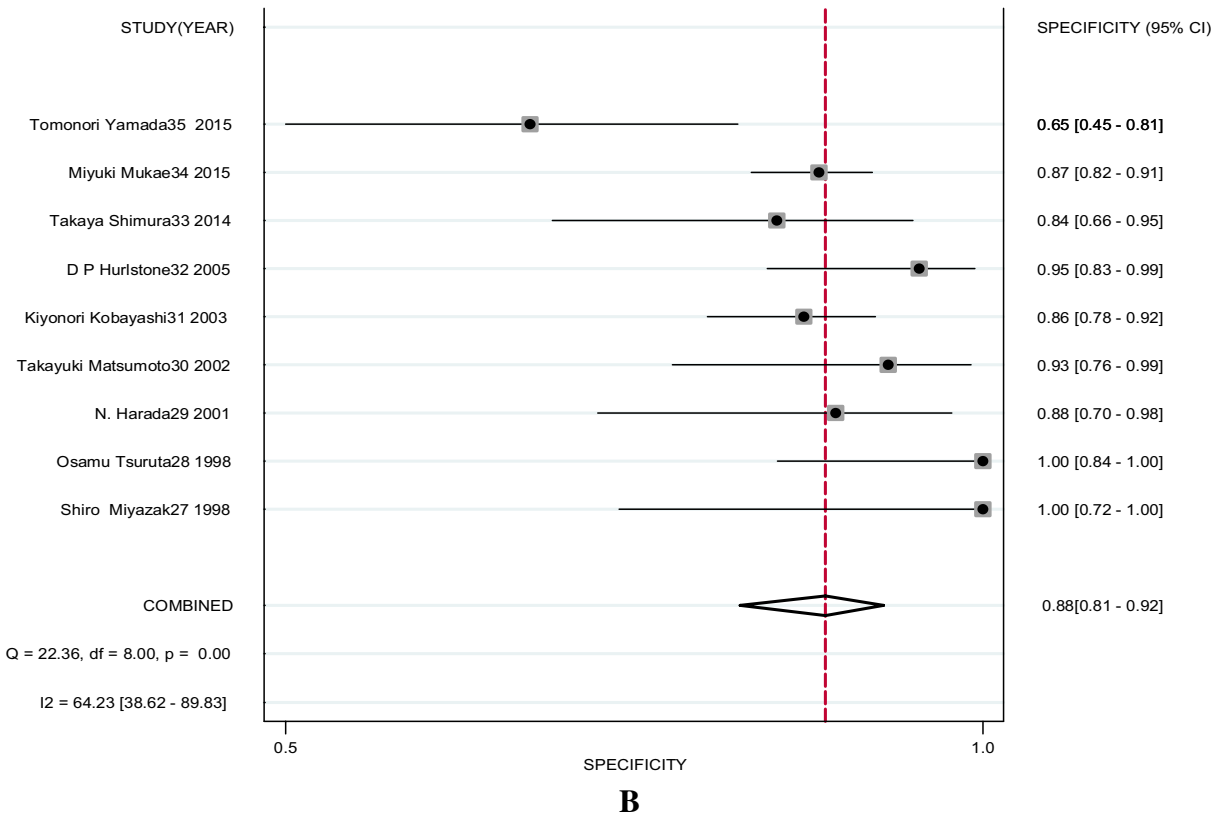


Fig. 2 ME-NBI diagnostic performance to distinguish SMS from SMD cancers: forest plot of the studies included in the meta-analysis. **a** Sensitivity; **b** specificity. *SMS* slight submucosal invasion, *SMD* massive submucosal invasion



A



B

Fig. 3 EUS diagnostic performance to distinguish SMS from SMD cancers: forest plot of the studies included in the meta-analysis. **a** Sensitivity; **b** specificity+

Table 3 The main pooled results for ME-NBI and EUS

Tool	AUC	DOR	NLR	PLR	SEN	SPE
ME-NBI	0.71	98.552	0.029	2.815	0.981	0.692
EUS	0.95	65.352	0.112	7.314	0.877	0.902

AUC area under the receiver operating characteristic curve, *DOR* diagnostic odds ratio, NLR) negative likelihood ratio, *PLR* positive likelihood ratio, *SEN* sensitivity, *SPE* specificity

(95% CI 0.863–0.930), the specificity was 0.877 (95% CI 0.810–0.922), positive likelihood ratio was 7.314 (95% CI 4.551–11.755) and negative likelihood ratio was 0.112 (95% CI 0.076–0.164), AUC was 0.95 (95% CI 0.93–0.96). The pooled sensitivity and specificity of NBI were 0.981 (95% CI 0.949–0.993) and 0.651 (95% CI 0.600–0.699), respectively, positive likelihood ratio was 2.815 (95% CI 2.432–3.258), negative likelihood ratio was 0.029 (95% CI 0.010–0.080) and AUC was 0.71 (95% CI 0.67–0.75). The pooled diagnostic OR estimate for NBI (98.558) was significantly higher than EUS (65.353) and it expresses how much greater the odds of having the disease are for the people with a positive test result than for the people with a negative test result. The forest plots for the sensitivity and specificity of EUS and NBI-ME are shown in Figs. 2, 3 and Table 3.

Test for heterogeneity

Heterogeneity was explored via the Chi-square test and likelihood ratio (LR) I^2. In the studies about NBI, Q was 1.930, p was 0.191, I^2 was 0.00 and studies about EUS Q was 0.358, p was 0.418, I^2 was 0.00. They were all considered to represent low heterogeneity.

Publication bias

We used Deeks' funnel plot to reveal publication bias in the available literature. The Deeks' funnel plot analysis revealed that the biased p values were 0.382 (NBI) and 0.981 (EUS), so there was no statistical significance for the evaluation of publication bias. The results are shown in Fig. 4.

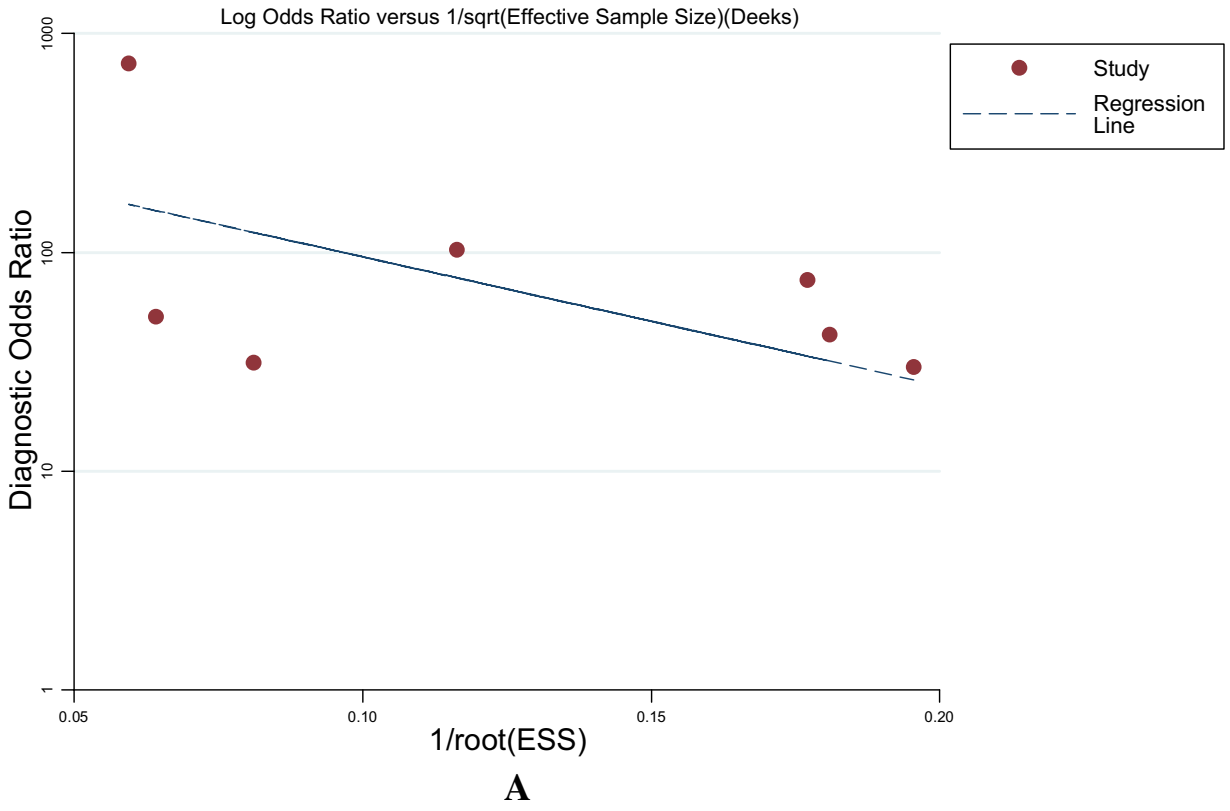
Discussion

Recently, curative endoscopic resection for CRC has attracted growing interest. The decision about whether an early CRC should be treated with an invasive surgical colectomy or endoscopically is made, mainly based on the preoperative endoscopic diagnosis of the invasion depth of the tumor.

In the past, EUS was considered as the method of examination that most accurately predicts the invasion depth of early CRC [36]. However, accuracy tended to be higher for advanced disease than for early disease. Compared with conventional EUS transducers, higher-frequency catheter probes provide higher-resolution images of the colorectal wall and make it possible to image the muscularis mucosae, and we excluded Konishi's study [37] to eliminate heterogeneity since the authors evaluated patients with early CRC only using 7.5 MHz. Meta-analyses of EUS in colon cancer staging show an increased sensitivity for T1 tumors (91%) [38], which is similar to sensitivity in our study (89%).

Several recent studies, mainly in Japan, have demonstrated that NBI-ME also provides a useful method for estimating superficial tumor depth. However, to the best of our knowledge, prior to our study, no meta-analysis examined the invasion depth of early CRC using NBI-ME. The NBI technique is based on a modification of the spectral characteristics of the optical filter in the light source, which leads to improved visibility of mucosal structures without the support of chromoendoscopy [39]. Also, NBI-ME is more useful for diagnosing the depth of invasion and abnormal vascular patterns than NBI without magnification [40]. In our study, we analyzed NBI-ME findings of early CRC using the Hiroshima classification [41]. In brief, types A, B, and C are indicators for hyperplasia, adenoma, and carcinoma, respectively. Type C comprises three subtypes (C1, C2 and C3); type C1/C2 was an index for slightly SM_S invasive carcinomas, and type C3 was an index for SM_D invasive carcinomas. So far, there are no gold standard criteria for NBI-ME findings of early CRC. All the articles included in this study analyzed NBI-ME findings of early CRC according to Hiroshima classification. The Hiroshima classification is based on the surface pattern and microvascular architecture. An alternative classification, the Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification, incorporates the lesion color in addition to the surface patterns and microvascular architecture [42]. In a recent study comparing these classifications, the NICE classification had higher accuracy in predicting mucosal cancer invasion depth than the Hiroshima classification. While the NICE classification is more complicated, its accuracy in predicting submucosal cancer invasion depth is similar to that of the Hiroshima classification [43].

In this meta-analysis, we found that NBI-ME has an impressive sensitivity in evaluating the invasion depth for SM_S although with a lower specificity than EUS. These results suggest that to avoid unnecessary surgery, it is advisable to diagnose the case according to ME-NBI when the infiltration depth of early CRC is first diagnosed.



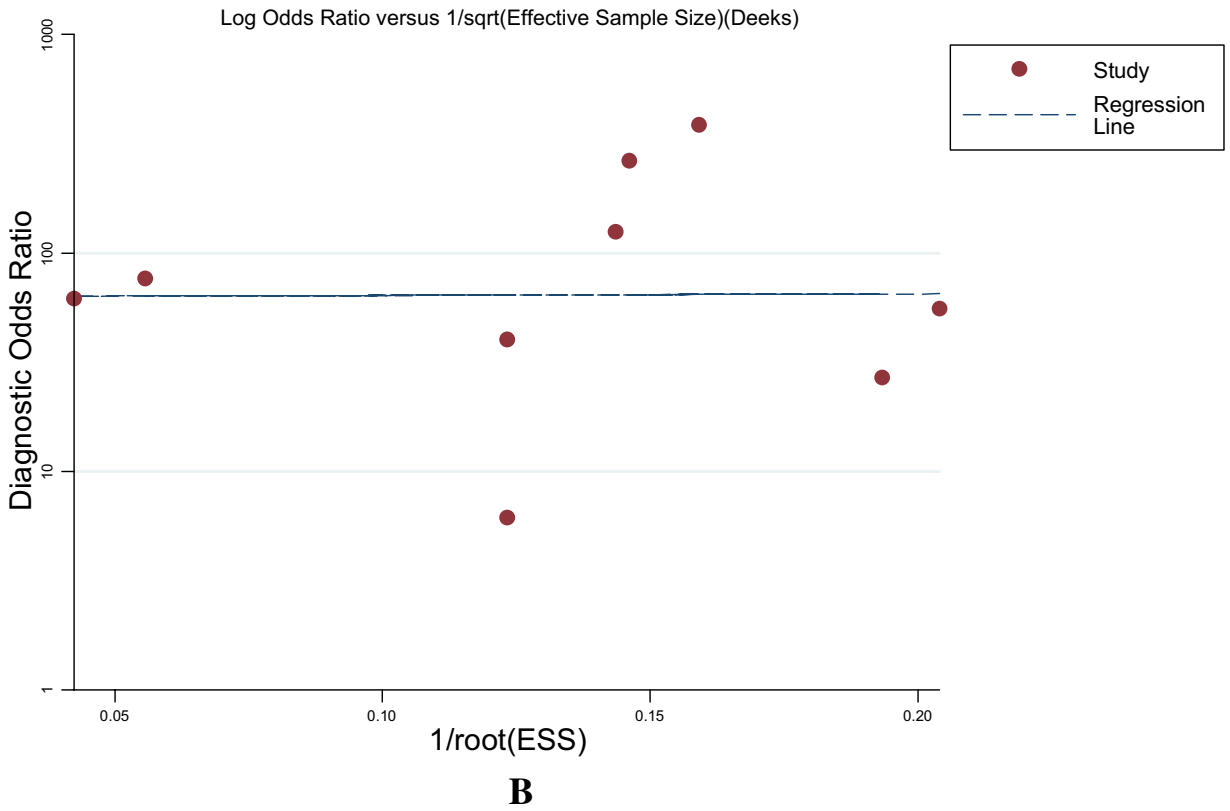


Fig. 4 Deeks' funnel plot asymmetry test for the studies. **a** ME-NBI; **b** EUS

Our meta-analysis has several limitations. First, the meta-analysis included only seven studies about NBI and nine studies about EUS, and the majority of the included patients were Asian. Consequently, the reported results may not be generalizable to other regions. Second, size and location of cancers and the most common features of patients were not clearly extracted in those studies. Third, the datas of the true positive, false positive, true negative and false negative could not be extracted from some related studies because the combined data of SM_S or SM_D invasion cancers.. However, a study about EUS that reported results for staging as Tis, T1a and T1b was included, because data on SM_S/SM_D staging could be extracted and analyzed. Fourth, we excluded non-English language literature, which may have limited the number of studies included in our meta-analysis. Fifth, none of the studies reported the time interval between EUS/NBI-ME and histopathology analysis (the gold standard).

Conclusions

Our results show that ME-NBI is suitable for estimating the early CRC invasion depth before treatment to avoid unnecessary surgery, whereas EUS should be applied to the cases of early CRC in which the decision to conduct endoscopic resection is difficult. When possible, it would be better to evaluate the invasion depth of early CRC using both ME-NBI and EUS before deciding to perform endoscopic resection.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study is a meta-analysis and does not require ethical reasoning.

Informed consent For this study, informed consent was not required.

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