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DISEASES OF THE ESOPHAGUS

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Systematic Review and Meta-analysis

Unsedated transnasal endoscopy for the detection of Barrett's esophagus: systematic review and meta-analysis

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SUMMARY. **Conventional esophagogastroduodenoscopy (cEGD) is currently the gold standard endoscopic procedure for diagnosis and surveillance of Barrett's esophagus (BE). This procedure is however less suitable for widespread screening because of its invasiveness and costs. An alternative endoscopic procedure is unsedated transnasal endoscopy (uTNE). We performed a systematic review and meta-analysis to evaluate the diagnostic accuracy, patient tolerability, technical success rate, and safety of uTNE compared with cEGD for detecting BE and related neoplasia. PubMed, EMBASE, and Cochrane Library were searched for studies that reported the diagnostic accuracy of uTNE compared with cEGD for detecting BE and related neoplasia. Eight prospective studies were included, in which 623 patients underwent both uTNE and cEGD. Pooled sensitivity and specificity of uTNE for detecting columnar epithelium were 98% (95% CI 83–100%) and 99% (95% CI 82–100%), respectively. Pooled sensitivity and specificity of uTNE for detecting intestinal metaplasia in biopsies were 89% (95% CI 78–95%) and 93% (95% CI 71–98%), respectively. In three of the six studies that reported patient tolerability, a higher patient tolerability of uTNE compared with cEGD was reported. The technical success rate of uTNE ranged from 89% to 100% and no (serious) adverse events were reported. This systematic review and meta-analysis provides evidence that uTNE is an accurate, safe, and well-tolerated procedure for the detection of columnar epithelium and can be considered as screening modality for BE.**

KEY WORDS: **Barrett's esophagus, biopsy, screening, transnasal endoscopy.**

INTRODUCTION

Esophageal cancer, including squamous cell carcinoma and adenocarcinoma (EAC), is the sixth most common cause of cancer death worldwide.[1,2] EAC is the most rapidly increasing cancer in the Western world and is mostly diagnosed at an advanced stage. This results in a poor prognosis with a 5-year survival rate of less than 20%.[2–4] Barrett's esophagus (BE), in which the squamous epithelium of the esophagus is replaced by intestinal-type columnar epithelium, is the main precursor of EAC.[5–7] EAC has been estimated to develop in approximately 0.1–0.5% of patients with BE anually.[8,9] The most important risk factor for both BE and EAC is gastro-esophageal reflux disease (GERD).[6]

To improve overall survival of EAC, timely detection and treatment of patients with an increased risk of developing EAC is of great importance. However, hitherto, BE is diagnosed prior to an EAC diagnosis in less than 10% of patients with EAC.[10] Currently, conventional esophagogastroduodenoscopy (cEGD) with biopsy sampling according to the Seattle protocol is the gold standard endoscopic procedure for diagnosis and surveillance of BE.[11–13] However, cEGD is less suitable for widespread screening for BE because its invasiveness and therefore patient-unfriendliness, and associated high costs.[14] For that reason, several less invasive endoscopic procedures for screening for BE are currently under investigation.[15–17]

An alternative, less invasive endoscopic procedure is unsedated transnasal endoscopy (uTNE), which was first introduced in 1994.[18] uTNE is performed with an ultrathin endoscope that can be introduced through the nose and performed without sedation. Until now, several studies have been published investigating the diagnostic accuracy of uTNE, but with equivocal results. Furthermore, previous reviews on uTNE focused on screening for upper GI disorders in general, not only for BE.

This systematic review and meta-analysis therefore aimed to evaluate the diagnostic accuracy, patient tolerability, technical success rate, and safety of uTNE

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compared with the gold standard endoscopic procedure cEGD for detecting BE and related neoplasia.

METHODS

We performed this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[19,20] The corresponding systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42020198674.

Search strategy

PubMed, EMBASE, and Cochrane Library were searched for articles published up to March 2022. The search terms comprised synonyms for 'Barrett's esophagus', 'transnasal', and 'ultrathin'. No limits or restrictions were applied in PubMed, EMBASE, and Cochrane Library. The full search strategy can be found in Supplementary 1.

Eligibility criteria

Studies were included that compared uTNE with cEGD for detecting BE and related neoplasia for at least one of the following primary outcome measures related to diagnostic accuracy, i.e. sensitivity, specificity, positive predictive value, and negative predictive value. If necessary, sensitivity and specificity were calculated in 2 × 2 tables with true and false positives, and true and false negatives. Apart from review articles, case reports, letters to the editor, commentaries, and conference abstracts, all other study designs were eligible for inclusion. We also excluded articles that were not available in full text as well as non-English and non-Dutch articles. Reference lists of included articles and review articles were evaluated to identify studies that may have been missed in our search strategy.

Study selection

After removing duplicate articles, titles and abstracts of the selected articles from our search strategy were independently screened by two reviewers (LH and DW) for inclusion based on our eligibility criteria. We collected full text articles for all titles and abstracts that were considered to fulfil the eligibility criteria. Any differences were resolved through discussion, and, if agreement could not be reached, a third reviewer (YP or PS) was involved.

Outcome measures

The primary outcome measure was the diagnostic accuracy of uTNE compared with cEGD for detecting columnar epithelium, intestinal metaplasia, and related neoplasia. We defined columnar epithelium as the presence of a salmon-colored mucosa segment of any length above the gastroesophageal junction, and intestinal metaplasia as the presence of intestinal-type columnar epithelium in biopsies.[21,22] Secondary outcome measures included patient tolerability, technical success rate, and safety of uTNE compared with cEGD. The technical success rate was defined by the successful introduction of the uTNE-endoscope in the esophagus. If both uTNE and cEGD were successfully completed, patients were included in the final analyses.

Data collection process and data items

The following variables from each study were independently extracted by two authors (LH and DW) and summarized in a standardized data extraction form, i.e. study characteristics (author and year of publication, country of origin, total sample size, sample size that underwent both uTNE and cEGD, study design, and diagnosis of BE (columnar epithelium and/or intestinal metaplasia in biopsies)), patient characteristics (gender, age, and length of BE-segment), index test (uTNE) characteristics (model, patient tolerability, technical success rate, and safety), and reference test (cEGD) characteristics (model, patient tolerability, technical success rate, and safety).

Risk of bias in individual studies

The QUADAS-2 checklist was used for quality assessment of studies included in a diagnostic test accuracy systematic review and meta-analysis.[23] Two reviewers (LH and DW) independently filled out the QUADAS-2 checklist for each study. Any differences were resolved through discussion. Studies judged as low on all domains relating to bias or applicability were considered as low risk of bias. Also, if a minimum of ten studies could be included, a funnel plot was intended to be made to evaluate for publication bias.

Statistical analysis

For each study, paired sensitivities and specificities with corresponding 95% confidence interval (CI) were presented using a forest plot and a summary receiver operating characteristic curve (SROC-curve) based on single test analysis. Pooled sensitivity and specificity were calculated using a hierarchical summary receiver operating characteristic (HSROC) model. This hierarchical model involves statistical distributions at two levels. At the first level, the cell counts in the 2 × 2 tables were modeled using binomial distributions and logistic (log-odds) transformations of proportions. At the second level, the HSROC model takes into account the correlation between sensitivity and specificity across studies while also allowing for variation in test performance between studies through the inclusion of random effects.[24] The

output of the HSROC model includes study estimate, summary point, HSROC-curve, and 95% confidence region. The I^2 statistic was calculated to test for heterogeneity. Percentages of around 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively.[25] Subgroup analyses were performed for country (UK and USA, UK, USA, Mexico, or South Korea), model of ultrathin endoscope (E.G. Scan (IntroMedic Co. Ltd., Seoul, South Korea), EndoSheath (TNE-5000 with EndoSheath Technology; Vision Sciences, Inc., New York, USA), or re-usable) and population (patients with known BE, patients with gastrointestinal symptoms, or patients with known BE and/or gastrointestinal symptoms) to determine whether the considered covariate may partly explain the observed between-study heterogeneity. A meta-analysis of binary data was performed to compare the technical success rate of uTNE with cEGD. Sensitivity analyses were performed including only studies classified as low risk of bias and low concerns regarding applicability for each domain of the QUADAS-2 checklist, with studies that included only the screening or only the surveillance population, and with studies that included only patients with long-segment BE. Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA 16.0 (College Station, TX: StataCorp LLC) were used to perform all statistical analyses.

RESULTS

Study selection

The search strategy resulted in 11,914 articles, of which 7,711 remained after removing duplicates. After screening titles and abstracts, 7,579 articles were excluded. Most excluded articles did not particularly focus on BE. The remaining 132 articles were read in full text, of which 8 articles met the inclusion criteria including a total of 683 patients (Fig. 1).[26–33]

Study characteristics

Patient characteristics are shown in Table 1. All eight studies prospectively compared uTNE with cEGD, of which four were randomized crossover studies[28,30,32,33] and four were prospective cohort studies.[26,27,29,31] Three studies reported both detection of columnar epithelium and detection of intestinal metaplasia in biopsies,[30,32,33] four studies only detection of columnar epithelium[26,27,29,31] and one study only detection of intestinal metaplasia in biopsies.[28] Of all 683 included patients, 623 successfully completed both uTNE and cEGD, and these patients were included in the final analyses. Most studies included patients with gastrointestinal symptoms, such as dyspepsia, heartburn, dysphagia, and nausea or vomiting. In five studies, also patients with known BE were included.[28,30–33] Ultrathin endoscopes with a diameter ranging from 3.4 to 5.9 mm were used, but endoscope models differed between studies. The E.G. Scan system (first, second, and third generation) was the most commonly used model of ultrathin endoscope and was used in three studies.[26,29,31]

Detection of columnar epithelium with uTNE compared with cEGD

Pooled sensitivity of uTNE for detecting columnar epithelium ($N = 7$)[26,27,29–33] was 98% (95% CI 83–100%) and pooled specificity was 99% (95% CI 82–100%) (Fig. 2). The I^2 statistic was 40.3%, which means moderate heterogeneity.

In one study that reported detection of columnar epithelium, a disposable ultrathin endoscope was used (EndoSheath) with a sensitivity and specificity of 100% for detection of columnar epithelium.[33] In three studies, the disposable E.G. Scan was used with a sensitivity ranging from 67% to 100% and a specificity ranging from 90% to 100% for detection of columnar epithelium.[26,29,31] In three other studies, a re-usable ultrathin endoscope was used with a sensitivity ranging from 98% to 100% and a specificity of 100%.[27,30,32]

Detection of intestinal metaplasia in biopsies obtained by uTNE compared with cEGD

Pooled sensitivity of uTNE for detecting intestinal metaplasia in biopsies ($N = 4$)[28,30,32,33] was 89% (95% CI 78–95%) and pooled specificity was 93% (95% CI 71–98%) (Fig. 3). The I^2 statistic was 0.0%, which means low heterogeneity.

In one study that reported detection of intestinal metaplasia in biopsies, a disposable ultrathin endoscope was used (EndoSheath) with a sensitivity of 67% and a specificity of 100% for detection of intestinal metaplasia in biopsies.[33] In three other studies, a re-usable ultrathin endoscope was used with a sensitivity ranging from 84% to 97% and a specificity ranging from 89% to 100%.[28,30,32] The four studies that reported detection of intestinal metaplasia in biopsies concluded that due to the smaller size of the forceps of uTNE, biopsies were smaller and more superficial, compared with biopsies obtained with cEGD.

Detection of dysplasia in biopsies obtained by uTNE and cEGD

Three of the four studies in which biopsies were obtained also reported the detection of dysplasia in biopsies.[28,30,32] The study by Shariff *et al*.[32] detected three cases of dysplasia (unknown grade) with both uTNE and cEGD.

The study by Jobe *et al*.[28] detected four cases of low-grade dysplasia (LGD) with cEGD while uTNE only confirmed one of these cases as LGD (25.0%) (Table 2). Also, one case of high-grade dysplasia (HGD) was only detected by cEGD.

Table 1 Characteristics of included studies

Author and year of publication	Country of origin	Total sample size	Sample size that underwent both uTNE and cEGD	Study design	Patient characteristics	Model of ultrathin endoscope	Diagnosis of BE	Length of BE-segment	Population and prevalence of BE (%)
Aedo *et al.*[26] (2014)	Mexico	96	96	Prospective cohort study	Men = 42 (44%) Mean age = 50	E.G. Scan I system, 3.6 mm disposable probe	Only presence of columnar epithelium	Unknown	Patients with gastrointestinal symptoms 12.5
Sami *et al.*[31] (2019)	UK and USA	200	178	Prospective multi-center diagnostic cohort study	Men = 134 (67%) Mean age = 58	E.G. Scan II system, 3.4 mm disposable probe	Only presence of columnar epithelium	BE of any length	Patients with known BE and/or gastrointestinal symptoms 52.8
Kang *et al.*[29] (2019)	South Korea	50	49	Prospective open-labeled cohort study	Men = 20 (41%) Mean age = 43	E.G. Scan III system, 4.9 mm disposable probe	Only presence of columnar epithelium	Unknown	Patients with gastrointestinal symptoms 10.2
Shariff *et al.*[33] (2016)	UK	25	21	Randomized crossover study	Men = 15 (60%) Median age = 59	EndoSheath 4.7 mm × 5.8 mm disposable	Both presence of columnar epithelium and intestinal metaplasia in biopsies	Longitudinal extent at least 2 cm	Patients with known BE and/or gastrointestinal symptoms 61.9
Catanzaro *et al.*[27] (2003)	USA	51	49	Prospective cohort study	Men = 24 (47%) Mean age = 53	4 mm (LF-GP Olympus or XEF 140I Olympus) re-usable	Only presence of columnar epithelium	Unknown	Patients with gastrointestinal symptoms 16.3
Shariff *et al.*[32] (2012)	UK	95	82	Randomized crossover study	Men = 32 (33.7%) Mean age = 60	5.9 mm (EG530N Fujinon) re-usable	Both presence of columnar epithelium and intestinal metaplasia in biopsies	Circumferential extent at least 2 cm	Patients with known BE and/or gastrointestinal symptoms 59.8
Saeian *et al.*[30] (2002)	USA	32	32	Randomized crossover study	Men = 30 (94%) Mean age = 64	Unknown diameter (FG16X Pentax or GIF-N30 Olympus) re-usable	Both presence of columnar epithelium and intestinal metaplasia in biopsies	BE of any length	Patients with known BE 100
Jobe *et al.*[28] (2006)	USA	134	116	Randomized crossover trial	Men = 107 (80%) Mean age = 59	5.1 mm (Olympus) re-usable	Only presence of intestinal metaplasia in biopsies	BE of any length	Patients with known BE and/or gastrointestinal symptoms 31.9

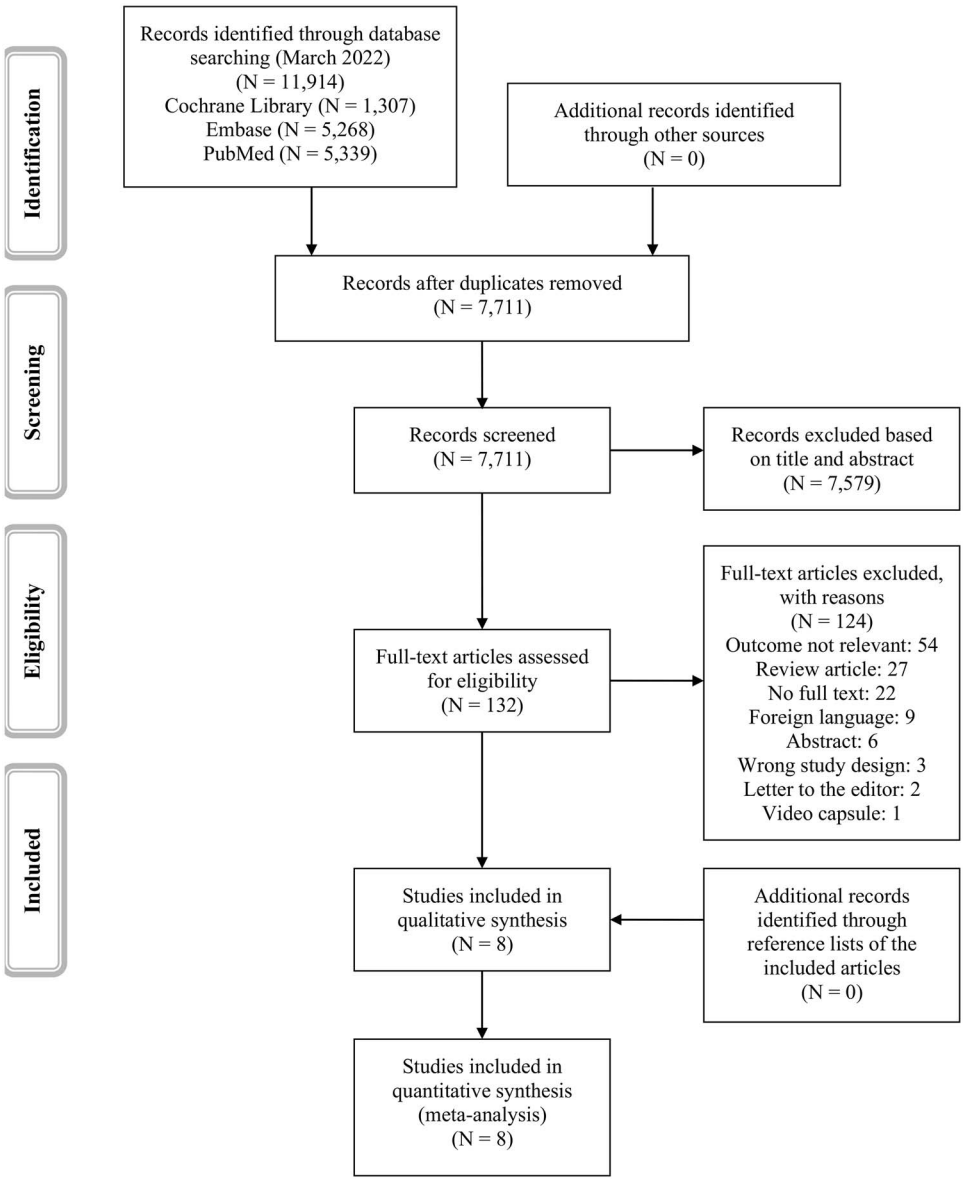

Fig. 1 Flowchart of the study selection process.

Table 2 The detection of dysplasia in biopsies in the study by Jobe *et al*.[28]

		cEGD				
		Squamous epithelium	**Intestinal metaplasia**	**LGD**	**HGD**	**Total**
uTNE	Squamous epithelium	70 88.6%	5 15.6%	1 25%	0 0%	76 65.5%
	Intestinal metaplasia	9 11.4%	24 75%	2 50%	1 100%	36 31.0%
	LGD	0 0%	3 9.4%	1 25%	0 0%	4 3.5%
	HGD	0 0%	0 0%	0 0%	0 0%	0 0%
	Total	79 100%	32 100%	4 100%	1 100%	116 100%

uTNE, unsedated transnasal endoscopy; cEGD, conventional esophagogastroduodenoscopy; LGD, low-grade dysplasia and HGD, high-grade dysplasia. Per-column percentages were added.

The study by Saeian *et al*.[30] detected twenty cases of LGD with cEGD while uTNE confirmed seventeen of these cases as LGD (85.0%) (Table 3). Furthermore, two cases of HGD were detected by both cEGD and uTNE.

Patient tolerability, technical success rate, and safety of uTNE compared with cEGD

Four studies measured patient tolerability using a validated 10-point visual analog scale (VAS),[30–33] two studies measured it using an endoscopic tolerability

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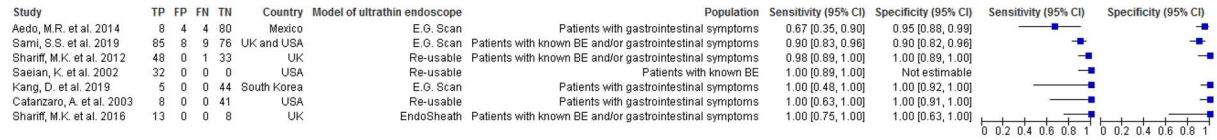
(A)

Study	TP	FP	FN	TN	Country	Model of ultrathin endoscope	Population	Sensitivity (95% CI)	Specificity (95% CI)
Aedo, M.R. et al. 2014	8	4	4	80	Mexico	E.G. Scan	Patients with gastrointestinal symptoms	0.67 [0.35, 0.90]	0.95 [0.88, 0.99]
Sami, S.S. et al. 2019	85	8	9	76	UK and USA	E.G. Scan	Patients with known BE and/or gastrointestinal symptoms	0.90 [0.83, 0.96]	0.90 [0.82, 0.96]
Shariff, M.K. et al. 2012	48	0	1	33	UK	Re-usable	Patients with known BE and/or gastrointestinal symptoms	0.98 [0.89, 1.00]	1.00 [0.89, 1.00]
Saeian, K. et al. 2002	32	0	0	0	USA	Re-usable	Patients with known BE	1.00 [0.89, 1.00]	Not estimable
Kang, D. et al. 2019	5	0	0	44	South Korea	E.G. Scan	Patients with gastrointestinal symptoms	1.00 [0.48, 1.00]	1.00 [0.92, 1.00]
Catanzaro, A. et al. 2003	8	0	0	41	USA	Re-usable	Patients with gastrointestinal symptoms	1.00 [0.63, 1.00]	1.00 [0.91, 1.00]
Shariff, M.K. et al. 2016	13	0	0	8	UK	EndoSheath	Patients with known BE and/or gastrointestinal symptoms	1.00 [0.75, 1.00]	1.00 [0.63, 1.00]



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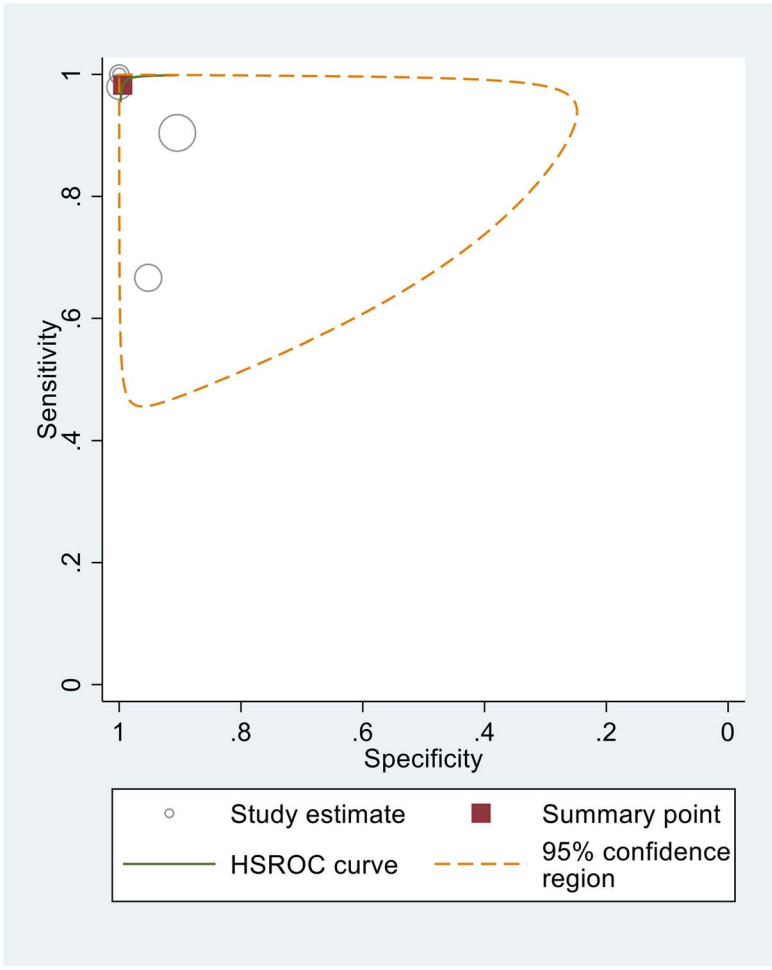


Fig. 2 (a) Forest plot with diagnostic accuracy of detecting columnar epithelium (sensitivity and specificity) of individual studies. (b) Graph including (1) 'Study estimate' = individual study estimates; (2) 'Summary point' = summary values for sensitivity and specificity; (3) 'HSROC-curve' = a summary curve from the HSROC model; and (4) '95% confidence region' = 95% confidence region for the summary point.

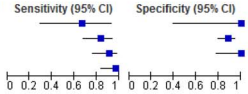
Table 3 The detection of dysplasia in biopsies in the study by Saeian *et al*.[30]

		cEGD				
		Intestinal metaplasia	**LGD**	**HGD**	**EAC**	**Total**
uTNE	Intestinal metaplasia	9 90%	2 10%	0 0%	0 NA	11 34.4%
	LGD	1 10%	17 85%	0 0%	0 NA	18 56.2%
	HGD	0 0%	0 0%	2 100%	0 NA	2 6.3%
	EAC	0 0%	1 5%	0 0%	0 NA	1 3.1%
	Total	10 100%	20 100%	2 100%	0 NA	32 100%

uTNE, unsedated transnasal endoscopy; cEGD, conventional esophagogastroduodenoscopy; LGD, low-grade dysplasia; HGD, high-grade dysplasia and EAC, adenocarcinoma. Per-column percentages were added.

(A)

Study	TP	FP	FN	TN	Country	Model of ultrathin endoscope	Population	Sensitivity (95% CI)	Specificity (95% CI)
Shariff, M.K. et al. 2016	6	0	3	4	UK	EndoSheath	Patients with known BE and/or gastrointestinal symptoms	0.67 [0.30, 0.93]	1.00 [0.40, 1.00]
Jobe, B.A. et al. 2006	31	9	6	70	USA	Re-usable	Patients with known BE and/or gastrointestinal symptoms	0.84 [0.68, 0.94]	0.89 [0.79, 0.95]
Shariff, M.K. et al. 2012	31	0	3	15	UK	Re-usable	Patients with known BE and/or gastrointestinal symptoms	0.91 [0.76, 0.98]	1.00 [0.78, 1.00]
Saeian, K. et al. 2002	31	0	1	0	USA	Re-usable	Patients with known BE	0.97 [0.84, 1.00]	Not estimable



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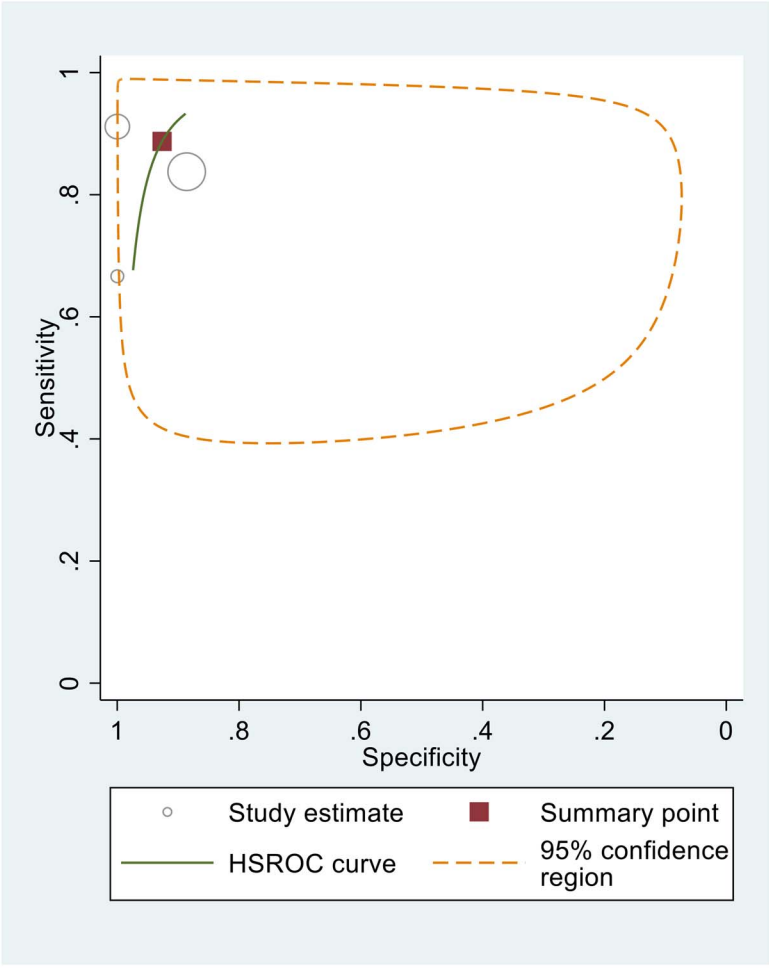

Fig. 3 (a) Forest plot with diagnostic accuracy of detecting intestinal metaplasia in biopsies (sensitivity and specificity) of individual studies. (b) Graph including (1) 'Study estimate' = individual study estimates; (2) 'Summary point' = summary values for sensitivity and specificity; (3) 'HSROC-curve' = a summary curve from the HSROC model; and (4) '95% confidence region' = 95% confidence region for the summary point.

questionnaire,[28,29] and two studies did not evaluate it.[26,27] Three studies reported a higher patient tolerability of uTNE compared with cEGD,[29,31,33] whereas, no difference in patient tolerability was found in the other three studies.[28,30,32]

The technical success rate of uTNE ranged from 89% to 100% in seven studies, while the technical success rate was unknown in one study.[33] The overall log-odds-ratio was 1.09 (95% CI 0.29–2.47), which means that the technical success rates of uTNE and cEGD were comparable. No serious adverse events were recorded in six studies, while two studies did not report the presence or absence of adverse events.[29,33] The risk of adverse events with uTNE was found to be low, approximately 2.0%, with the most commonly reported adverse events being vasovagal symptoms and epistaxis (Supplementary 2).

Subgroup analysis

Assessing clinically relevant subgroups, such as country (UK and USA, UK, USA, Mexico, or South Korea), model of ultrathin endoscope (E.G. Scan, EndoSheath, or re-usable) and population (patients with known BE, patients with gastrointestinal symptoms, or patients with known BE and/or gastrointestinal symptoms) by visual examination of

the SROC-curves in seven studies that reported the diagnostic accuracy of detecting columnar epithelium did not reveal any major sources of heterogeneity (Supplementary 3–5). Because the number of studies per subgroup was too low, a bivariate meta-regression model of these covariates could not be performed.

Risk of bias within studies

Quality assessment was performed for the four QUADAS-2 domains. Four studies were rated as high risk based on one or more domains for risk of bias,[27,29,30,33] while four studies were rated as low risk based on all domains for risk of bias.[26,28,31,32] Funnel plots to detect publication bias were not possible, as the number of included studies was lower than ten. Quality assessment results are summarized in Supplementary 6 and 7.

Sensitivity analysis

Three of the seven studies that reported the diagnostic accuracy of detecting columnar epithelium were classified as low risk of bias.[26,31,32] It was therefore not possible to perform a reliable sensitivity analysis of studies classified as low risk of bias. Sensitivities and specificities in these studies ranged from 67% to 98% and from 90% to 100%, respectively. Two of the four studies that reported the diagnostic accuracy of detecting intestinal metaplasia in biopsies were classified as low risk of bias.[28,32] Sensitivities and specificities in these studies for detecting intestinal metaplasia in biopsies ranged from 84% to 91% and from 89% to 100%, respectively.

Three studies[26,27,29] included only patients with gastrointestinal symptoms and one study[30] included only patients with known BE. Therefore, it was not possible to perform a reliable sensitivity analysis of studies that included only the screening or only the surveillance population.[34]

Two studies included BE patients with a minimum length for the longitudinal extent or the circumferential extent.[32,33] It was therefore again not possible to perform a reliable sensitivity analysis of studies that included only patients with a minimum BE length of 3 cm.[34] Nevertheless, one study[31] concluded that uTNE was accurate for the detection of columnar epithelium of any length with superior accuracy for long-segment compared with short-segment BE.

DISCUSSION

This systematic review and meta-analysis showed that uTNE is an excellent modality for the detection of columnar epithelium with a pooled sensitivity and specificity of 98% and 99%, respectively. Furthermore, the pooled sensitivity and specificity for the detection of intestinal metaplasia in biopsies were 89% and 93%, respectively. Overall patient tolerability of uTNE was higher or equal compared with cEGD, technical success rate of uTNE ranged from 89% to 100%, and no (serious) adverse events relating to uTNE were observed.

The main differences between uTNE and cEGD are the insertion route and the diameter of the endoscope. Although both the camera and the working channel of a transnasal endoscope are smaller compared with a conventional gastroscope, it did not negatively affect the sensitivity and specificity for the detection of columnar epithelium and the detection of intestinal metaplasia in biopsies, respectively. One study showed that the optical image quality of the EndoSheath was significantly inferior compared with cEGD, which was likely due to the fact that assessment of quality was done on low quality still images rather than on videos.[33] In another study by Crews *et al*.,[35] it was however concluded that the optical image quality of the EndoSheath and cEGD was comparable.

Only three included studies investigated the detection of dysplasia in biopsies.[28,30,32] Both Jobe *et al*.[28] and Saeian *et al*.[30] concluded that in biopsies obtained by uTNE, it was possible to differentiate between squamous epithelium and intestinal metaplasia with or without LGD or HGD. However, these findings should be interpreted with caution because the number of patients in whom the detection of dysplasia in biopsies obtained by uTNE was evaluated was relatively small, with a total of 197 patients included. Moreover, it is unknown whether biopsies obtained by uTNE were taken according to the Seattle protocol or not, which is according to current guidelines required to confirm or exclude the presence of dysplasia. Furthermore, biopsies obtained by uTNE are usually smaller, i.e. 1.8 mm versus 2.4 mm by cEGD.[36] In clinical practice, it is therefore often decided to perform a confirmatory cEGD with biopsy sampling according to the Seattle protocol.[37]

In 2015, a systematic review and meta-analysis investigating patients' preference and acceptability of uTNE compared with cEGD concluded that patients' preference was significantly higher for uTNE.[38] In 2019, a qualitative interview analysis in a high-risk population with BE and esophageal varices also found a higher patients' preference for uTNE.[39] It has been suggested that the diameter of a transnasal endoscope should be 6.0 mm or less for 'comfortable' transnasal passage.[40] Although the endoscope diameter was 6.0 mm or less in all included studies that reported endoscope diameter, we found that in studies with a higher patients' preference for uTNE compared with cEGD, endoscope diameter was actually smaller (3.4–4.9 mm vs. 5.1–5.9 mm, respectively), suggesting that endoscope diameter indeed affects patients' tolerability.

Self-limited epistaxis, nasal pain, vasovagal events, light-headedness, and nausea are commonly reported adverse events as a result of uTNE.[16,18,41–45] Based on this meta-analysis, the risk of adverse events as a result of uTNE seems very low, approximately 2.0%. As uTNE is performed without conscious sedation and it has been shown that uTNE may be performed by nurse practitioners or physician assistants with minimal training,[46] uTNE has the potential to be performed in an outpatient setting or even in general practices.[44,47,48]

This meta-analysis clearly has some strengths. First, it only focuses on the use of uTNE for BE, which makes the results applicable to the target population of patients that are eligible to be screened for BE. Furthermore, both detection of columnar epithelium and detection of intestinal metaplasia and/or dysplasia in biopsies, and patient tolerability and safety of uTNE were investigated. Lastly, all included studies had a prospective design, which is the preferred methodology for evaluating diagnostic test accuracy.

Nonetheless, some limitations should also be discussed. First, a bivariate regression model of covariates (country, model of ultrathin endoscope, and population) could not be performed because of the low number of studies per subgroup. Second, only three studies that reported detection of columnar epithelium and two studies that reported detection of intestinal metaplasia in biopsies were classified as low risk of bias. In two studies, it was unknown whether endoscopists were blinded for the indication for performing endoscopy or not and in one study the endoscopists were not blinded for the indication.[29–31] In one study, the same endoscopist (blinded for the indication for performing endoscopy) performed both uTNE and cEGD after each other, which may have introduced bias. Furthermore, only three studies reported the detection of dysplasia. Therefore, these results should be interpreted with caution and further studies are needed, not only focusing on the detection of columnar epithelium but also on obtaining biopsies with histological evaluation. Lastly, the models of ultrathin endoscopes used in the studies differed that could have introduced bias.

The use of uTNE for screening for BE has been suggested to be a cost-effective method in a high-risk population with GERD.[49] An economic analysis showed that screening for BE with uTNE in the community is more cost-effective than sedated cEGD, which is obviously a prerequisite when used as screening method for BE in a high-risk population.[50] Besides uTNE, other minimally invasive screening techniques are available, such as Cytosponge,[51] EsophaCap,[52] and EsoCheck.[53] Although Cytosponge and uTNE are comparably effective, it has been suggested that uTNE may be more cost-effective, but more comparative studies are needed.[54] Another novel approach is based on assaying volatile organic compounds (VOCs) by detecting conductance changes in the breath with an electronic nose device, which has shown promising diagnostic accuracy.[17] However, in contrast to uTNE, an electronic nose device is not (yet) suitable as screening method for BE due to the small number of studies regarding reliability of these results.

In an effort to improve overall survival of EAC, screening for and surveillance of BE is of great importance. This meta-analysis provides evidence that uTNE can accurately detect BE. Therefore, endoscopic screening for BE with uTNE could be considered in individuals with GERD who have multiple other risk factors such as male sex, Caucasian ethnicity, central adiposity, age older than 50 years, and a family history of BE or EAC.[54,55] Currently, only the American College of Gastroenterology considers uTNE as an alternative to cEGD for BE screening.[56] Both the EndoSheath and E.G. Scan are no longer commercially available; however, two companies have recently introduced a new single-use disposable duodenoscope (EXALT Model D Single-use Duodenoscope (Boston Scientific, Marlborough, MA) and aScope Duodeno (Ambu, Ballerup, Denmark)). As the disposable duodenoscope market may continue to develop, single-use disposable (gastro) duodenoscopes with working channels for biopsy sampling may also be introduced soon which can be used for screening for BE, not only in a clinical setting but also in a non-clinical setting, such as office-based practices.

In conclusion, uTNE is an accurate, safe, and well-tolerated endoscopic procedure for the detection of columnar epithelium and has the potential to be used as an endoscopic screening method for BE. Therefore, it seems logical to implement the use of uTNE in current guidelines on BE screening. Nonetheless, further studies need to evaluate: (i) the willingness of the high-risk population for BE to undergo uTNE, (ii) the ability to indisputable detect columnar epithelium and demonstrate the presence of intestinal metaplasia with or without dysplasia in biopsies obtained by uTNE, (iii) whether or not a confirmatory cEGD is indicated following uTNE, and (iv) whether or not uTNE is indeed patient-friendly and a cost-effective approach.

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SUPPLEMENTARY DATA

Supplementary data mentioned in the text are available to subscribers in DOTESO online.

CONFLICT OF INTEREST

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AVAILABILITY OF DATA, CODE, AND OTHER MATERIALS

Available on request via the corresponding author.

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