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Bibliography

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ABSTRACT

Background and study aims Upper gastrointestinal (UGI) endoscopy lacks established quality indicators. We conducted an umbrella systematic review of potential quality indicators for the detection of UGI cancer and dysplasia.

Methods Bibliographic databases were searched up to December 2021 for systematic reviews and primary studies. Studies reporting diagnostic accuracy, detection rates or the association of endoscopy or endoscopist-related factors with UGI cancer or dysplasia detection were included. AMSTAR2 and JBI checklists were used to assess systematic review and primary study quality. Clinical heterogeneity precluded meta-analysis and findings are summarized narratively.

Results Eight systematic reviews and nine primary studies were included. Image enhancement, especially narrow band imaging, had high diagnostic accuracy for dysplasia and early gastric cancer (pooled sensitivity 0.87 (95% CI 0.84–0.89) and specificity 0.97 (0.97–0.98)). Higher detection rates with longer endoscopy examination times were reported in three studies, but no difference was observed in one study. Endoscopist biopsy rate was associated with increased gastric cancer detection (odds ratio 2.5; 95% confidence interval [CI] 2.1–2.9). Early esophageal cancer (0.17% vs 0.14%, $P=0.04$) and gastric cancer (0.16% vs 0.12%, $P=0.02$) detection rates were higher with propofol sedation compared to no sedation. Endoscopies performed by trained endoscopists on dedicated Barrett's surveillance lists had higher detection rates (8% vs 3%, $P<0.001$). The neoplasia detection rate during diagnostic endoscopies for Barrett's esophagus was 7% (95% CI 4%-10%).

Conclusions Image enhancement use, longer examination times, biopsy rate and propofol sedation are potential quality indicators for UGI endoscopy. Neoplasia detection rate and dedicated endoscopy lists are additional potential quality indicators for Barrett's esophagus

Introduction

Endoscopy is the investigation of choice to detect upper gastrointestinal (UGI) cancers and premalignant conditions. However, 7% to 11% patients with UGI cancer have had an endoscopy within the 3 years prior to their cancer diagnosis which failed to diagnose cancer [1,2,3,4]. Improving endoscopy quality can therefore potentially detect UGI cancer at an earlier, or even premalignant, stage enabling organ-preserving endoscopic therapy and improve the often poor prognosis of UGI cancer.

Endoscopic societies have recommended a number of performance measures to optimize endoscopy quality but these are focused predominantly on the overall performance of diagnostic endoscopy, rather than cancer and dysplasia detection [5,6,7]. However, the recent Asian consensus guideline focused on the early detection of UGI neoplasia [8] and recommended premedication and antispasmodic agents, intravenous sedation, image enhancing techniques and sufficient observation time. Although, limited evidence was noted reporting the association of these factors with the detection of UGI cancer and dysplasia.

We have performed an umbrella review summarizing the evidence for the association of potential endoscopic quality indicators with the detection of UGI cancer and dysplasia.

Methodology

The systematic review protocol was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/ID=CRD42020225339). The reporting of the review was in accordance with the PRISMA guidelines (**Supplementary Table 1**). Study selection and data extraction (including quality assessment) was undertaken independently by at least two reviewers (U.K., N.U., A.A or I.T.). Disagreements were resolved through discussion or referral to the senior authors when consensus could not be reached.

Search strategy

A list of potential quality indicators was formulated from scoping searches and published guidelines (**Supplementary Table 2**). Searches for existing systematic reviews were undertaken in Embase, MEDLINE, MEDLINE In-Process, Cochrane Database of Systematic Reviews and Epistemonikos to December 2021. Supplementary searches for primary studies were undertaken in Embase, MEDLINE and CINAHL for quality indicators not examined by a recent high-quality systematic review. Searches combined index terms and text words relating to endoscopy, UGI tract and dysplasia or neoplasm, and used filters for systematic reviews where applicable. There was no restriction by study design in searches for primary studies. Reference lists of included studies and published guidelines were searched for additional primary studies. There were no language restrictions. Examples of search strategies are provided in **Supplementary Table 3** and **Supplementary Table 4**.

Study eligibility and selection

Systematic reviews and primary studies were included if they: 1) reported the detection rate of UGI cancer or dysplasia in relation to one or more endoscopic factors (procedural, endoscopist or endoscopy unit related); 2) reported diagnostic accuracy of endoscopic factors for UGI cancer or dysplasia detection; or 3) reported the association between detection rate and endoscopic factors. Eligible populations were adult patients undergoing endoscopy for screening for UGI cancer or dysplasia, to investigate UGI symptoms or for the surveillance of high-risk conditions (e.g. Barrett's esophagus, gastric atrophy and gastric intestinal metaplasia). Exclusion criteria included narrative (non-systematic) reviews, case reports, conference abstracts and studies with no primary data (e.g. commentaries). A systematic review was defined as a review that at minimum used several data sources to identify studies. Studies which only assessed performance of transnasal or capsule endoscopy, or endoscopic modalities not widely used e.g. artificial intelligence and confocal laser endomicroscopy were also excluded. Where more than one systematic review was identified for an indicator, inclusion was limited to the most recent, comprehensive and/or methodologically robust systematic review. Primary studies of the discarded systematic reviews were cross referenced with the studies included in the most recent systematic review to ensure there were no omissions.

Data extraction and quality assessment

Data extraction was carried out using a piloted data extraction form. Data were collected on study design, population characteristics, sample size, endoscopy indicators, and results (detection rates or diagnostic accuracy measures). Pooled summary estimates were extracted from systematic reviews.

The AMSTAR 2 tool was used to assess systematic review quality. The quality assessment standards included: multiple databases searched; data extraction and quality assessment performed by more than one reviewer; quality and risk of bias assessment of included studies performed; adequate consideration of heterogeneity of included studies in the synthesis [9].

The revised Cochrane risk of bias tool (ROB2) was used to assess randomized controlled trial quality and risk of bias arising from the process of randomization, assignment and adherence to the intervention, missingness of outcome data, measurement of outcome and reporting of results was assessed [10]. A modified JBI (The Joanna Briggs Institute) checklist for cohort studies was used to assess the primary study quality. The quality assessment standard included: criteria to recruit the study population; reliability of measures used to assess the exposure; differences in the experience and training of endoscopists between the groups; strategies to identify and deal with confounding factors; and generalisability of study findings [11].

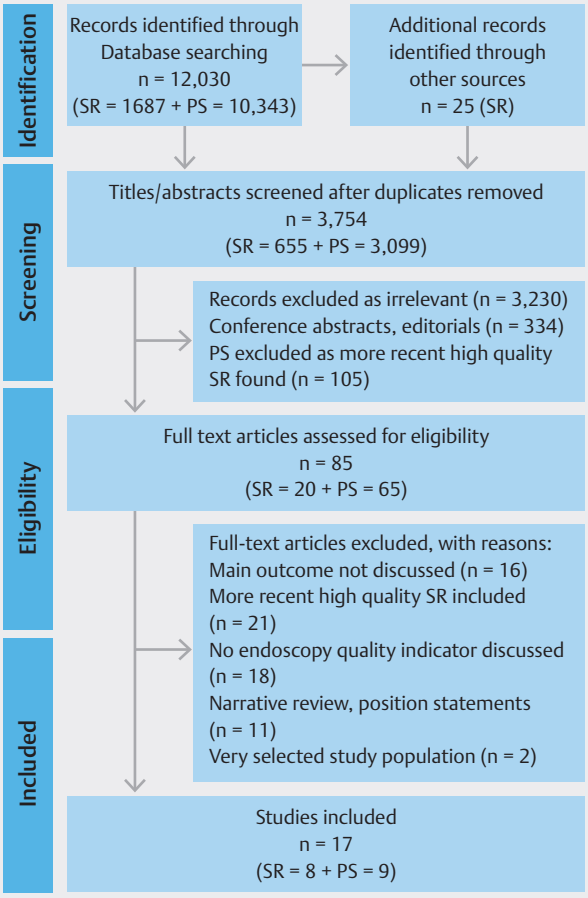
Data synthesis

Results are presented for each quality indicator separately. As Barrett's esophagus is the most common premalignant condition studied, quality indicators associated with the detection of cancer and dysplasia in Barrett's esophagus were categorized separately. All results were described narratively. For endoscopy examination time, summary estimates were presented in forest plots to show the direction of effect and consistency among studies; pooling of results was not feasible due to significant heterogeneity due to differences in study population and endoscopist experience. Findings were interpreted in the context of study quality, taking into account whether any associations identified were adjusted for confounders.

Results

In total, 3,754 studies were screened after removing duplicates and 17 fulfilled the inclusion criteria. These included eight systematic reviews, eight retrospective cohort studies, and one randomized controlled trial (▶ **Fig. 1**) [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28]. List of the studies excluded after full text review and reasons of exclusion are provided in **Supplementary Table 5**.

The characteristics of the included studies are presented in ▶ **Table 1** (systematic reviews) and ▶ **Table 2** (primary studies). Results of all meta-analyses included were based on random effect models.



▶ **Fig. 1** Flowchart of selecting eligible studies. SR, systematic reviews; PS, primary studies.

Potential quality indicators

The results of the studies reporting potential quality indicators for UGI endoscopy are presented in ▶ **Table 3**.

Image enhancement techniques

Three systematic reviews reported the role of advanced imaging techniques in the detection of gastric cancer or dysplasia [12, 13, 14]. A meta-analysis of 19 studies reported that narrow-band imaging (NBI) had a pooled sensitivity of 0.87 (95% confidence interval 0.84–0.89) and pooled specificity of 0.97 (0.97–0.98) [13]. Diagnostic accuracy was higher in depressed-type lesions (pooled sensitivity 0.88 (0.80–0.93), pooled specificity 0.96 (0.93–0.97)) than elevated-type lesions (pooled sensitivity 0.88 (0.82–0.92), pooled specificity 0.87 (0.80–0.92)). On subgroup analysis, the use of magnification endoscopy with NBI (ME-NBI) was associated with diagnostic odds ratio of 114.08 (46.30–281.08) compared to 60.34 (9.26–393.14) for non-ME-NBI [13].

A network meta-analysis of eight prospective studies reported that the use of magnification was superior to standard white light endoscopy in detecting early gastric cancer (odds ratio 2.97 [1.68–5.25]) [12].

▶ **Table 1** Characteristics of included systematic reviews.

Serial number	First author (publication year)	Quality indicators examined	Searched years	No. and design of studies included	Population studied	No. of patients	Main risk of bias
1	Parasa S (2019) [25]	Neoplasia detection rate	2009–2018	11 (7 retrospective, 4 prospective)	Patients with GERD symptoms undergoing screening for Barrett's	10,632	Paucity of data on patient demographics. Pooled results of different study designs (Retrospective and Prospective)
2	Coletta M (2016) [23]	Acetic acid chromoendoscopy	Inception to 2014	13 (prospective)	Patients with Barrett's esophagus	1690	Variation in unit of analyses across studies i.e per patient, per area and per procedure analyses
3	Hajelssedig O (2018) [24]	NBI and targeted biopsies	Inception to 2018	6 (4 RCT, 1 cross-sectional, 1 single-arm crossover)	Patients referred for routine surveillance or were referred for further evaluation of dysplasia in Barrett's esophagus	493	Unblinded comparison between NBI and WLE in four studies
4	Qumseya B (2013) [22]	Advanced imaging techniques	Inception to October 2012	14 (11 RCT, 1 prospective, 1 cross-sectional, 1 post hoc analysis of images)	Patients undergoing Barrett's surveillance	843	Searches limited to English language
5	Rodriguez M (2020) [13]	Image enhancing techniques	Inception to December 2018	44 (5 RCT, 32 prospective and 7 retrospective)	Not specified	10175	52% of studies reported selection bias as highly selected patients/ gastric area or lesion type
6	Le H (2021) [12]	Magnification endoscopy	Inception to March 2020	8 (prospective)	Not specified	5948	
7	Zhao Z (2016) [14]	Dye-based chromoendoscopy	Inception to September 2015	10 (9 prospective, 1 retrospective)	Not specified	699	Details of quality assessment not reported
8	Morita F (2017) [28]	Narrow band imaging	Inception to November 2015	12 (1 prospective, 11 cross-sectional)	Not specified	1911	False negative rate cannot be assessed as only suspicious lesions were biopsied

GERD, gastroesophageal reflux disease; NBI, narrow band imaging; WLE, white light endoscopy; RCT, randomized controlled trial.

The use of dye-based chromoendoscopy (including acetic acid, indigo carmine, methylene blue and hematoxylin) favored detection of early gastric cancer (pooled risk difference 0.36 [0.11–0.61]) and premalignant conditions (pooled risk difference 0.17 [0.07–0.28]), compared to standard white light endoscopy [14]. No subgroup analyses were performed to examine the diagnostic accuracy of individual dyes and most of the studies (80%) included were conducted in Asian countries with a high prevalence of gastric cancer and associated premalignant conditions [14].

▶ **Table 2** Characteristics of included primary studies.

Serial number	First author (Publication year, country)	Study design	Factor examined	Definition of intervention/exposure	Comparator arms	Sample size	Target population
1	Park J (2017, South Korea) [17]	Retrospective, Single center	Inspection time	Time from duodenal intubation to withdrawal from mouth	Fast (<3 min) vs slow endoscopists (≥3 min)	111962	Asymptomatic patients undergoing screening
2	Kawamura T (2017, Japan) [18]	Retrospective, single center	Inspection time	Time from the first image capture in the pharynx or the upper esophagus to when the exit button was pushed	Fast (<5 min) vs moderate (5–7 min) vs slow (>7 min)	15763	Asymptomatic patients undergoing screening
3	Teh J (2015, Singapore) [15]	Retrospective, single center	Inspection time	Time the endoscope was inserted into the patient's mouth to the time it was withdrawn	Fast <7 min vs Slow >7 min	837	Symptomatic patients
4	Yoshimizu S (2018, Japan) [20]	Retrospective, single center	Inspection time	Time from first image capture in the pharynx to scope removal	Fast (<7 min) vs Moderate (≥7 min and <10 min) vs Slow (≥10 min)	3295	Asymptomatic patients undergoing screening
5	Gupta N (2012, United States) [26]	Retrospective post hoc analysis of Multicenter RCT	Inspection time	Time spent on inspection of Barrett's mucosa on HD-WLE (Excluded time spent using image enhancement techniques or for biopsies)	Inspection time >1 min/cm vs ≤1 min/cm	112	Patients undergoing Barrett's surveillance or referred to confirm dysplasia
6	Ooi J (2017, United Kingdom) [27]	Retrospective control vs prospective intervention, multicenter	Dedicated list by trained endoscopists	Endoscopies performed on dedicated lists by endoscopists trained in Barrett's surveillance	Dedicated lists vs non-dedicated lists	729	Patients undergoing Barrett's surveillance
7	Januszewicz W (2019, Poland) [16]	Retrospective cohort, multicenter	Endoscopist biopsy rate	Proportion of endoscopies where at least one biopsy was taken (Biopsies for urease test not included)	Low (22.4% to 36.7%) vs moderate (36.8% to 43.7%) vs high (43.8% to 51.6%) vs very high (51.7% to 65.8%)	12,433 (Derivation cohort) 11,333 (Validation cohort)	Outpatient, Symptomatic and under surveillance
8	Zhou J (2021, China) [19]	Retrospective, multicenter	Intravenous sedation	Use of propofol without intubation by anaesthesiologist	Propofol vs no sedation (propensity matched groups)	306202	Adults undergoing diagnostic endoscopies
9	Liu X (2018, China) [21]	Multicenter RCT	Premedications	Use of simethicone and pronase mixed with water	A 100 mL water + 20,000 units Pronase + 1 g $NaHCO_3$ B 100 mL water + 80 mg Simethicone C 100 mL water + 20,000 units Pronase + 1 g $NaHCO_3$ + 80 mg Simethicone D 100 water	7143	Patients attending endoscopy for screening

▶ **Table 3** Results of studies reporting potential quality indicators associated with detection of dysplasia and cancer on upper gastrointestinal endoscopy.

Quality indicator	Systematic review or primary study	Outcome	Pooled odds ratio	Pooled sensitivity	Pooled specificity	Pooled risk difference	Adjusted odds ratio	Detection rates	Comments
Image enhancing techniques									
Narrow band imaging	SR and MA [13]	Early gastric cancer or dysplasia		0.87 (0.84–0.89)	0.97 (0.97–0.98)				Use of magnification associated with higher DOR and specificity. Most studies performed in Eastern countries with higher prevalence of gastric cancer
	SR and MA [28]	Squamous cell cancers and HGD of esophagus		Per lesion: 0.94 (0.90–0.97) Per patient: 0.88 (0.82–0.93)	Per lesion: 0.65 (0.60–0.69) Per patient: 0.88 (0.86–0.90)				NBI had higher specificity than Lugol chromoendoscopy, although sensitivity and area under curve were similar
Magnification endoscopy	SR and network MA [12]	Early gastric cancer	Overall: 2.97 (1.68–5.25) M-NBI: 2.56 (2.13–3.13) M-BLI: 3.13 (1.85–5.71) M-WLI:1.43 (1.12–1.85)						Magnification with NBI and BLI were superior to magnification with WLE. Important confounders e.g endoscopist experience not adjusted for
Dye-based chromoendoscopy	SR and MA [14]	Early gastric cancer and dysplasia		0.90 (0.87–0.92)	0.82 (0.79–0.86)	Early gastric cancer: 0.36 (0.11–0.61) Gastric dysplasia: 0.17 (0.07–0.28)			Most studies from Asia. No subgroup analysis based on different dyes

▶ **Table 3** (Continuation)

Quality indicator	Systematic review or primary study	Outcome	Pooled odds ratio	Pooled sensitivity	Pooled specificity	Pooled risk difference	Adjusted odds ratio	Detection rates	Comments
Observation time	Primary study [17]	Esophageal and gastric cancers						Fast 0.20% vs Slow 0.28%, $P = 0.005$	Endoscopists with examination time >3 min detected 8% more small cancers, no difference in detection of large cancers. Screening asymptomatic patients
	Primary study [18]	Esophageal and gastric cancers					Moderate 1.90 (1.06–3.40) Slow 1.89 (0.98–3.64)	Fast 0.57% vs moderate 0.97% vs slow 0.94%	Examination time 5–7 minutes was associated with higher cancer detection rate. Factors adjusted for: sex, age, use of sedation, gastric atrophy, type of scope
	Primary study [15]	Gastric cancer and high-risk lesions					Slow 3.42 (1.25–10.38)	Fast 6.1% vs slow 14.0% $P < 0.01$	Examination time >7 min was associated with 3 times increased likelihood of detection of gastric cancer. Factors adjusted for: age, sex, endoscopist experience
	Primary study [20]	Esophageal and gastric cancers						Fast 3.6 % vs moderate 3.3 % vs Slow 3.1 % ($P = 0.807$)	No difference in cancer detection rate. All endoscopists in fast group had intense training, compared to 66% in slow group
Biopsy rate	Primary study [16]	Gastric cancers and premalignant conditions					Moderate 0.8 (0.5–1.2) High 3.0 (2.4–3.7) Very high 5.6 (3.2–9.8)		Factors adjusted for: age, sex and endoscopy unit. Strong correlation between endoscopist biopsy rate and detection of all UGI premalignant lesions

▶ **Table 3** (Continuation)

Quality indicator	Systematic review or primary study	Outcome	Pooled odds ratio	Pooled sensitivity	Pooled specificity	Pooled risk difference	Adjusted odds ratio	Detection rates	Comments
Intravenous sedation	Primary study [19]	Early esophageal cancer						Sedation vs no sedation: 0.17% vs 0.14%, $P=0.04$	Sedation group had higher detection rate of early UGI cancer
		Early gastric cancer						Sedation vs no sedation: 0.16% vs 0.12%, $P=0.02$	
Premedications	Primary study [21]	Early esophageal or gastric cancers						A: 1.3%, B:1.4%, C: 1.5% and D: 1.6%, $P=0.878$	Use of simethicone and Pronase on their own or as combination did not improve detection rate of cancer or precancerous lesions. All endoscopists had experience of 3000–5000 endoscopies
		Esophageal and gastric premalignant conditions						A: 8.7%, B: 8.4%, C: 10.0%, D: 10.3% $P=0.138$	

SR, systematic review; MA, meta-analysis; HGD, high-grade dysplasia; DOR, diagnostic odds ratio; NBI, narrow band imaging; WLE, white light endoscopy; BLI, blue laser imaging; UGI, upper gastrointestinal.

A systematic review of 18 studies (12 studies included in a meta-analysis) compared NBI with Lugol chromoendoscopy in the detection of esophageal squamous cell cancer and/or high-grade dysplasia.[28] Pathological diagnosis was used as the gold standard. Specificity was higher for NBI (0.88 (0.86–0.90)) than Lugol chromoendoscopy (0.82 (0.80–0.85)). However, there was no difference in sensitivity and area under receiver operating curve between the two modalities.

Endoscopic examination time

Four retrospective studies compared neoplastic detection rates based on the endoscopic examination time [15, 17, 18, 20]. Three studies analyzed the detection of all UGI neoplasms [17, 18, 20], and one analyzed detection of gastric malignant and premalignant lesions only [15]. There was heterogeneity among studies with regards to the definition of examination time. Three studies recorded the time from endoscope insertion into the mouth or pharynx to the scope withdrawal from the mouth [15, 18, 20], and one recorded the scope withdrawal time from duodenum to the mouth [17]. Two studies reported that a longer examination time was associated with higher neoplasm detection rate [15, 17]. Kawamura et al. reported that the endoscopists with moderate (5–7 minutes) and longer (>7 minutes) examination times had higher UGI cancer detection rates than the endoscopists with shorter (<5 minutes) examination time, however detection rates were similar between endoscopists in moderate and longer examination time groups [18]. One study reported that the esophageal and gastric cancer detection rates were not statistically different between fast, moderate and slow endoscopists [20]. Although all endoscopists included in this study had an overall experience of performing more than 1000 endoscopies, only 66% of the endoscopists with longer examination times had received intense training in lesion detection, compared to the all endoscopists

with shorter examination times [20]. **Supplementary Fig. 1** shows the forest plot of neoplastic detection rates based on examination time.

Biopsy rate

A multicenter retrospective cohort study reported the association of endoscopists' biopsy rates and the rates of both gastric cancer and premalignant diagnoses, and missed gastric cancers (diagnosed between 1 month to 3 years after an endoscopy without a cancer diagnosis) [16]. The biopsy rate was calculated as the proportion of endoscopies where at least one biopsy was taken (excluding samples for rapid urease testing). Endoscopists' biopsy rates strongly correlated with gastric premalignant lesions detection (ρ 0.83; P <0.001). After adjusting for age, sex and endoscopy unit, biopsy rate was strongly associated with gastric cancer detection (OR for highest biopsy rate 5.6 [95% CI 3.2–9.8]). The incidence of missed gastric cancer in the lower biopsy rate group was 49.6 per 100,000 person-years compared to 23.1 per 100,000 person-years in higher biopsy rate.

Intravenous sedation

A multicenter retrospective study compared detection rates of early esophageal and gastric cancers in patients who underwent endoscopic examination under sedation (propofol without tracheal intubation) with patients who underwent endoscopy without sedation, after propensity matching [19]. Patients in the sedation group had higher early esophageal cancer (0.17% vs 0.14%, P = 0.04) and gastric cancer detection rates (0.16% vs 0.12%, P = 0.02). Mean examination time was longer in the sedation group, and more patients in the sedation group were examined using image enhancement and magnification techniques.

Mucolytics and defoaming agents

A multicenter randomized control trial examined the effect of defoaming (Simethicone) and mucolytic (Pronase) agents on the detection of early UGI cancers or premalignant lesions (primary endpoint) and mucosal visibility (secondary endpoint). Although premedication improved mucosal visibility at all important anatomical landmarks in the esophagus and stomach (P<0.001), neoplasia detection rates were not statistically different between intervention and control groups [21].

Potential quality indicators for Barrett's esophagus

The results of the studies reporting potential endoscopy quality indicators specific to the assessment and surveillance of Barrett's esophagus are presented in ▶ **Table 4**.

Image enhancement techniques

Three systematic reviews and meta-analyses, including 33 studies, analyzed the role of image enhancement techniques in the detection of dysplasia and cancer during Barrett's surveillance [22, 23, 24]. Compared to standard white light endoscopy, both virtual and dye-based chromoendoscopy increased the diagnostic yield for dysplasia or cancer by 34% (95% CI 20–48), however no significant difference was found between virtual and dye-based chromoendoscopy and the findings were not adjusted for important confounding factors e. g. endoscopist experience [22].

The use of acetic acid with targeted biopsies had a sensitivity of 0.92 (0.83–0.97) and specificity of 0.96 (0.85–0.99) for high-grade dysplasia (HGD) and early esophageal adenocarcinoma.[23] NBI with targeted biopsies had a high diagnostic accuracy for all-grade dysplasia (sensitivity 0.76 [0.61–0.91] and specificity 0.99 [0.99–1.00]) and HGD (sensitivity 0.83 [0.73–0.93] and specificity 0.99 [0.99–1.00]), in comparison to the Seattle protocol biopsies. However, its sensitivity was lower for low-grade dysplasia (0.60 [0.11–1.00]) [24]. Compared to random biopsies, the numbers needed to detect an additional patient with HGD and low-grade dysplasia using NBI were 1.95 and 3.95 respectively. None of the studies included in this meta-analysis reported data for the median prevalence of dysplasia. No statistically significant difference in the results was observed in a sensitivity analysis of four studies which used magnification.

Examination time

In a post hoc analysis of a multicenter clinical trial, a greater proportion of patients were found to have endoscopically suspicious lesions as the total inspection time of Barrett's esophagus with high-definition white light endoscopy increased (P<0.001) [26]. This effect persisted even after excluding overtly suspicious lesions. Endoscopists with average inspection times of >1 min per centimeter of Barrett's mucosa had higher detection rates of endoscopically suspicious lesions (54.2% vs 13.3%, P = 0.04) but the difference in rates of HGD/early esophageal adenocarcinoma just failed to reach statistical significance (40.2% vs 6.7%, P = 0.06).

Dedicated endoscopy lists by trained endoscopists

A multicenter study prospectively analyzed the dysplasia detection rate of endoscopists trained in lesion recognition, Prague classification and Seattle biopsy protocol technique, undertaking Barrett's surveillance on dedicated lists with extra time for the endoscopies and compared these interventions with historic data of Barrett's surveillance endoscopies [27]. Dedicated sessions had higher detection rates for all grades of dysplasia (18% vs 8%, P <0.001) and HGD/early esophageal adenocarcinoma (8% vs 3%, P <0.001).

Neoplasia detection rate

A systematic review including 11 studies (10,632 patients) defined the neoplasia detection rate (NDR) as the pooled prevalence of HGD and early esophageal adenocarcinoma on the index endoscopy for patients with chronic gastro-esophageal reflux symptoms undergoing screening for Barrett's esophagus [25]. NDR was estimated at 7% (95% CI 4–10) and proposed as a quality measure for such endoscopies.

Other potential quality indicators

No studies have directly examined the association between the detection rate of UGI cancer/dysplasia and the use of antispas-

▶ **Table 4** Results of studies reporting potential quality indicators associated with the detection of dysplasia and cancer on upper gastrointestinal endoscopy for Barrett's esophagus.

Quality indicator	Systematic review or primary study	Outcome	Pooled prevalence	Pooled sensitivity	Pooled specificity	Pooled risk difference	Detection rates	Comment
Image enhancing techniques								
Narrow band imaging guided targeted biopsies	SR and MA [24]	All-grade dysplasia		0.76 (0.61–0.91).	0.99 (0.99–1.00)			NBI targeted biopsies have high diagnostic accuracy for all-grade dysplasia but low sensitivity for LGD
		HGD		0.83 (0.73–0.93)	0.99 (0.99–1.00)			
		LGD		0.60 (0.11–1.00)	0.98 (0.95–1.00)			
Acetic Acid	SR and MA [23]	HGD and early esophageal cancer		0.92 (0.83–0.97)	0.96 (0.85–0.99)			Median prevalence of HGD/ early esophageal cancer was 13%, higher than expected in general surveillance population
Virtual and chromoendoscopy	SR and MA [22]	All-grade dysplasia				0.34 (0.20–0.48)		Heterogenous studies due to use of different imaging modalities
Observation time	Primary study [26]	Endoscopic lesions suspicious of dysplasia					Observation time >1 min/cm vs ≤1 min/cm: 54.2% vs 13.3%, P = 0.04	High prevalence of HGD/ early esophageal cancer (i. e. 34%) in study population. All endoscopies performed by experienced endoscopists in academic referral center. Relatively smaller sample size may have resulted in type II error
		Histologically proven HGD/ early esophageal cancer					Observation time >1 min/cm vs ≤ 1 min/cm: 40.2% vs 6.7%, P= 0.06	
Dedicated list by trained endoscopist	Primary study [27]	All-grade dysplasia					18% vs 8% (P <0.001)	
		HGD/early esophageal cancer					8% vs 3%, (P<0.001)	
Neoplasia detection rate	SR and MA [25]	HGD/early esophageal cancer	7% (4–10)					Higher prevalence in US studies 11% (7–16) vs non-US studies 5% (3–8)

SR, systematic review; MA, meta-analysis; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NBI, narrow band imaging.

▶ **Table 5** Summary of quality indicators for upper gastrointestinal endoscopy in national and international guidelines as evidence from this systematic review.

Quality indicator	BSG (2017) [5]	ESGE (2016) [6]	AGA (2015) [7]	Asian consensus (2019) [8]	Evidence (Summary of evidence for the detection of UGI cancer or dysplasia)
Mucolytic and defoaming agents	Recommended	Not specified	Not specified	Recommended	No evidence-one RCT: no difference in the detection rates.
Intravenous sedation	When required	Not specified	Recommended	Recommended	Insufficient evidence- one retrospective study: Sedation (Propofol) improved detection rates
Minimum number of procedures to maintain competence	≥100 per year	Not specified	Not specified	Not specified	No evidence
Examination time	≥7 minutes	≥7 minutes	Not specified	≥8 minutes	Insufficient evidence- 3 retrospective cohort studies favor longer observation time, but unable to recommend minimum cut off due to heterogeneity. One study did not find a difference.
Image enhancement techniques	Recommended if squamous neoplasia suspected in esophagus	Recommended if squamous neoplasia suspected in esophagus	Not specified	Recommended	Quality indicator recommended as multiple systematic reviews support use of image enhancement techniques
Photo documentation	Minimum 8 images	Minimum 10 images	Not specified	Minimum 22 images	No evidence
Endoscopist Biopsy rate	Not specified	Not specified	Not specified	Not specified	Insufficient evidence- strong correlation with detection of gastric cancer and all UGI premalignant conditions
Barrett's mucosa inspection time	≥1 min per cm	≥1 min per cm	Not specified	≥1 min per cm	Insufficient evidence- post hoc analysis of RCT: higher rate of endoscopic suspicious lesion but no difference in detection of HGD or cancer
Dedicated list by trained endoscopist for Barrett's surveillance	Not specified	Not specified	Not specified	Not specified	Insufficient evidence-prospective cohort compared with retrospective data showed improved detection rates
Neoplasia detection rate on index endoscopy for Barrett's screening	Not specified	Not specified	Not specified	Not specified	Insufficient evidence- one systematic review reported the prevalence of HGD and esophageal adenocarcinoma for patients undergoing screening for Barrett's esophagus.

BSG, British Society of Gastroenterology; ESGE, European Society of Gastrointestinal Endoscopy; AGA, American Gastroenterological Association; UGI, upper gastrointestinal; RCT, randomized controlled trial; HGD, high-grade dysplasia.

modic medications, photo documentation, endoscopists' specialty or the annual volume of endoscopies.

A summary of the evidence and comparison with published endoscopy society guidelines is presented in ▶ **Table 5**.

Quality assessment

The quality assessment of the systematic reviews is summarized in **Supplementary Table 6**. Overall, the reviews were of high methodological quality. The main risk of bias was the heterogeneity due to a wide variation in the prevalence of UGI cancer and dysplasia, use of different imaging modalities and non-adjustment for important confounding factors, e. g. endoscopist experience.

The summary of the quality assessment of primary studies is shown in **Supplementary Table 7**. The main concern in 88% of the studies was that the included study population was not always representative of the standard endoscopy population in terms of underlying risk (of cancer and dysplasia). There was a difference in the endoscopists' training and experience between the two study groups in 50% of studies [17, 18, 20, 27] and confounding factors were not identified in two studies [26, 27]. The randomized controlled trial on premedication presented an overall low risk of bias, except for some concern due to the lack of strict adherence to the timing of the mucolytic and defoaming agents [21].

Discussion

Gastric and esophageal cancers are the fourth and fifth leading causes of cancer related deaths worldwide, mainly owing to their typically late presentation [29]. Screening programs have been developed for some high incidence populations, but they have not been implemented in most parts of the world and endoscopy is generally limited to investigating UGI symptoms and for the surveillance of premalignant conditions [30, 31, 32]. High-quality endoscopy still has a critical role in identifying and monitoring premalignant conditions and in the detection of associated cancer and dysplasia, which may be amenable to endoscopic treatment. In this umbrella review we have summarized the evidence for potential quality indicators to improve the diagnostic yield of endoscopy for the detection of UGI cancer and dysplasia.

British and European endoscopic society guidelines recommend white light endoscopy and random biopsies to diagnose premalignant conditions and targeted biopsies for suspected malignant lesions [5, 6]. Dye and targeted image enhancement techniques were recommended for better characterization if squamous dysplasia is suspected in the esophagus. However, routine use of chromoendoscopy was not recommended due to a lack of robust evidence. The current review found evidence in favor of image enhancement techniques, especially NBI; Olympus, Japan). NBI uses filters to enhance microvascular patterns, mainly as a result of the differential optical absorption of light by hemoglobin in the mucosa. NBI, with or without magnification, had a high diagnostic accuracy for the detection of early gastric and esophageal cancers. However, studies included endoscopists who were experienced in using NBI, or had training in using NBI patterns in enriched populations with a high risk of cancer or dysplasia. This may not be reflective of the routine practice as the majority of endoscopists are not trained in lesion recognition using NBI. A standardized training program to use image enhancement techniques can potentially improve endoscopist performance [33]. Several other chromoendoscopy systems are also available, including i-scan (Pentax, Japan), FICE (Flexile spectral imaging color enhancement; Fujifilm, Japan), SPICE (STORZ professional imaging enhancement system, Storz, Germany) and BLI (Blue laser imaging; Fujifilm, Japan). However, performance of each system has not been compared to date. The value of image enhancement was endorsed in the more recent Asian consensus guidelines [8]. We recommend from this umbrella systematic review that image enhancement techniques should be considered to enhance the earlier detection and delineation of UGI cancer and dysplastic lesions particularly in high-risk patients.

For Barrett's surveillance, chromoendoscopy guided biopsies had high diagnostic accuracy to detect HGD and early esophageal adenocarcinoma, however, the sensitivity was only 60% for low-grade dysplasia (LGD). LGD is the histological or clinical marker associated with the highest risk of progression to HGD or esophageal adenocarcinoma and there is increasing evidence that LGD can be successfully treated endoscopically, which can halt its progression [34]. Based on current evidence, chromoendoscopy targeted biopsies therefore cannot replace Seattle protocol biopsies, given the low sensitivity for LGD and chromoendoscopy should be used as an adjunct in Barrett's surveillance.

Colonoscopic withdrawal time is a well-established quality indicator for colonoscopy and longer withdrawal times have been shown to be associated with higher adenoma detection rates and a reduced incidence of interval colorectal cancers [35]. Western guidelines have recommended a minimum procedure time of 7 minutes for endoscopy [5, 6], but that recommendation was based on a single retrospective cohort study [15]. The Asian consensus guideline suggested that the systematic observation of the UGI tract should take a minimum of 8 minutes. In the current review, we found three additional retrospective studies. All except one study reported that a longer examination time can increase the diagnostic yield of endoscopy for cancer or dysplasia. Yoshomizu et al. did not find a difference in the UGI cancer detection rates based on the difference in endoscopic examination time [20]. However, all of the endoscopists who had shorter examination times had received ≥1 year of intense training in lesion detection, compared to only 66% of the endoscopists with longer examination times in this study, likely introducing performance bias, as the endoscopists with ≥1 year of intense training were more likely to find UGI cancers (OR 1.65 (1.02–2.68)). Longer inspection times of Barrett's mucosa have also been shown to increase the detection rate of endoscopic suspicious lesions. Although the difference in the rate of detection of HGD and esophageal adenocarcinoma was not statistically significant, the relatively smaller sample size in this study may have resulted in type II error [26]. Although most of the studies favored longer examination times, it is not possible to comment on the minimum cut off

time due to significant heterogeneity among studies and further data in different populations are clearly needed on this important indicator with adjustment for the experience of the endoscopists.

The endoscopist biopsy rate was found to have a strong correlation with the detection of gastric cancer and premalignant conditions and was associated with a lower incidence of missed gastric cancers. However, this observation was based on a single retrospective study from Poland and should be validated in other parts of the world [16].

The use of sedation can improve patient acceptance and tolerance of endoscopy, which are both important for a high-quality examination. Only one study has investigated impact of sedation on the diagnostic yield and reported that the detection rate for early UGI cancer was higher among patients who received sedation with propofol [19]. However, results in this study were not adjusted for the important confounders e. g. the use of image enhancement and magnifying techniques, observation time and the number of biopsies taken. Furthermore, propofol was used for sedation in this study, in addition to midazolam and opioid, which is not a routine practice in most parts of the world, indicating that the study findings may not be generalizable and warrant further validation.

The NDR at the index or first diagnostic endoscopy has been proposed as a quality indicator for patients undergoing screening for Barrett's esophagus. Four to ten percent of patients with Barrett's esophagus are found to have advanced neoplasia on their index endoscopy [25]. Given the relatively low progression rates of non-dysplastic Barrett's esophagus to advanced neoplasia, this high prevalence rate suggests that a high-quality index endoscopy will have the most significant impact in preventing death from neoplasia in Barrett's patients. Similar to the concept of adenoma detection rate in colonoscopy, endoscopists performing high-quality Barrett's surveillance endoscopies would be expected to find a higher proportion of patients with advanced neoplasia. However, the association of higher NDRs with the outcomes of missed or interval UGI cancers and cancer related mortality have not been studied to date.

For Barrett's surveillance, appropriate time slots and training in the Prague classification, Seattle protocol biopsy regimen and lesion recognition resulted in improvements in the endoscopists' performance and a more than two-fold increase in all grades of dysplasia and esophageal adenocarcinoma detection. These measures should be investigated in further prospective studies and considered as potential quality indicators for Barrett's surveillance.

Some limitations have to be considered. The majority of the studies examined were carried out in Eastern countries where the prevalence of gastric cancer is much higher than in Western countries. There were high levels of heterogeneity among the studies regarding study population, endoscopist experience and the strategies used to measure the exposure of interest e. g. examination time. The formal assessment of small study effects (including publication bias) was not possible. Interventions such as artificial intelligence and confocal laser endomicroscopy, which could potentially improve the diagnostic yield of endoscopy were not included as they lack published data.

Conclusions

This review has found evidence for image enhancement techniques, which should be considered to improve the diagnostic yield of UGI endoscopy. Examination time, endoscopist biopsy rate and intravenous sedation are other potential quality indicators, but need further investigation in prospective studies. Neoplasia detection rate and dedicated lists by trained endoscopists were identified as additional quality indicators for Barrett's esophagus.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

[1] Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis Endosc Int Open 2014; 2: E46–E50 doi:10.1055/s-0034-1365524

[2] Chadwick G, Groene O, Hoare J et al. A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. Endoscopy 2014; 46: 553–560 doi:10.1055/s-0034-1365646

[3] Chadwick G, Groene O, Riley S et al. Gastric cancers missed during endoscopy in England. Clin Gastroenterol Hepatol 2015; 13: 1264–1270.e1

[4] Pimenta-Melo AR, Monteiro-Soares M, Lib â nio D et al. Missing rate for gastric cancer during upper gastrointestinal endoscopy. Europ J Gastroenterol Hepatol 2016; 28: 1041–1049

[5] Beg S, Ragunath K, Wyman A et al. Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS). Gut 2017; 66: 1886–1899 doi:10.1136/gutjnl-2017-314109

[6] Bisschops R, Areia M, Coron E et al. Performance measures for upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. Endoscopy 2016; 48: 843–864 doi:10.1055/s-0042-113128

[7] Park WG, Shaheen NJ, Cohen J et al. Quality indicators for EGD. Am J Gastroenterol 2015; 110: 60–71 doi:10.1016/j.gie.2014.07.054

[8] Chiu PWY, Uedo N, Singh R et al. An Asian consensus on standards of diagnostic upper endoscopy for neoplasia. Gut 2019; 68: 186–197 doi:10.1136/gutjnl-2018-317111

[9] Shea BJ, Reeves BC, Wells G et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017; 358: doi:10.1136/bmj.j4008

[10] Sterne JA, Savović J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898

[11] Moola S, Munn Z, Tufanaru C et al. Chapter 7: Systematic reviews of etiology and risk. Joanna briggs institute reviewer's manual. The Joanna Briggs Institute. 2017

[12] Le H, Wang L, Zhang L et al. Magnifying endoscopy in detecting early gastric cancer: A network meta-analysis of prospective studies. Medicine 2021; 100: e23934 doi:10.1097/MD.0000000000023934

[13] Rodríguez-Carrasco M, Esposito G, Lib â nio D et al. Image-enhanced endoscopy for gastric preneoplastic conditions and neoplastic lesions: a systematic review and meta-analysis. Endoscopy 2020; 52: 1048–1065 doi:10.1055/a-1205-0570

[14] Zhao Z, Yin Z, Wang S et al. Meta-analysis: The diagnostic efficacy of chromoendoscopy for early gastric cancer and premalignant gastric lesions. J Gastroenterol Hepatol 2016; 31: 1539–1545 doi:10.1111/jgh.13313

[15] Teh JL, Tan JR, Lau LJF et al. Longer examination time improves detection of gastric cancer during diagnostic upper gastrointestinal endoscopy. Clin Gastroenterol Hepatol 2015; 13: 480–487.e2

[16] Januszewicz W, Wieszczy P, Bialek A et al. Endoscopist biopsy rate as a quality indicator for outpatient gastroscopy: a multicenter cohort study with validation. Gastrointest Endosc 2019; 89: 1141–1149

[17] Park JM, Huo SM, Lee HH et al. Longer observation time increases proportion of neoplasms detected by esophagogastroduodenoscopy. Gastroenterology 2017; 153: 460–469.e1

[18] Kawamura T, Wada H, Sakiyama N et al. Examination time as a quality indicator of screening upper gastrointestinal endoscopy for asymptomatic examinees. Dig Endosc 2017; 29: 569–575 doi:10.1111/den.12804

[19] Zhou J, Li Z, Ji R et al. Influence of sedation on the detection rate of early cancer and precancerous lesions during diagnostic upper gastrointestinal endoscopies: a multicenter retrospective study. Am J Gastroenterol 2021; 116: 1230–1237

[20] Yoshimizu S, Hirasawa T, Horiuchi Y et al. Differences in upper gastrointestinal neoplasm detection rates based on inspection time and esophagogastroduodenoscopy training. Endosc Int Open 2018; 6: E1190–E1197 doi:10.1055/a-0655-7382

[21] Liu X, Guan CT, Xue LY et al. Effect of premedication on lesion detection rate and visualization of the mucosa during upper gastrointestinal endoscopy: a multicenter large sample randomized controlled double-blind study. Surg Endosc 2018; 32: 3548–3556

[22] Qumseya BJ, Wang H, Badie N et al. Advanced imaging technologies increase detection of dysplasia and neoplasia in patients with Barrett's Esophagus: a meta-analysis and systematic review. Clin Gastroenterol Hepatol 2013; 11: 1562–1570.e2

[23] Coletta M, Sami SS, Nachiappan A et al. Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc 2016; 83: 57–67.e1

[24] Hajelssedig OE, Pu LZC, Thompson JY et al. Diagnostic accuracy of narrow-band imaging endoscopy with targeted biopsies compared with standard endoscopy with random biopsies in patients with Barrett's esophagus: A systematic review and meta-analysis. J Gastroenterol Hepatol 2021; 36: 2659–2671

[25] Parasa S, Desai M, Vittal A et al. Estimating neoplasia detection rate (NDR) in patients with Barrett's oesophagus based on index endoscopy: a systematic review and meta-analysis. Gut 2019; 68: 2122–2128

[26] Gupta N, Gaddam S, Wani SB et al. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus. Gastrointest Endosc 2012; 76: 531–538

[27] Ooi J, Wilson P, Walker G et al. Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. Endoscopy 2017; 49: 524–528 doi:10.1055/s-0043-103410

[28] Morita FHA, Bernardo WM, Ide E et al. Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: a systematic review and meta-analysis. BMC Cancer 2017; 17: 54 doi:10.1186/s12885-016-3011-9

[29] Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209–49 doi:10.3322/caac.21660

[30] Gastrointestinal tract (upper) cancers – recognition and referral. Accessed January 01, 2000: https://cks.nice.org.uk/topics/gastrointestinal-tract-upper-cancers-recognition-referral/

[31] Fitzgerald RC, di Pietro M, Ragunath K et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014; 63: 7–42 doi:10.1136/gutjnl-2013-305372

[32] Banks M, Graham D, Jansen M et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut 2019; 68: 1545–1575 doi:10.1136/gutjnl-2018-318126

[33] Chiu PW, Sano Y, Uedo N et al. Utility of a standardized training program for endoscopic diagnosis of early gastrointestinal neoplasia. Endosc In Open 2019; 7: E452–E458 doi:10.1055/a-0854-3525

[34] di Pietro M, Fitzgerald RC. BSG Barrett's guidelines working group. Revised British Society of Gastroenterology recommendation on the diagnosis and management of Barrett's oesophagus with low-grade dysplasia. Gut 2018; 67: 392–393

[35] Shaukat A, Rector TS, Church TR et al. Longer withdrawal time is associated with a reduced incidence of interval cancer after screening colonoscopy. Gastroenterology 2015; 149: 952–957