SURVEILLANCE OF BARRETT'S ESOPHAGUS
GUIDELINE TABLES

Table 1. Summary of Recommendations and Implementation Considerations

Recommendations	Strength of Recommendation	Certainty of Evidence
1. In patients with non-dysplastic Barrett's esophagus, the AGA suggests performing endoscopic surveillance compared to no surveillance.	Conditional	Low
Implementation Considerations for Recommendation #1: a. Endoscopic surveillance is suggested every 3 years in patients diagnosed with non-dysplastic Barrett's esophagus if a high-quality endoscopic examination was performed. Surveillance intervals may be extended to every 5 years in patients at lower risk of progression, for instance those with short-segment Barrett's esophagus. b. Discontinuation of surveillance endoscopy in patients with non-dysplastic Barrett's esophagus should be considered based on age and comorbidities.		
2. In patients undergoing screening or surveillance endoscopy for Barrett's esophagus, the AGA recommends using a combination of high-definition white light endoscopy plus chromoendoscopy compared white light endoscopy alone.	Strong	Moderate
Implementation Considerations for Recommendation #2: a. Among the chromoendoscopy modalities that meet optimal performance characteristics, the choice of chromoendoscopy modality (virtual or dye-based chromoendoscopy) should be based on endoscopist and center expertise. b. Chromoendoscopy-directed biopsies should be used as an adjunct to sampling using a structured biopsy protocol rather than a substitutive technique to a structured biopsy protocol.		
Implementation Considerations Related to Surveillance Endoscopic Examination: a. Endoscopic evaluation in patients with suspected or confirmed Barrett's esophagus should meet the requirements of a high-quality endoscopic examination. b. All patients with suspected or established Barrett's esophagus undergoing screening or surveillance endoscopy should be sampled using a structured biopsy protocol that includes targeted biopsies from any visible lesions and random 4-quadrant biopsies every 2 cm if no prior history of dysplasia and every 1 cm if there is a history of dysplasia.		
3. In patients undergoing screening or surveillance endoscopy for Barrett's esophagus, the AGA makes no recommendation for or against the use of wide-area transepithelial sampling as an adjunctive sampling technique to a structured biopsy protocol (*knowledge gap*)	NA	NA
Implementation Considerations for Recommendation #3: a. Wide-area transepithelial sampling should not be used as a substitutive sampling technique to a structured biopsy protocol. b. Findings of neoplasia on wide-area transepithelial sampling but a structured biopsy protocol without neoplasia (discordant results) should undergo repeat surveillance endoscopy by an expert endoscopist within 3-6 months on high-dose acid suppressive regimen with repeat sampling using a structured biopsy protocol and endoscopic resection of any visible lesions. c. If embarking on endoscopic eradication therapy in patients with high-grade dysplasia or esophageal adenocarcinoma solely based on wide-area transepithelial sampling, discuss risks and benefits of endoscopic eradication therapy, need for adherence with reflux management, expected outcomes, need for continued surveillance after completion of endoscopic eradication therapy, with adequate time to assess patient values and preferences. d. In patients with Barrett's esophagus and crypt dysplasia, indefinite for dysplasia or low-grade dysplasia solely based on wide-area transepithelial sampling, endoscopic eradication therapy should not be performed.		

Recommendations	Strength of Recommendation	Certainty of Evidence
4. In patients diagnosed with non-dysplastic Barrett's esophagus, Barrett's esophagus with indefinite for dysplasia or Barrett's esophagus with low-grade dysplasia, the AGA makes no recommendation for or against the routine use of p53 assessment as an adjunct test to histopathology (*knowledge gap*)	NA	NA
5. In patients diagnosed with non-dysplastic Barrett's esophagus, Barrett's esophagus with indefinite for dysplasia or Barrett's esophagus with low-grade dysplasia, the AGA makes no recommendation for or against the routine use of TissueCypher testing as an adjunct test to histopathology (*knowledge gap*).	NA	NA
6. In adult patients with Barrett's esophagus, the AGA suggests the use of daily proton pump inhibitor therapy compared to no proton pump inhibitor therapy for the prevention of neoplastic progression of BE	Conditional	Low
Implementation Considerations for Recommendation #6: In patients with Barrett's esophagus, counsel tobacco cessation and weight loss if overweight.		
7. In adult patients with Barrett's esophagus, the AGA suggests use of proton pump inhibitors over surgery for the prevention of neoplastic progression to high-grade dysplasia or esophageal adenocarcinoma.	Conditional	Low
8. In adult patients with columnar lined esophagus <1 cm with intestinal metaplasia, the AGA suggests against surveillance endoscopy	Conditional	Very Low

Implementation Considerations for Management of Barrett's Esophagus Patients with Indefinite for Dysplasia and Low-grade Dysplasia:

a. Refer patients with Barrett's esophagus-related neoplasia, including patients diagnosed with low-grade dysplasia and indefinite for dysplasia to high volume endoscopists with expertise in endoscopic eradication therapy, pathologists with expertise in BE neoplasia and access to multi-disciplinary care.
b. Histologic diagnosis of Barrett's esophagus related dysplasia or early cancer should be confirmed by an expert pathologist.
c. The diagnosis of Barrett's esophagus and indefinite for dysplasia and low-grade dysplasia should be confirmed by a repeat endoscopy by an expert endoscopist within 6 months on high dose acid suppressive therapy primarily to rule out prevalent high-grade dysplasia or esophageal adenocarcinoma.
d. Patients with confirmed Barrett's esophagus and low-grade dysplasia choosing surveillance should continue high dose acid suppressive therapy and undergo an upper endoscopy at 6-month intervals for 1 year, then annually, by expert endoscopists, until there is a change in histologic grade of dysplasia.
e. Endoscopic eradication therapy in patients with Barrett's esophagus and indefinite for dysplasia, confirmed by expert pathology review, is not recommended.
f. Patients with Barrett's esophagus and indefinite for dysplasia should undergo repeat endoscopy in 1 year and then annually, by expert endoscopists, until there is a change in histologic grade of dysplasia.

Implementation Considerations Related to Quality Indicators in Barrett's Esophagus Surveillance:

a. To monitor care performance, endoscopists and practices are encouraged to utilize published quality indicators in screening and surveillance of patients with Barrett's esophagus.
b. The most widely utilized quality indicators in surveillance include adhering to appropriate endoscopic surveillance intervals among patients with non-dysplastic Barrett's esophagus and appropriate sampling technique using the Seattle biopsy protocol in patients with suspected or confirmed Barrett's esophagus.
c. Endoscopists and practices should consider monitoring post-endoscopy esophageal adenocarcinoma (PEEC) and post-endoscopy esophageal neoplasia (PEEN) cases to understand contributing factors and areas of improvement.

Table 2. Interpretation of the Certainty of Effects Using the GRADE Framework

Certainty of Evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident that the true effect lies close to that of the estimate of the effect. There is a possibility that it is substantially different.
Low	Our confidence that the true effect lies close to that of the estimate of the effect is low. The true effect may be substantially different from the estimate of the effect.
Very low	Our confidence that the true effect lies close to that of the estimate of the effect is very low. The true effect is likely substantially different from the estimate of the effect.

Table 3. Interpretation of a Strong and Conditional Recommendation

Implications	Strong Recommendation	Conditional Recommendation
For Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For Clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For Policy Makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

Table 4. PICO Questions

Focused Question	Patients	Intervention	Comparator	Outcomes
1.Should patients with BE without dysplasia undergo endoscopic surveillance?	Adult patients with non-dysplastic BE	Endoscopic surveillance	No surveillance	Benefits: 1. Reduction in EAC-related mortality (critical) 2. Reduction in all-cause mortality (critical) 3. Earlier stage of EAC detection (critical) Harms: 1. Bleeding 2. Perforation 3. Serious adverse events
2.What is the optimal imaging strategy for BE patients undergoing endoscopic surveillance	Adult patients with BE undergoing screening or surveillance	Chromoendoscopy (standard or virtual) plus high-definition white light endoscopy	White light endoscopy	Benefits: 1. Increased yield of neoplasia (dysplasia and EAC) detection (critical) 2. Reduction in rates of PEEC and PEEN 3. Improved diagnostic characteristics for neoplasia detection (sensitivity and specificity) 4. Reduction in the number of biopsies required 5. Time to complete endoscopy Harms: 1. Bleeding 2. Perforation 3. Adverse events related to dye-based chromoendoscopy 4. Serious adverse events
3.What is the role of adjunctive sampling techniques in patients undergoing surveillance endoscopy?	Adult patients with BE undergoing screening or surveillance	Structured biopsy protocol plus WATS-3D sampling	Structured biopsy protocol	Benefits: 1. Increased yield of neoplasia (dysplasia and EAC excluding crypt or indefinite for dysplasia) detection (critical) 2. Reduction in rates of PEEC and PEEN 3. Prediction of development of dysplasia or progression Harms: 1. Bleeding 2. Perforation 3. Serious adverse events
4.In patients with BE undergoing surveillance endoscopy, is the use of biomarkers superior to grade of dysplasia in prediction of progression?	Adult patients with BE undergoing surveillance endoscopy (stratified by NDBE, IND/LGD)	a. Combination of p53 staining with histology b. Combination of TissueCypher with or without histology	Standard histopathology	Benefits: 1. Diagnostic characteristics (sensitivity, specificity, true positive, true negative, false positive and false negative) (critical outcome) 2. Improved prediction of progression to HGD/EAC (critical outcome) 3. Proportion of cases with change in management (EET, change in frequency of surveillance endoscopy)

Focused Question	Patients	Intervention	Comparator	Outcomes
5.What is the role of chemopreventive strategies in prevention of progression in patients with BE?	Adult patients with BE	a.Once daily PPI b.PPI plus aspirin c.BID PPI therapy	No PPI therapy Daily PPI therapy	Benefits: 1. Reduction in progression to EAC (critical) 2. Reduction in progression to HGD/EAC (critical) 3. Reduction in EAC mortality Harms: 1. Adverse events related to PPI therapy 2. Adverse events related to aspirin therapy
6.What is the role of anti-reflux procedures in the prevention of progression in patients with BE?	Adult patients with BE	Anti-reflux procedures	PPI therapy	Benefits: 1.Reduction in progression to EAC (critical) 2.Reduction in progression to HGD/EAC (critical) 3.Reduction in EAC mortality Harms: 1. Adverse events related to PPI therapy 2. Adverse events related to anti-reflux surgery
7.Should patients with columnar lined esophagus <1 cm with intestinal metaplasia undergo endoscopic surveillance	Adult patients with columnar lined esophagus <1cm	Endoscopic surveillance	No surveillance	Benefits: 1.Progression to EAC (critical) 2.Progression to HGD/EAC (critical) 3.Reduction in EAC mortality Harms: 1.Bleeding 2.Perforation 3.Serious adverse events

BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, HGD: high-grade dysplasia, LGD: low-grade dysplasia, ND: non-dysplastic, IND: indefinite for dysplasia, PEEC: post-endoscopy esophageal adenocarcinoma, PEEN: post-endoscopy esophageal neoplasia, WATS-3D: wide-area transepithelial sampling, EET: endoscopic eradication therapy, PPI: proton pump inhibitors

Table 5. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 1: Role of endoscopic surveillance in patients with non-dysplastic Barrett's esophagus

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	surveillance	no surveillance	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	333/1733 (19.2%)	356/1719 (20.7%)	HR 0.95 (0.82 to 1.10)	9 fewer per 1,000 (from 34 fewer to 18 more)	⨁⨁◯◯ Low[a]	CRITICAL
EAC Diagnosis												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	40/1733 (2.3%)	31/1719 (1.8%)	RR 1.28 (0.80 to 2.04)	5 more per 1,000 (from 4 fewer to 19 more)	⨁⨁◯◯ Low[b]	IMPORTANT
Early stage EAC and HGD detection rates												
1	randomised trials	not serious	not serious	serious[c]	serious[b]	none	58/1733 (3.3%)	20/1719 (1.2%)	RR 2.82 (1.73 to 4.56)	21 more per 1,000 (from 8 more to 41 more)	⨁⨁◯◯ Low[b,c]	CRITICAL
Reduction in EAC-related Mortality from NRS												
4	non-randomised studies	serious[d]	not serious	not serious	not serious	none	335/677 (49.5%)	3834/13465 (28.5%)	RR 0.73 (0.57 to 0.94)	77 fewer per 1,000 (from 122 fewer to 17 fewer)	⨁◯◯◯ Very low[d]	CRITICAL
EAC - related mortality (NRS-cohort studies with well-defined surveillance)												
4	non-randomised studies	serious[e]	not serious	not serious	not serious	none	101/282 (35.8%)	144/249 (57.8%)	RR 0.60 (0.50 to 0.71)	231 fewer per 1,000 (from 289 fewer to 168 fewer)	⨁◯◯◯ Very low[e]	CRITICAL
Complications from diagnostic EGD, data from large cohort study with 387,647 patients												
1	non-randomised studies	not serious	not serious	not serious	not serious	none	Retrospective, observational cohort study with total of 387,647 patients that underwent EGD. - Bleeding rate was 7.9/10,000 persons - Perforations 0.4/10,000 persons - CVA, AMI, and CHF 2.8/10,000, 4.4/10,000, and 1.5/10,000 persons, respectively				⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Confidence interval crosses the MID threshold of 1-1.4%: from clinically significant mortality reduction to clinically significant increase in mortality

b. Very small event number and confidence interval crossing from clinically no important cancer diagnosis to clinically important cancer diagnosis

c. Surrogate outcome, for patient important outcome such as decrease in EAC mortality

d. Lead and length time biases: 3 studies in this group had data adjusting for lead time bias and no studies adjusted for length time bias. Sensitivity analysis after accounting for lead-time bias resulted in a substantial attenuation in mortality benefit, (HR = 0.85; 95% CI = 0.75–0.95)

e. Lead and length time biases: adjusting for lead-time with additional adjustment for stage and treatment of cancer eliminated the association between endoscopic surveillance and EAC-related mortality (HR = 1.27; 95% CI = 0.78–2.07)

Table 6. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 2: Role of chromoendoscopy (overall, dye-based chromoendoscopy, virtual chromoendoscopy) in BE patients undergoing surveillance endoscopy – neoplasia detection rates between chromoendoscopy plus white-light endoscopy versus white-light endoscopy alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chromoendoscopy (standard or virtual) plus high-definition white light endoscopy	White light endoscopy	Relative (95% CI)	Absolute (95% CI)		
Dysplasia detection												
10	randomized trials	not serious	not serious	serious[a]	not serious[b]	none	368/817 (45.0%)	311/817 (38.1%)	RR 1.16 (1.07 to 1.27)	61 more per 1,000 (from 27 more to 103 more)	⊕⊕⊕◯ Moderate[a,b]	IMPORTANT
HGD/cancer detection												
11	randomized trials	not serious	not serious	serious[a]	not serious[c]	none	166/795 (20.9%)	133/795 (16.7%)	RR 1.20 (1.03 to 1.40)	33 more per 1,000 (from 5 more to 67 more)	⊕⊕⊕◯ Moderate[a,c]	CRITICAL
Dysplasia detection with dye-based chromoendoscopy												
6	randomized trials	not serious	not serious	not serious[a]	serious[b]	none	155/443 (35.0%)	123/443 (27.8%)	RR 1.19 (1.02 to 1.39)	53 more per 1,000 (from 6 more to 108 more)	⊕⊕⊕◯ Moderate[a,b]	IMPORTANT
HGD/cancer detection with dye-based chromoendoscopy												
5	randomized trials	not serious	not serious	not serious[a]	Serious[c]	none	28/323 (8.7%)	21/323 (6.5%)	RR 1.18 (0.96 to 1.46)	12 more per 1,000 (from 3 fewer to 30 more)	⊕⊕⊕◯ Moderate[a,d]	CRITICAL
Dysplasia detection with virtual chromoendoscopy												
4	randomised trials	not serious	not serious	not serious[a]	Serious[b]	none	213/374 (57.0%)	188/374 (50.3%)	RR 1.16 (0.99 to 1.37)	80 more per 1,000 (from 5 fewer to 186 more)	⊕⊕⊕◯ Moderate[a,d]	IMPORTANT
HGD/EAC detection with virtual chromoendoscopy												
6	randomized trials	not serious	not serious	not serious[a]	Serious[c]	none	138/472 (29.2%)	112/472 (23.7%)	RR 1.22 (0.97 to 1.52)	52 more per 1,000 (from 7 fewer to 123 more)	⊕⊕⊕◯ Moderate[a,d]	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
a. Although considered indirectness of the outcome due to no longitudinal follow up to determine long term impact of chromo endoscopy, however detection of dysplasia and EAC increased by using chromoendoscopy on both targeted and random samples, and the effect should not change with time, so we decided not to rate down for indirectness
b. The CI cross the presumed MID of 5%
c. The CI cross the presumed 1% -1.4% of MID

Table 7. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 3: Role of adjunctive sampling techniques (WATS-3D) in BE patients undergoing screening or surveillance – neoplasia detection rates between WATS-3D plus structured biopsy protocol versus structured biopsy protocol alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WATS-3D + FB	FB	Relative (95% CI)	Absolute (95% CI)		
HGD/EAC detection (diagnostic yield- Additional cases detected by using WATS-3D as a add on test)												
8	non-randomised studies	serious[a]	not serious	not serious	not serious	none	138/22548 (0.6%)	82/22548 (0.4%)	RR 1.61 (1.25 to 2.08)	2 more per 1,000 (from 1 more to 4 more)	⨁◯◯◯ Very low[a]	CRITICAL
LGD/HGD/EAC detection (diagnostic yield- Additional cases detected by using WATS-3D as a add on test)												
6	non-randomised studies	serious[a]	not serious	not serious	not serious	none	214/19901 (1.1%)	177/19901 (0.9%)	RR 1.18 (0.96 to 1.45)	2 more per 1,000 (from 0 fewer to 4 more)	⨁◯◯◯ Very low[a]	CRITICAL
Harms												
1	randomised trials	not serious	not serious	not serious	extremely serious[b]	none	- In the RCT there was only 1 SAE in the WATS-3D group – perforation- Cross-sectional studies with adjunctive diagnostic yield without referent standard test were used. Thus, no downstream harms from FP testing are available. Less concern for FN given the adjunctive role of the test				⨁◯◯◯ Very low[b]	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
a. Limited follow-up to assess outcomes related to increased dysplasia detection on WATS and lack of confirmation
b. In the RCT there was just 1 event and very wade CI

Table 8. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 4: Role of biomarkers (p53 staining) in predicting progression in patients with Barrett's esophagus undergoing surveillance endoscopy

a. Test accuracy in non-dysplastic Barrett's esophagus

Sensitivity	0.48 (95% CI: 0.39 to 0.57)
Specificity	0.85 (95% CI: 0.77 to 0.90)

Prevalences	0.6%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0.6%	
True positives (patients with progression to EAC/HGD)	9 studies 686 patients	cohort & case-control type studies	very serious[a]	not serious	serious[b]	not serious	none	3 (2 to 3)	⨁◯◯◯ Very low[a,b]
False negatives (patients incorrectly classified as not having progression to EAC/HGD)								3 (3 to 4)	
True negatives (patients without progression to EAC/HGD)	9 studies 2170 patients	cohort & case-control type studies	very serious[a]	not serious	serious[b]	serious[c]	none	845 (765 to 895)	⨁◯◯◯ Very low[a,b,c]
False positives (patients incorrectly classified as having progression to EAC/HGD)								149 (99 to 229)	

Explanations

a. Quadas 2 tool was used for assessing risk of bias and there were issues in multiple domains: (1) Patient selection: case-control sudy design was used in more than a half of the studies, not all the studies stratify for base-line pathology; (2) Index test: there were concerns regarding applicability if the index test since there were significant variability in interpretation of the test results; (3) Reference test was standard biopsy and progression to EAC, but the follow up period and therefore interpretation varies in between the studies.

b. Serious inconsistency. I^2 of 75% and 95% for sensitivity and specificity respectively

c. The false positive range crosses the clinical threshold of 20% (200/1000)

b. Test accuracy in Barrett's esophagus with indefinite for dysplasia

Sensitivity	0.71 (95% CI: 0.47 to 0.87)
Specificity	0.79 (95% CI: 0.59 to 0.90)

Prevalences	1.3%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.3%	
True positives (patients with progression to EAC/HGD)	7 studies 271 patients	cohort & case-control type studies	very serious[a]	not serious	serious[b]	not serious	none	9 (6 to 11)	⨁◯◯◯ Very low[a,b]
False negatives (patients incorrectly classified as not having progression to EAC/HGD)								4 (2 to 7)	
True negatives (patients without progression to EAC/HGD)	7 studies 706 patients	cohort & case-control type studies	very serious[a]	not serious	serious[b]	serious[c]	none	780 (582 to 888)	⨁◯◯◯ Very low[a,b,c]
False positives (patients incorrectly classified as having progression to EAC/HGD)								207 (99 to 405)	

Explanations

a. Quadas 2 tool was used for assessing risk of bias and there were issues in multiple domains: (1) Patient selection: case-control sudy design was used in more than a half of the studies, not all the studies stratify for base-line pathology; (2) Index test: there were concerns regarding applicability if the index test since there were significant variability in interpretation of the test results; (3) Reference test was standard biopsy and progression to EAC, but the follow up period and therefore interpretation varies in between the studies.

b. Serious inconsistency. I^2 of 53% and 77% for sensitivity and specificity respectively

c. The false positive range crosses the clinical threshold of 20% (200/1000)

c. Test accuracy in Barrett's esophagus with low-grade dysplasia

Sensitivity	0.85 (95% CI: 0.68 to 0.94)
Specificity	0.68 (95% CI: 0.62 to 0.72)

Prevalence	1.73%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.73%	
True positives (patients with progression to EAC/HGD)	7 studies 271 patients	cohort & case-control type studies	very serious[a]	not serious	serious[b]	not serious	none	15 (12 to 16)	⨁◯◯◯ Very low[a,b]
False negatives (patients incorrectly classified as not having progression to EAC/HGD)								2 (1 to 5)	
True negatives (patients without progression to EAC/HGD)	7 studies 706 patients	cohort & case-control type studies	very serious[a]	not serious	serious[b]	not serious	none	668 (609 to 708)	⨁◯◯◯ Very low[a,b]
False positives (patients incorrectly classified as having progression to EAC/HGD)								315 (275 to 374)	

Explanations

a. Quadas 2 tool was used for assessing risk of bias and there were issues in multiple domains: (1) Patient selection: case-control sudy design was used in more than a half of the studies, not all the studies stratify for base-line pathology; (2) Index test: there were concerns regarding applicability if the index test since there were significant variability in interpretation of the test results; (3) Reference test was standard biopsy and progression to EAC, but the follow up period and therefore interpretation varies in between the studies.

b. Serious inconsistency. I^2 of 74% and 19% for sensitivity and specificity respectively

Table 9. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 5: Role of biomarkers (TissueCypher) in predicting progression in patients with Barrett's esophagus undergoing surveillance endoscopy

a. Test accuracy in non-dysplastic Barrett's esophagus

Sensitivity	0.52 (95% CI: 0.43 to 0.61)
Specificity	0.85 (95% CI: 0.78 to 0.92)

Prevalence	0.6%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0.6%	
True positives (patients with progression to EAC/HGD)	5 studies 112 patients	cohort & case-control type studies	very serious[a]	not serious	not serious	not serious	none	3 (3 to 4)	⨁⨁◯◯ Low[a]
False negatives (patients incorrectly classified as not having progression to EAC/HGD)								3 (2 to 3)	
True negatives (patients without progression to EAC/HGD)	5 studies 360 patients	cohort & case-control type studies	very serious[a]	not serious	not serious	serious[b]	none	845 (775 to 914)	⨁◯◯◯ Very low[a,b]
False positives (patients incorrectly classified as having progression to EAC/HGD)								149 (80 to 219)	

Explanations

a. Quadas 2 tool was used for assessing risk of bias and there were issues in multiple domains: (1) Patient selection: case-control sudy design was used in more than a half of the studies, not all the studies stratify for base-line pathology; (2) Index test: there were concerns regarding applicability if the index test since there were significant variability in interpretation of the test results; (3) Reference test was standard biopsy and progression to EAC, but the follow up period and therefore interpretation varies in between the studies.

b. The false positive range crosses the clinical threshold of 20% (200/1000)

b. Test accuracy in Barrett's esophagus and indefinite for dysplasia/low-grade dysplasia

Sensitivity	0.66 (95% CI: 0.58 to 0.74)
Specificity	0.76 (95% CI: 0.69 to 0.83)

Prevalences	1.73%	1.3%	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1.73%	pre-test probability of 1.3%	
True positives (patients with progression to EAC/HGD)	5 studies 40 patients	cohort & case-control type studies	very serious[a]	not serious	not serious	not serious	none	11 (10 to 13)	9 (8 to 10)	⨁⨁◯◯ Low[a]
False negatives (patients incorrectly classified as not having progression to EAC/HGD)								6 (4 to 7)	4 (3 to 5)	
True negatives (patients without progression to EAC/HGD)	5 studies 40 patients	cohort & case-control type studies	very serious[a]	not serious	not serious	serious[b]	none	747 (678 to 816)	750 (681 to 819)	⨁◯◯◯ Very low[a,b]
False positives (patients incorrectly classified as having progression to EAC/HGD)								236 (167 to 305)	237 (168 to 306)	

Explanations

a. Quadas 2 tool was used for assessing risk of bias and there were issues in multiple domains: (1) Patient selection: case-control sudy design was used in more than a half of the studies, not all the studies stratify for base-line pathology; (2) Index test: there were concerns regarding applicability if the index test since there were significant variability in interpretation of the test results; (3) Reference test was standard biopsy and progression to EAC, but the follow up period and therefore interpretation varies in between the studies.

b. The false positive range crosses the clinical threshold of 20% (200/1000)

Table 10. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 6: Role of chemopreventive strategies – proton pump inhibitor therapy to prevent neoplastic progression in patients with Barrett's esophagus

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acid suppression	no treatment	Relative (95% CI)	Absolute (95% CI)		
Progression to HGD/ EAC PPI vs. no PPI Data from observational studies												
12	non-randomised studies	not serious[a]	serious[b]	not serious	not serious	none	Not reported in the SR	132/753 (17.5%)	OR 0.47 (0.32 to 0.71)	84 fewer per 1,000 (from 112 fewer to 44 fewer)	⨁◯◯◯ Very low[a,b]	CRITICAL
Progression to HGD/EAC in High dose PPI vs. Low dose PPI. Follow up time of 8.9 years												
1	randomised trials	not serious	not serious	serious[c]	serious[d]	none	84/1270 (6.6%)	100/1265 (7.9%)	RR 0.84 (0.63 to 1.11)	13 fewer per 1,000 (from 29 fewer to 9 more)	⨁⨁◯◯ Low[c,d]	IMPORTANT
Composite outcome, progression to HGD/ EAC and mortality High dose PPI vs. low dose PPI												
1	randomised trials	not serious	not serious	serious[c]	serious[e]	none	139/1270 (10.9%)	174/1265 (13.8%)	HR 0.79 (0.63 to 0.99)	27 fewer per 1,000 (from 49 fewer to 1 fewer)	⨁⨁◯◯ Low[c,e]	IMPORTANT
Progression to EAC, High dose PPI vs. low dose PPI												
1	randomised trials	not serious	not serious	serious[c]	serious[e]	none	40/1270 (3.1%)	41/1265 (3.2%)	HR 0.97 (0.63 to 1.50)	1 fewer per 1,000 (from 12 fewer to 16 more)	⨁⨁◯◯ Low[c,f]	
C.diff and other enteric infections (COMPASS)												
1	randomised trials	not serious	not serious	not serious	Serious[f]	none	128/8791 (1.5%)	94/8807 (1.1%)	OR 1.37 (1.05 to 1.79)	4 more per 1,000 (from 1 more to 8 more)	⨁⨁⨁◯ Moderate[g]	CRITICAL
CKD progression (COMPASS)												
1	randomised trials	not serious	not serious	not serious	Serious[g]	none	184/8791 (2.1%)	158/8807 (1.8%)	OR 1.17 (0.94 to 1.45)	3 more per 1,000 (from 1 fewer to 8 more)	⨁⨁⨁◯ Moderate[h]	CRITICAL
Dementia (COMPASS)												
1	randomised trials	not serious	not serious	not serious	serious[g]	none	55/8791 (0.6%)	46/8807 (0.5%)	OR 1.20 (0.81 to 1.78)	1 more per 1,000 (from 1 fewer to 4 more)	⨁⨁⨁◯ Moderate[g]	CRITICAL
Fracture (COMPASS)												
1	randomised trials	not serious	not serious	not serious	not serious	none	203/8791 (2.3%)	211/8807 (2.4%)	OR 0.96 (0.79 to 1.17)	1 fewer per 1,000 (from 5 fewer to 4 more)	⨁⨁⨁⨁ High	CRITICAL
C. difficile, pooled data												
2	randomised trials	not serious	not serious	not serious	not serious	none	11/9077 (0.1%)	4/9077 (0.0%)	RR 2.48 (0.83 to 7.44)	1 more per 1,000 (from 0 fewer to 3 more)	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acid suppression	no treatment	Relative (95% CI)	Absolute (95% CI)		
Fracture, pooled data												
2	randomised trials	not serious	not serious	not serious	not serious	none	214/9077 (2.4%)	218/9077 (2.4%)	RR 0.98 (0.81 to 1.18)	0 fewer per 1,000 (from 5 fewer to 4 more)	⨁⨁⨁⨁ High	CRITICAL
Pneumonia, pooled data												
2	randomised trials	not serious	not serious	not serious	not serious	none	329/9077 (3.6%)	320/9077 (3.5%)	RR 1.03 (0.88 to 1.20)	1 more per 1,000 (from 4 fewer to 7 more)	⨁⨁⨁⨁ High	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Although most of the studies are case control studies with concern for residual cofounding, the pooled OR in the prior SR used the multivariable adjusted estimates, thus we did not further rate down for risk of bias

b. There were studies showing significant benefit of PPIs, but there were studies that did not show any benefit. I^2 is 78%

c. Serious indirectness on the level of comparison the comparison group is low dose PPI we considered it for difference in acid suppression level

d. Small event number, also the CI includes some benefit to no benefit at all

e. Wide CI, includes some benefit to no clinically significant benefit

f. Low event number

g. Wide CL from no harms to some harms

Table 11. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 7: Role of anti-reflux surgery in the prevention of progression in patients with Barrett's esophagus

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-reflux surgery	medical management	Relative (95% CI)	Absolute (95% CI)		
Progression to HGD/EAC, anti-reflux surgery vs. medical management												
6	non-randomized studies	Not serious[a]	not serious	not serious	Serious[b]	none	19/765 (2.5%)	443/33528 (1.3%)	RR 0.86 (0.30 to 2.41)	2 fewer per 1,000 (from 9 fewer to 19 more)	⨁⨁◯◯ lLow[a,b]	CRITICAL
Progression to EAC, anti-reflux surgery vs. medical management												
6	non-randomized studies	Not Ssrious[a]	not serious	not serious	Serious[b]	none	14/765 (1.8%)	438/33528 (1.3%)	RR 1.33 (0.29 to 6.16)	4 more per 1,000 (from 9 fewer to 67 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. There was a concern for selection bias because majority of studies lacked inclusion of consecutive patients and baseline equivalence of treatment groups however the larger studies were without concerns, so we did not rate down for risk of bias

b. Wide CI ranging from benefit with surgery to benefit with medical treatment

Table 12. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 8: Role of endoscopic surveillance in patients with columnar lined esophagus <1 cm

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Progression to HGD/EAC									
6	non-randomised studies	serious[a]	not serious	serious[b]	not serious	none	No comparative data from RCT or non-randomized studies were found that informs of the benefits or harms of surveillance vs. no surveillance in patients with CLE IM <1cm. We identified only single arm studies reporting on natural progression of CLE IM <1cm to HGD/EAC of patients who underwent follow-up EGDs. The pooled incidence was 0.1 per 100 patient-years.	⊕◯◯◯ Very low[a,b]	CRITICAL
Complications from diagnostic EGD, data from large cohort study with 387,647 patients									
1	non-randomised studies	not serious	not serious	not serious	not serious	none	Retrospective, observational cohort study with total of 387,647 patients that underwent EGD. - Bleeding rate was 7.9/10,000 persons - Perforations 0.4/10,000 persons - CVA, AMI, and CHF 2.8/10,000, 4.4/10,000, and 1.5/10,000 persons, respectively	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval

Explanations

a. Suspected selection bias, given small studies and limited follow up time

b. All the studies are single arm studies on natural progression of the patients with IM in CLE <1cm and no real intervention

Table 13: Key Considerations for a High-Quality Endoscopic Exam in Barrett's Esophagus

Pre-Procedure	**Informed Consent**: Discuss indications, benefits, and potential risks of the procedure in detail. **Acid Suppressive Therapy**: Optimize therapy prior to BE screening/surveillance to minimize interpretation challenges due to active esophagitis. **Antithrombotic Management**: Follow published guidelines for periprocedural management of antithrombotic agents.
Intra-Procedure	**Visualization Techniques**: Use a distal attachment cap, appropriate insufflation/desufflation, and mucosal cleansing agents and washing to enhance mucosal visibility. **Landmark Identification**: Accurately document the top of the squamocolumnar junction (both maximal and circumferential extent), gastroesophageal junction, and diaphragmatic hiatus. **Systematic Inspection**: Conduct multiple pull-throughs using high-definition white light endoscopy and chromoendoscopy (virtual or dye-based) including retroflexion and inspection of the distal esophagus, gastroesophageal junction and gastric cardia, spend adequate time inspecting the Barrett's mucosa to improve detection of Barrett's related neoplasia **Standardized Reporting**: Use the *Prague classification* to describe BE segment extent and length; *Paris classification* for any visible lesions; *Los Angeles classification* to describe presence of esophagitis **Photodocumentation**: Capture routine landmarks and mark suspicious lesions with annotations and descriptive details. **Biopsy Protocol**: Utilize the Seattle protocol for systematic sampling.
Post-procedure	- Provide follow-up recommendations and timing to resume antithrombotics - Document pending pathology review for further guidance. - Ensure surveillance intervals align with guidelines.

Table 14: Quality measures and other proposed quality metrics in Barrett's esophagus surveillance

Quality Measures	Type of Measure	Rationale
Appropriate sampling technique using the Seattle biopsy protocol	Process	Adequate sampling increases neoplasia detection compared with random biopsy sampling
Patients with non-dysplastic Barrett's esophagus patients undergo surveillance endoscopy no sooner than 3 years	Process	Reduction in overutilization of endoscopy
Proposed Quality Metrics		
Performing surveillance endoscopy using a combination of high-definition white light endoscopy (HD-WLE) with chromoendoscopy (dye-based or virtual chromoendoscopy)	Process	Combination of HD-WLE and chromoendoscopy associated with higher neoplasia rates compared to white-light endoscopy alone
Neoplasia detection rate (NDR) defined by percent detection of dysplasia on index endoscopy for screening for Barrett's esophagus	Process	Reflects the overall quality of the endoscopic examination
Barrett's inspection time that suggests inspection time of 1 minute per cm of circumferential Barrett's esophagus	Process	Reflects the quality of the endoscopic examination and may lead to increased NDR
Documenting the extent of suspected or confirmed Barrett's esophagus using the Prague criteria	Process	Consistent reporting that facilitates evidence-based decision making, improves communication and patient monitoring
Post-endoscopy esophageal cancer (PEEC) and post-endoscopy esophageal neoplasia (PEEN)	Outcome	Reflects the overall performance of endoscopy as most cases of PEEC and PEEN are due to missed lesions

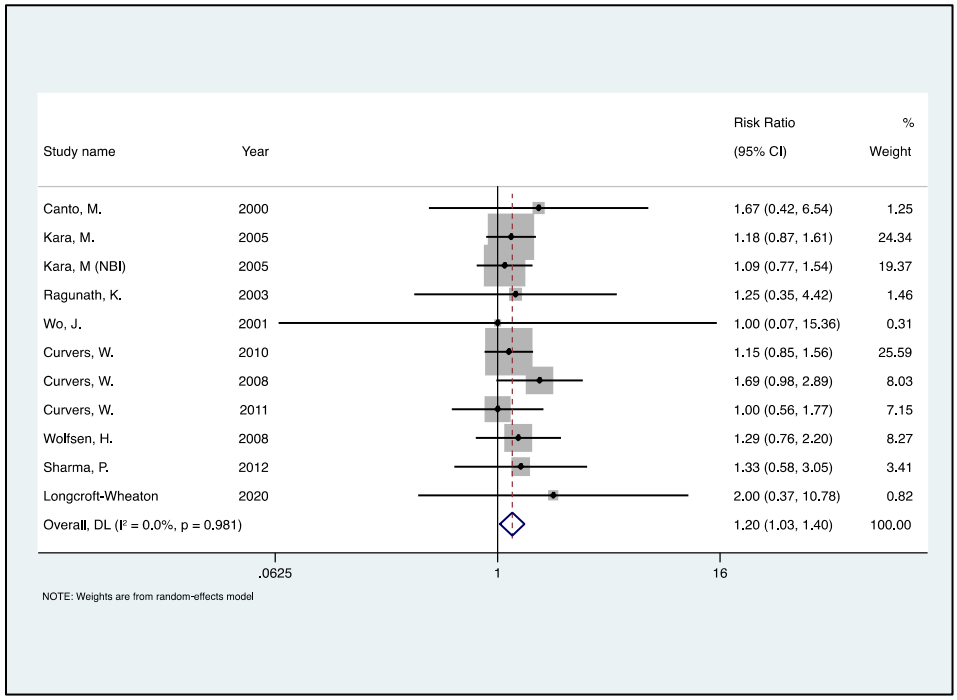
Table 15: Knowledge gaps

Knowledge gaps
The role of surveillance needs to be assessed in study designs that minimize contamination and is adequately powered to assess differences in esophageal adenocarcinoma mortality.
Future studies need to identify risk stratification tools to better guide endoscopic surveillance intervals, risk of progression and discontinuation of surveillance.
The role of artificial intelligence in enhancing dysplasia and early cancer detection among Barrett's esophagus patients undergoing endoscopic screening and surveillance examinations needs to be defined (ideally in randomized controlled trials).
The role of advanced sampling techniques such as wide-area transepithelial sampling as an adjunctive and substitutive technique to a structured biopsy protocol needs to be addressed in future randomized controlled trials.
Validation of biomarkers needs to be performed in prospective trials (ideally in randomized controlled trials) that assess critical endpoints of esophageal adenocarcinoma incidence and mortality.
The role of potassium-competitive acid blockers in patients with Barrett's esophagus needs to be evaluated in future studies for the outcomes of reflux control, healing of erosive esophagitis, reduction in neoplastic progression and outcomes in patients undergoing endoscopic eradication therapy.
Future research needs to define patients with Barrett's esophagus who are most likely to benefit from anti-reflux procedures to prevent neoplastic progression.

SURVEILLANCE OF BARRETT'S ESOPHAGUS
GUIDELINE FIGURES

Figure 1: Forest plot of incremental neoplasia detection using chromoendoscopy plus high-definition white light endoscopy compared with white light endoscopy alone

a. HGD/EAC detection (overall)



b. Detection of LGD/HGD/EAC (overall)

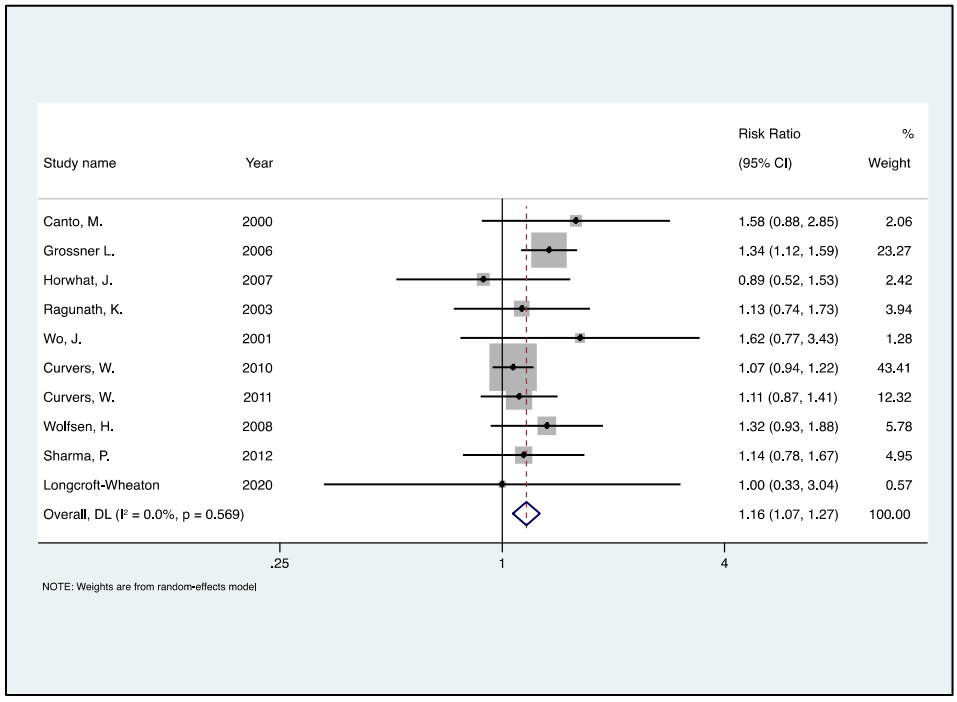


Figure 2: Sampling of Barrett's esophagus using a structured biopsy protocol

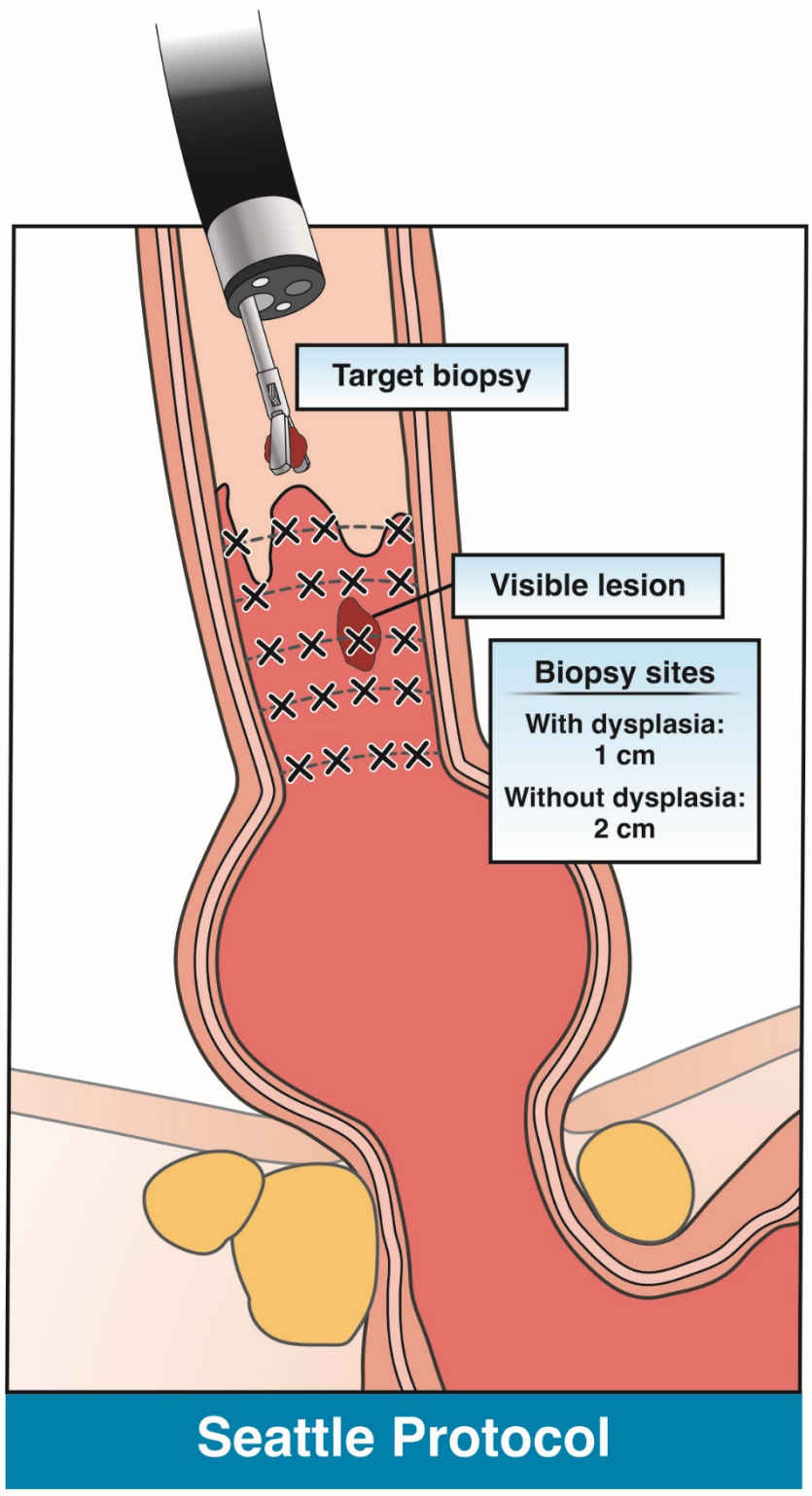
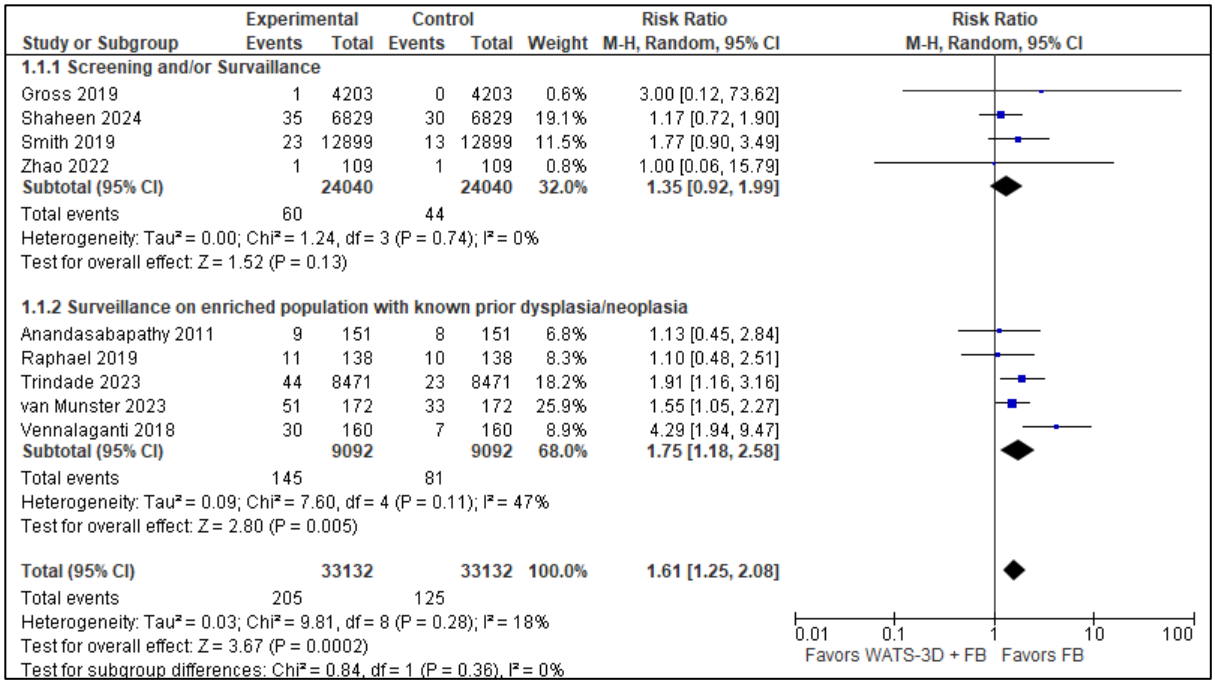


Figure 3: Forest plot of incremental neoplasia detection using WATS-3D plus structured biopsy protocol compared with structured biopsy protocol alone

a. Detection of HGD/EAC



b. Detection of LGD/HGD/EAC

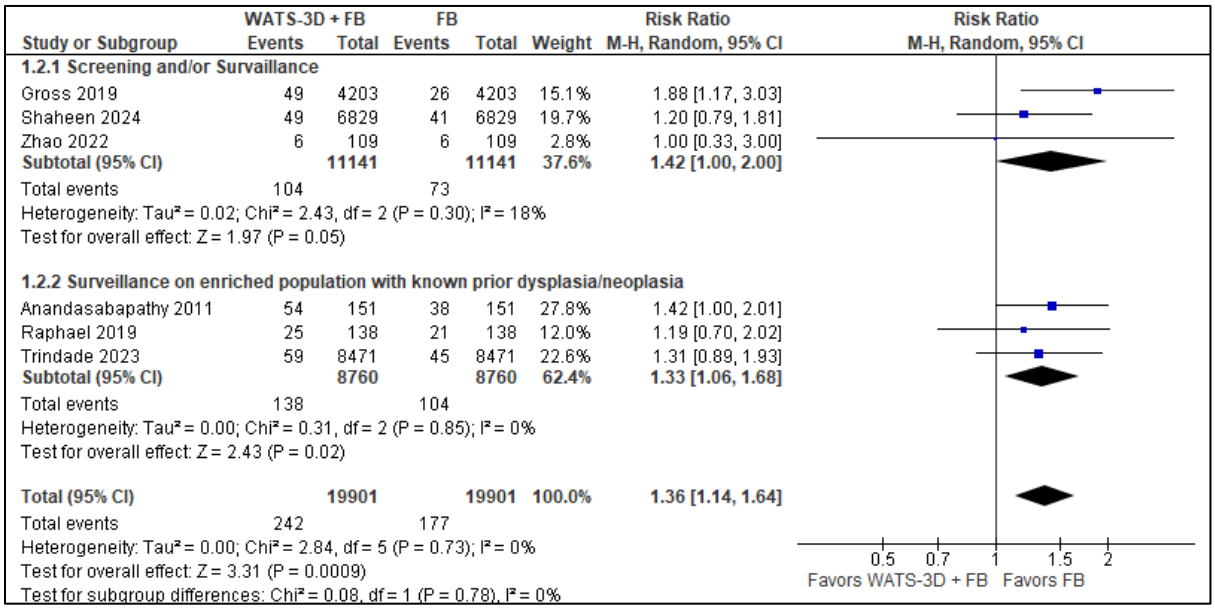


Figure 4: Prague classification system to define the length of the Barrett's segment

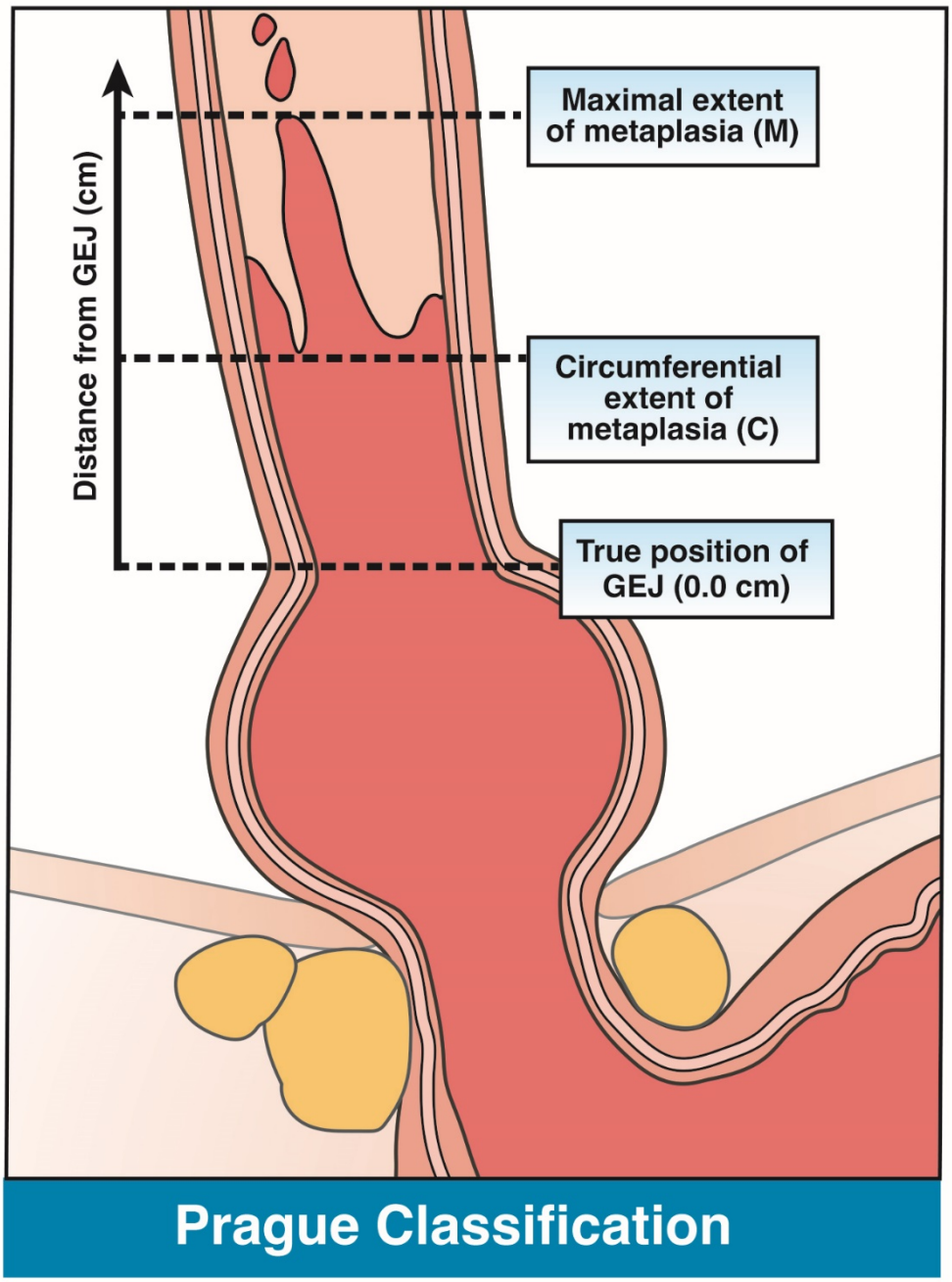


Figure 5: Paris classification system to define any visible lesion within the Barrett's segment

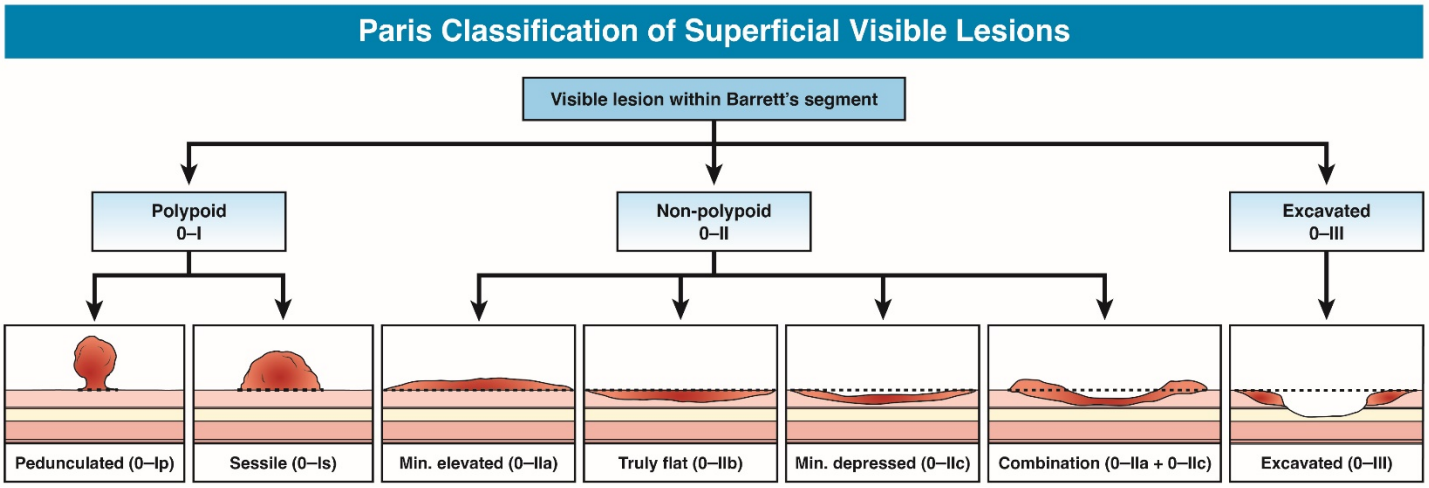


Figure 6: Representative images of visible lesions in patients with Barrett's esophagus

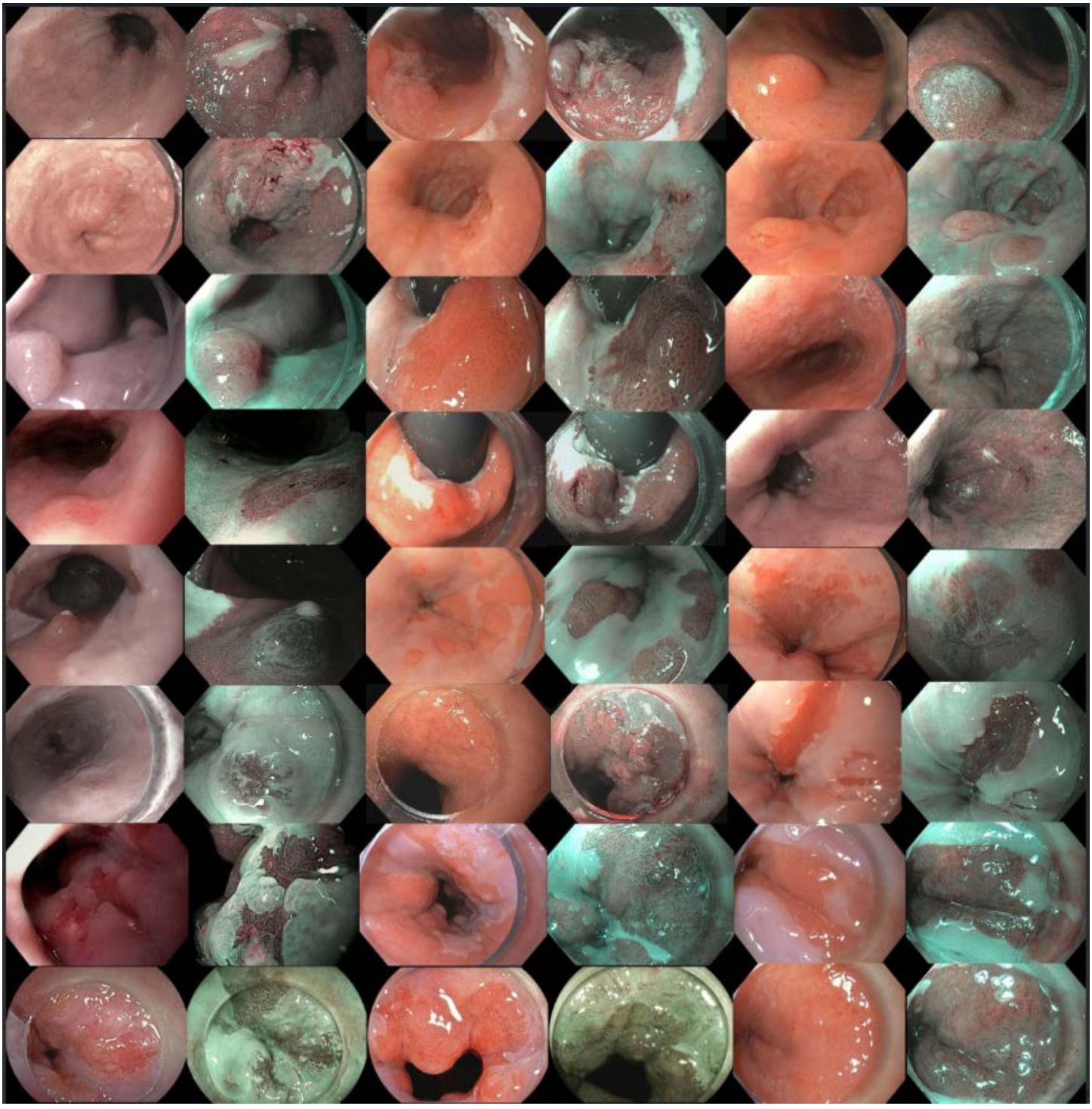


Figure 7: Los Angeles classification system for erosive esophagitis

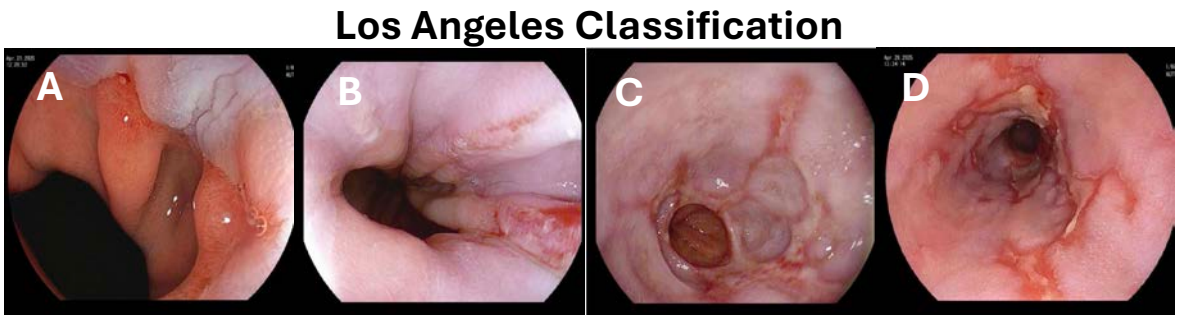
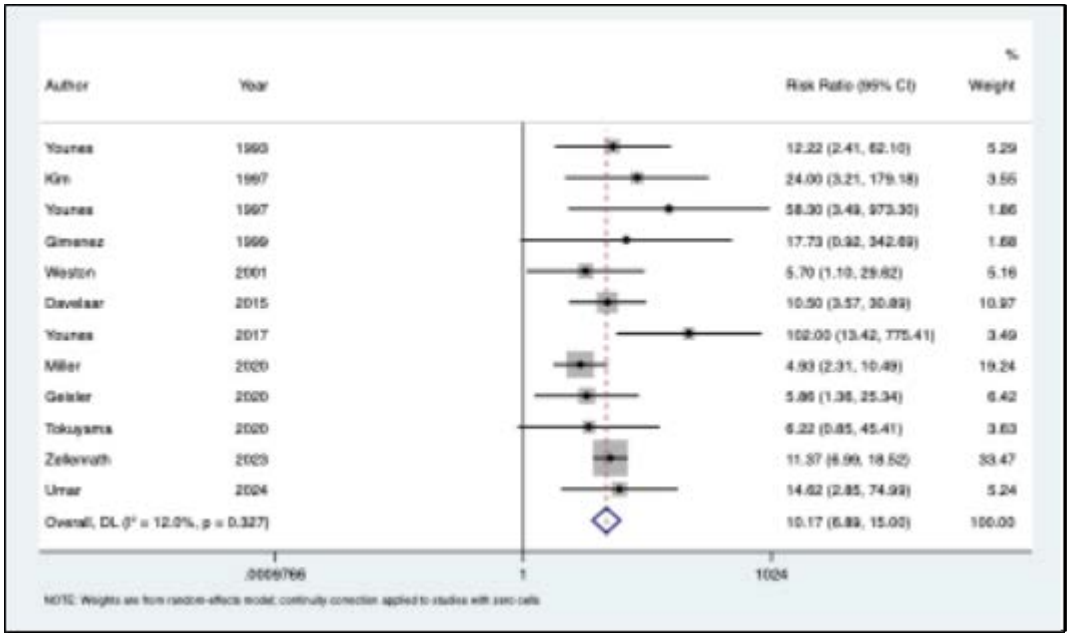
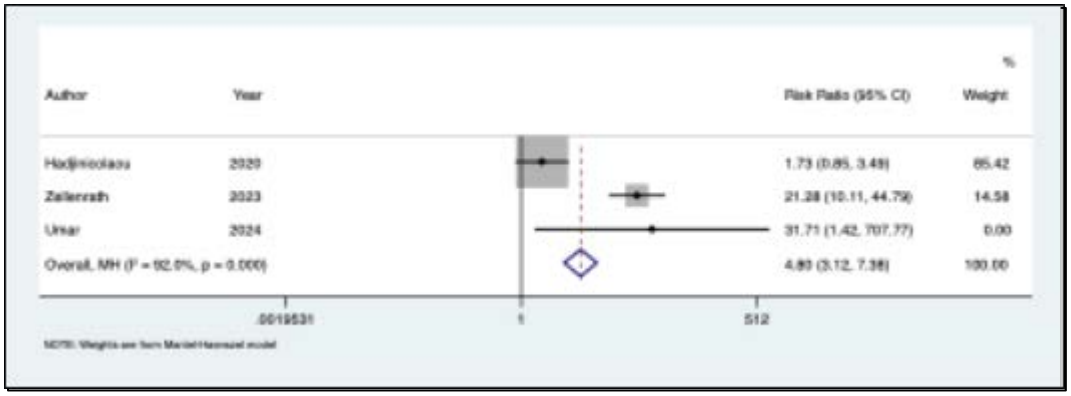


Figure 8: Forest plots for pooled outcome of progression to HGD/EAC in patients with BE with aberrant p53 expression compared to those without

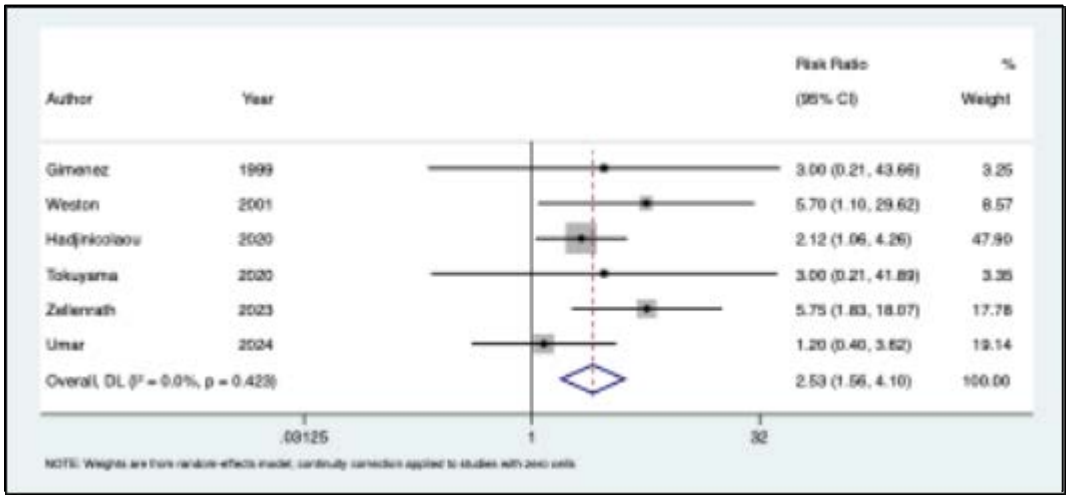
a. BE with NDBE, IND and LGD



b. NDBE



c. BE with LGD



d. BE with IND

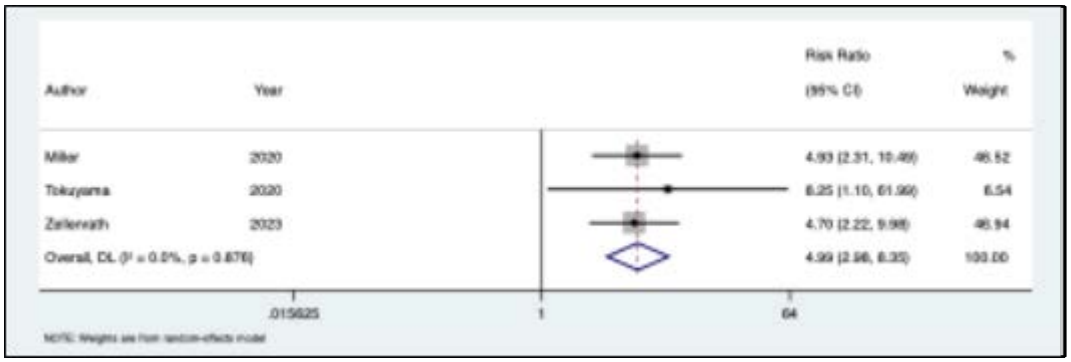
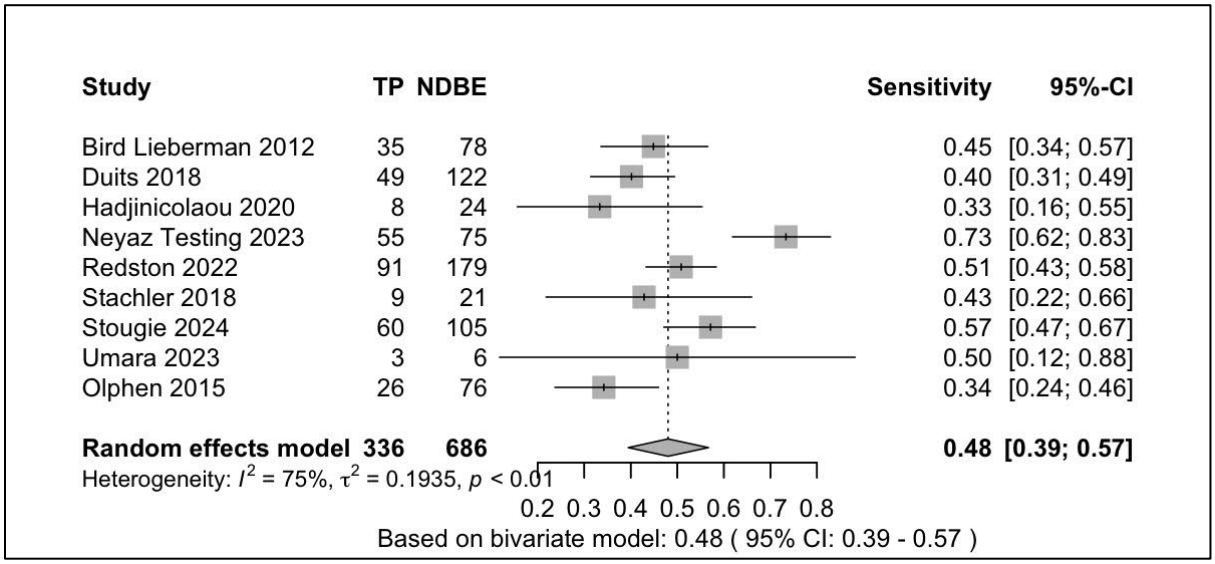
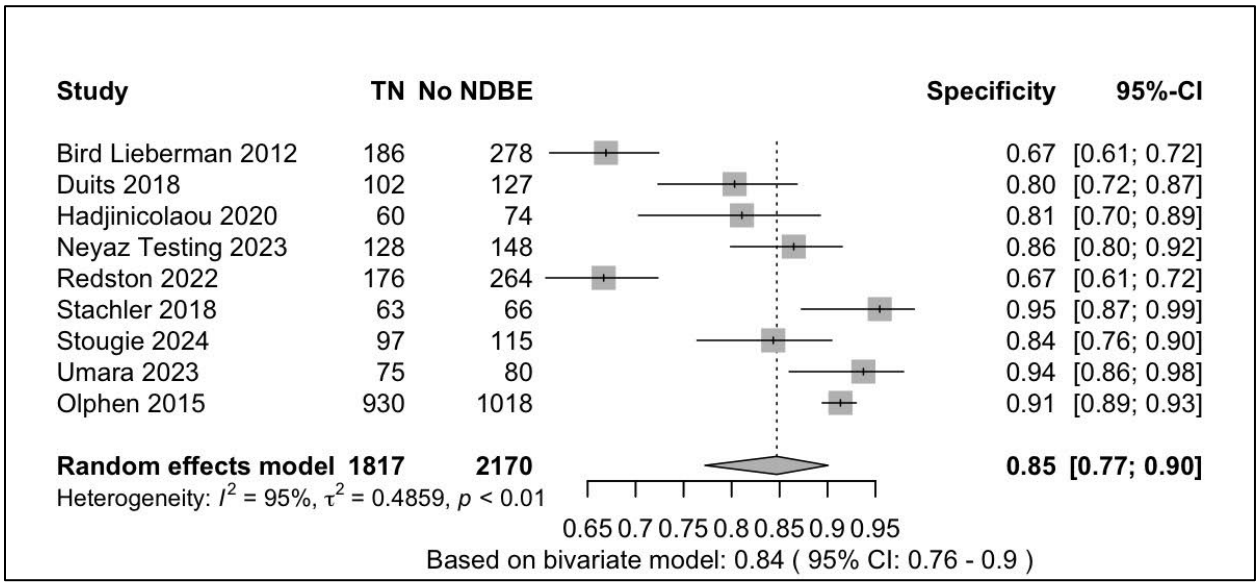


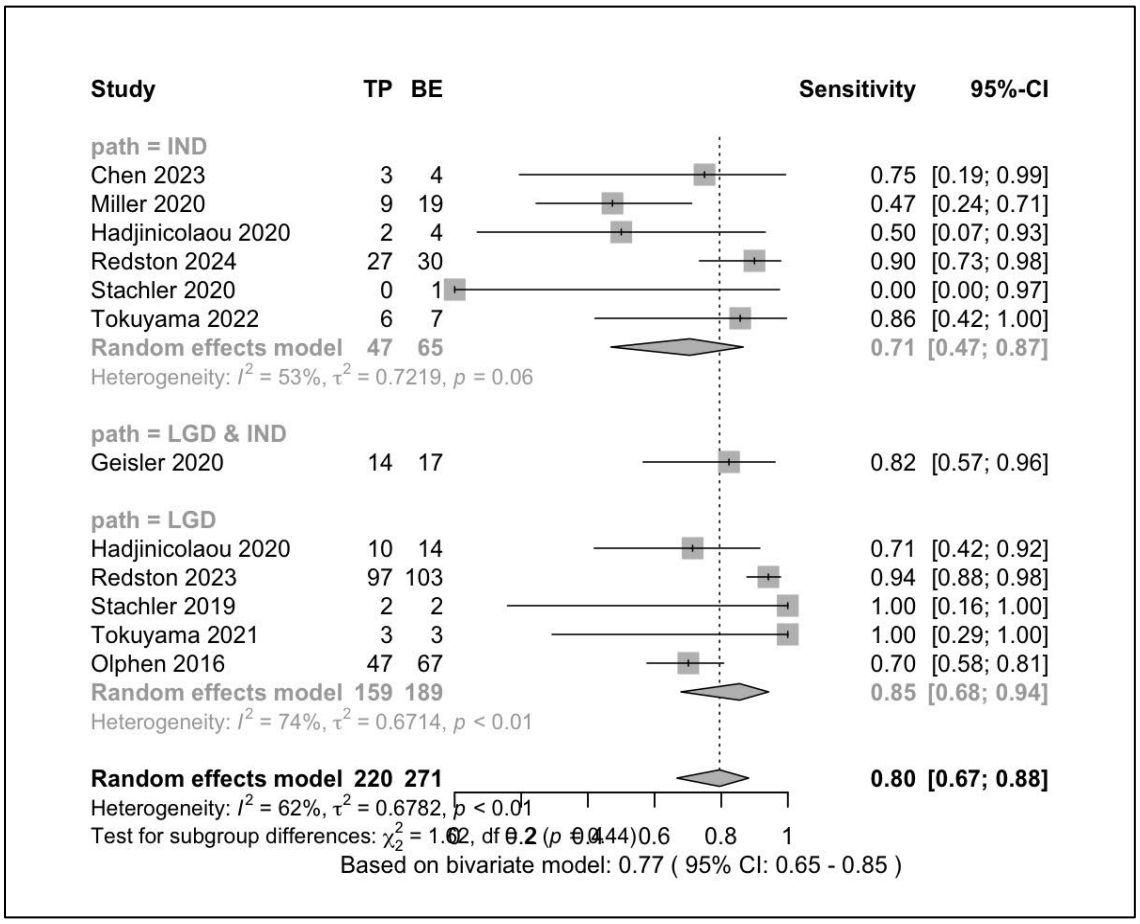
Figure 9: Forest plots for pooled sensitivity and specificity of p53 assessment among patients with Barrett's esophagus undergoing surveillance endoscopy

a. NDBE – Sensitivity and specificity





b. BE with IND/LGD - Sensitivity and specificity



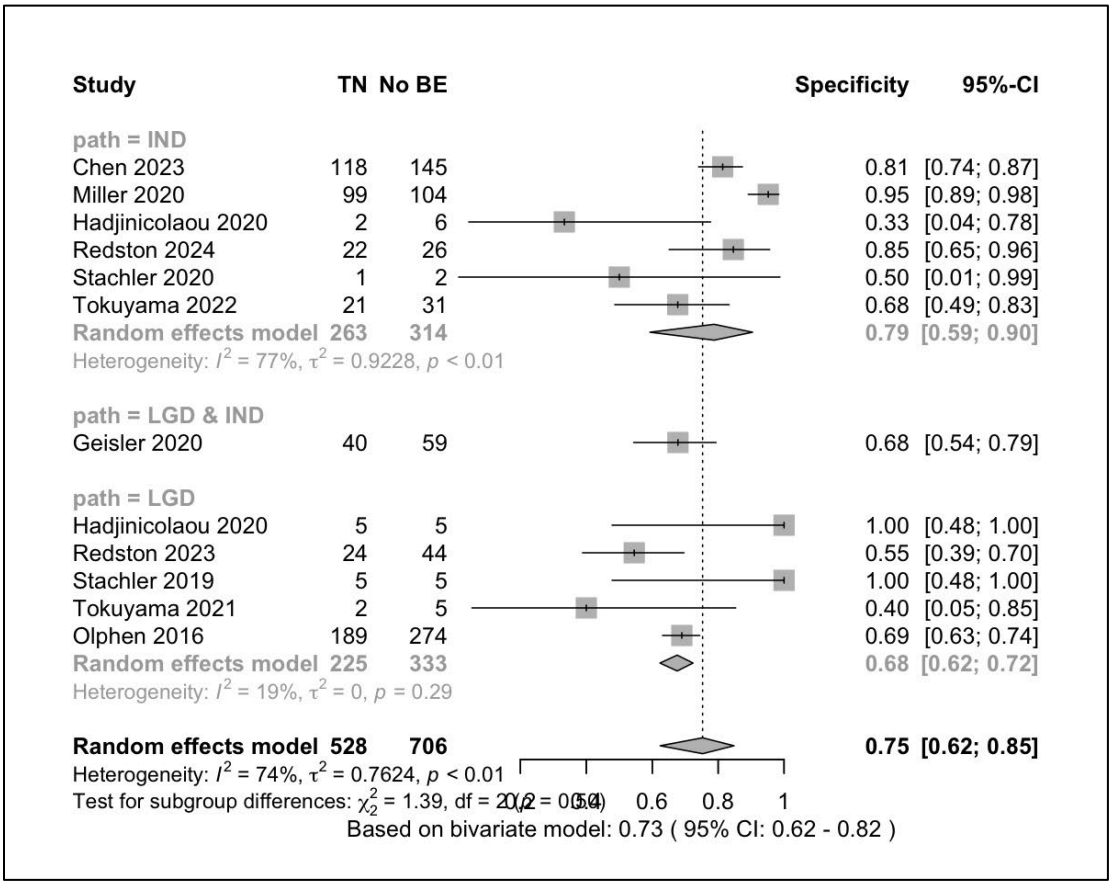


Figure 10: Forest plots for progression to high-grade dysplasia or esophageal adenocarcinoma in patients with columnar lined esophagus <1 cm with intestinal metaplasia