ENDOSCOPY

Opportunistic upper endoscopy during colonoscopy as a screening strategy for countries with intermediate gastric cancer risk

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Abstract

Background and Aim: Screening upper endoscopy can detect esophagogastric (OG) cancers early with improved outcomes. Recent cost-utility studies suggest that opportunistic upper endoscopy at the same setting of colonoscopy might be a useful strategy for screening of OG cancers, and it may be more acceptable to the patients due to cost-saving and convenience. We aim to study the diagnostic performance of this screening strategy in a country with intermediate gastric cancer risk.

Methods: A retrospective cohort study using a prospective endoscopy database from 2015 to 2017 was performed. Patients included were individuals age > 40 who underwent opportunistic upper endoscopy at the same setting of colonoscopy without any OG symptoms. Neoplastic OG lesions are defined as cancer and high-grade dysplasia. Pre-neoplastic lesions include Barrett's esophagus (BE), intestinal metaplasia (IM), and atrophic gastritis (AG).

Results: The study population involved 1414 patients. Neoplastic OG lesions were detected in five patients (0.35%). Pre-neoplastic lesions were identified in 174 (12.3%) patients. IM was found in 146 (10.3%) patients with 21 (1.4%) having extensive IM. The number needed to scope to detect a neoplastic OG lesion is 282.8 with an estimated cost of USD$141 400 per lesion detected. On multivariate regression, age ≥ 60 (RR: 1.84, 95% CI: 1.29–2.63) and first-degree relatives with gastric cancer (RR: 1.64, 95% CI: 1.06–2.55) were independent risk factors for neoplastic or pre-neoplastic OG lesion.

Conclusion: For countries with intermediate gastric cancer risk, opportunistic upper endoscopy may be an alternative screening strategy in a selected patient population. Prospective trials are warranted to validate its performance.

Introduction

Gastric and esophageal cancer is the third and sixth leading cause of cancer-related mortality in the world.[1] Endoscopic examination with histological evaluation is the gold standard for diagnosis of esophagogastric (OG) cancer.[2] While early OG cancer confers favorable prognosis, the majority of patients present late at diagnosis. Screening endoscopy for OG cancers is beneficial, but it is not practiced in most countries due to cost, the expertise required, and compliance.

One alternative strategy is to offer an opportunistic upper endoscopy at the same setting of a scheduled colonoscopy. Due to the high prevalence of colorectal cancer in many parts of the world, screening colonoscopy is well-established in many countries.[3] Performing upper endoscopy at the time of colonoscopy would be more acceptable to patients due to convenience. Also, the

overall cost is reduced as the need for repetitive services such as sedation and recovery are limited to one session. Two cost-utility analyses in Europe and the USA have shown that it was cost-effective for screening for OG cancers.[4,5]

The age-standardized incidence rate (ASIR) of gastric cancer in Singapore between 2013 to 2017 is 10.2 per 100 000 while that of colorectal cancer is 22.7 per 100 000.[6] The risk of developing gastric cancer increases with age with the peak occurring for patients age 80 and above.[6] In men, 65 years and older, the ASIR for gastric cancer rises to 92.1 per 100 000.[6]

The aim of this study was to evaluate the diagnostic performance of opportunistic upper endoscopy at the time of a scheduled colonoscopy at our unit. The primary endpoint was the detection rate of asymptomatic neoplastic esophagogastric (OG) lesions. Also, we evaluated the incidence of pre-neoplastic OG lesions, the associated risk factors, and the cost-effectiveness of this strategy in our population.

Methods

Study design. We conducted a retrospective cohort study in a single tertiary institution in Singapore. Majority of the patients were seen in the outpatient clinic with the decision for concurrent upper endoscopy and colonoscopy made during the consultation at the discretion of the attending physicians or surgeons. All patients were registered into a prospectively collected database when they underwent the endoscopic procedures. The study included all consecutive patients identified within the prospectively collected database who underwent concurrent upper endoscopy and colonoscopy in the same setting between January 2015 and December 2017.

We excluded patients younger than 40 years and those who underwent endoscopy for variceal screening, transplant workup, and malignancy workup. Patients who were consented for upper endoscopy secondary to OG symptoms were excluded. OG symptoms were defined as dyspepsia, anemia, loss of weight, upper bleeding gastrointestinal symptoms, reflux symptoms, and dysphagia. Also, patients who were on follow-up for resolution of peptic ulcer disease, on surveillance of pre-neoplastic OG lesions, or had undergone an upper endoscopy within 2 years were excluded.

All endoscopies were performed by accredited physicians or surgeons from gastroenterology or surgery departments. Diagnosis of OG lesions such as malignant tumors, intestinal metaplasia, atrophic gastritis, and Barret's esophagus was based on the report by the performing endoscopist. The diagnosis of endoscopic lesions was verified with the endoscopy and the corresponding histology report. *Helicobacter pylori* was diagnosed with endoscopic biopsy placed in campylobacter-like organism (CLO) test kits or on histology. This study has been reported in line with STROBE criteria.[7] The study was approved by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB, 2018/00341, date of approval: 25 April 2018).

The primary endpoint was the incidence of patients diagnosed with neoplastic OG lesions. These included malignant OG tumor or high-grade dysplasia. The secondary endpoint was the incidence of patients diagnosed with pre-neoplastic OG lesions, which included atrophic gastritis (AG), intestinal metaplasia (IM), and Barrett's esophagus (BE) on histology. Also, we assessed the

number of patients with clinically significant upper gastrointestinal pathologies who required treatment which included peptic ulcer disease and *H. pylori* infection.

Statistical analysis. Stepwise statistical analysis of the data set was performed to assess for significant associations between pre-scope risk factors and identification of neoplastic or pre-neoplastic OG lesions. Univariate analysis using the χ^2 test for discrete variables and an independent sample *t*-test for continuous variables were used. A multivariate binary logistic regression analysis was then used for factors that had a *P*-value ≤ 0.2 in the univariate analysis. The final model consisted of the relative risk, 95% confidence interval, and *P*-value. *P*-value ≤ 0.05 after the multivariate analysis was considered to be independent factors that increased the patient's risk of detecting neoplastic or pre-neoplastic OG lesions. Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY, USA).

Results

Patient's characteristics. The study identified 8567 patients from the prospective endoscopy database in our institution who underwent upper endoscopy and colonoscopy in the same setting. Patients who underwent upper endoscopy for OG symptoms were excluded. This includes patients with dyspepsia (*n* = 3375), anemia (*n* = 1622), loss of weight (*n* = 590), upper bleeding gastrointestinal symptoms (*n* = 435), reflux symptoms (*n* = 405), dysphagia (*n* = 85), and others (*n* = 234). Among the remaining 1821 patients, their clinical records were reviewed. An additional 407 patients were excluded. These were patients who were under the age of 40 (*n* = 99), had upper endoscopy for variceal screening (*n* = 112), transplant workup (*n* = 23), malignancy workup (*n* = 69), had recent upper endoscopy within 2 years (*n* = 66), and others (*n* = 38) (Fig. 1).

Hence, the study population consisted of 1414 patients who were asymptomatic and had undergone an opportunistic screening upper endoscopy during a scheduled colonoscopy. Their median age was 60.3 years (range, 40–88.3 years) with a slight male predominance (52.5%). Family history with a first-degree relative diagnosed with gastric cancer was identified in 175 patients (12.4%). The details of the demographic data are listed in Table 1.

Indications and findings of colonoscopy. Over half of the study population (53%) were asymptomatic and underwent a colonoscopy to screen for colorectal cancer (Table 1). Other indications for colonoscopy include a positive fecal occult blood test (FOBT), modifications of bowel habits (i.e. per-rectal bleed, diarrhea, or constipation) and raised tumor markers (i.e. carcinoembryonic antigen [CEA] or CA19-9). Among the 750 (53%) patients who underwent screening colonoscopy, 243 patients (32.4%) were detected to have adenomatous polyps which were resected, and four patients (0.53%) were diagnosed with malignant colorectal tumors. There was no statistical difference between the risk of identifying OG lesions and indications of colonoscopy or findings of adenomatous polyps (*P* = 0.416).
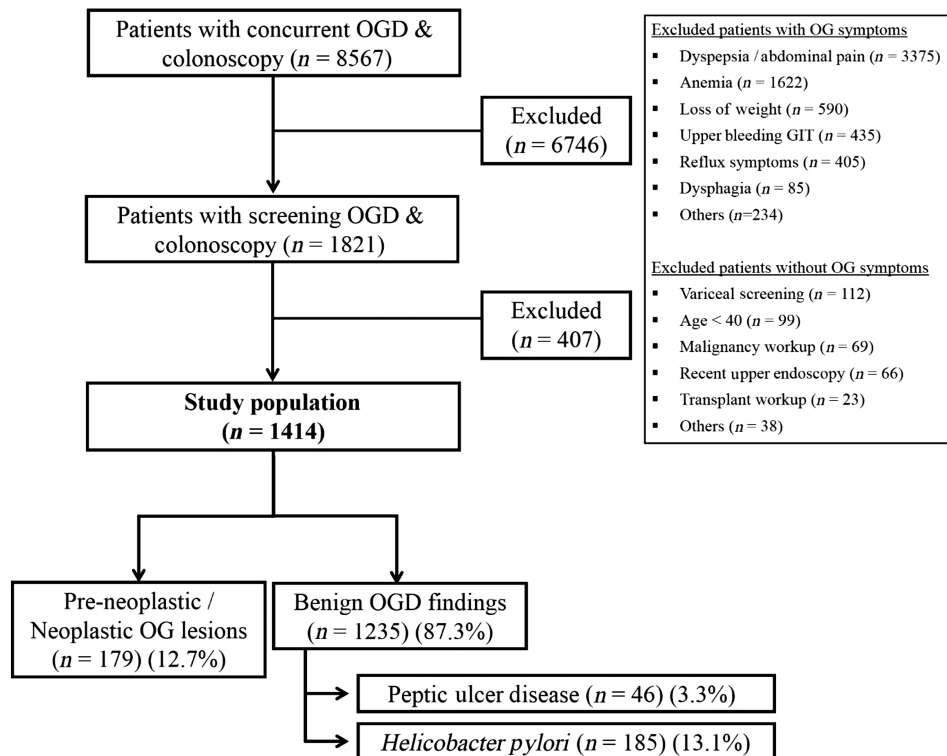
FIGURE 1   Study flow diagram with opportunistic OGD (*n* = 1414).

Findings of opportunistic upper endoscopy. A total of five patients (0.35%) were diagnosed with neoplastic OG lesions. Three patients had early-stage gastric adenocarcinoma. In the first case, the patient was a 75-year-old Chinese woman diagnosed with T2N0 moderately differentiated gastric adenocarcinoma, intestinal type. Second, a 47-year-old Chinese woman was diagnosed with T1N0 poorly differentiated adenocarcinoma, diffuse type. Third, a 67-year-old Chinese man was diagnosed with T1N0 gastroesophageal junctional adenocarcinoma. All three patients underwent curative surgery. In another case, a 67-year-old Chinese woman was diagnosed with MALT lymphoma and was treated with *H. pylori* eradication therapy. Lastly, a 61-year-old man was diagnosed with Barrett's esophagus (BE) with high-grade dysplasia who underwent endoscopic mucosal resection.

Pre-neoplastic findings such as AG, IM, and BE were identified in 174 patients. Out of the 146 patients with IM, 21 patients had extensive IM on histology. The prevalence of high-risk lesions including gastric malignancies, high-grade dysplasia, and extensive IM was 1.8%. Overall, the prevalence of both neoplastic and pre-neoplastic lesions was 12.7%.

Peptic ulcer disease was detected in 46 patients (3.3%). This included 32 patients with gastric ulcers and 14 patients with duodenal ulcers. *H. pylori* was identified in 185 patients (13.1%) via campylobacter-like organism (CLO) test or on histology. These patients underwent eradication therapy. Benign gastric tumors were identified in four patients who were treated conservatively. The rest of the upper endoscopy findings are listed in Table 1. No adverse events such as bleeding requiring repeat intervention or perforation were noted among all the patients in this study.

Risk factors associated with neoplastic and pre-neoplastic esophagogastric lesions. Univariate and multivariate analyses for risk factors associated with neoplastic and pre-neoplastic OG lesions are presented in Table 2. Univariate analysis showed that age ≥ 60 years, Chinese ethnicity, family history of first-degree relative with gastric cancer, and the presence of *H. pylori* was associated with increased risk of detecting OG lesions. On multivariate analysis, age (RR: 1.84, 95% CI: 1.29–2.63, *P* = 0.001) and family history of first-degree relative with gastric cancer (RR: 1.64, 95% CI: 1.06–2.55, *P* = 0.027) were found to be significant (Table 2). We also investigated the optimal age cut-off by plotting a ROC curve between age and pre-neoplastic OG lesions. With an area under the curve (AUC) of 0.582, we chose an age cut-off of 60 years with a sensitivity of 64% and specificity of 51%.

Cost–benefit for opportunistic upper endoscopy.
A cost–benefit model was created to determine the value of performing opportunistic upper endoscopy in various populations of patients (Table 3). For all opportunistic upper endoscopy, 179 patients out of 1414 patients had neoplastic or pre-neoplastic OG lesions, giving us a number needed to scope (NNS) of 7.90. Using USD$500 as an estimated cost of an OGD in Singapore, the estimated cost of detecting one pre-neoplastic or neoplastic OG lesion for all opportunistic endoscopies is USD$3950. The NNS to identify a neoplastic lesion is 282.80 with an estimated cost of USD $141 400.

Table 1 Patient demographics

	No. (%)
Demographic and clinico-pathological details	
Median age/years (range)	60.3 (40–88.3)
Gender	
Male	743 (52.5)
Female	671 (47.5)
Ethnicity	
Chinese	1144 (80.9)
Malay	66 (4.7)
Indians	57 (4.0)
Others	147 (10.4)
Smoker	
No	1072 (75.8)
Current/previous	221 (15.6)
Unknown	121 (8.6)
Family history of cancer	
Family history of cancer (any)	542 (38.3)
Family history of first-degree relative with colorectal cancer	199 (14.1)
Family history of first-degree relative with gastric cancer	175 (12.4)
Unknown	222 (15.7)
Upper endoscopy findings	
Pre-neoplastic and neoplastic esophagogastric lesions (n = 179)	
Atrophic gastritis	23 (1.6)
Barret's esophagus	19 (1.3)
Intestinal metaplasia	146 (10.3)
Focal	112 (7.9)
Moderate/Extensive	21 (1.5)
Malignant gastric tumors	5 (0.35)
Other clinically significant OG lesions	
Peptic ulcer disease	
Gastric ulcer	32 (2.3)
Duodenal ulcer	14 (1.0)
Helicobacter pylori	
Yes	185 (13.1)
Unknown	322 (22.8)
Other Findings	
Non-erosive gastritis	572 (40.5)
Benign gastric tumors	4 (0.3)
Hiatus hernia	163 (11.5)
Colonoscopy indications and findings	
Colonoscopy indications	
Screening (asymptomatic)	750 (53.0)
Fecal occult blood test positive	310 (21.9)
Modification of bowel habits	160 (11.3)
Raised tumor markers	102 (7.2)
Others	92 (6.5)
Colonoscopy findings	
Diverticulosis	302 (21.4)
Adenomatous polyps	490 (34.7)
Malignant colorectal tumor	20 (1.4)
Colonoscopy findings among patients who underwent screening colonoscopy (n = 750)	
Adenomatous polyps	243 (32.4)
Malignant colorectal tumor	4 (0.5)

All values are stated as *n* (%) unless otherwise stated.

Discussion

In this study, we evaluated the findings of patients with no OG symptoms who underwent opportunistic upper endoscopy at the same setting of colonoscopy. Neoplastic OG lesions were identified in 0.35% of this population. All were early OG neoplasia. In total, 179 patients (12.7%) were found to have both neoplastic and pre-neoplastic lesions. Older patients and patients with first-degree relatives of gastric cancer were independent predictive factors for detecting these OG lesions. The number needed to scope to detect a neoplastic OG lesion is 282.8 with an estimated cost of USD$141 400 per lesion detected.

The benefit of performing screening upper endoscopy for asymptomatic individuals for gastric cancer remains controversial.[2] Screening upper endoscopy is common in countries with high incidence of gastric cancer. In Japan and Korea, individual aged 40 and above are recommended for gastric cancer screening.[2] In Japan and Korea, the implementation of population-based screening had resulted in over 60% of gastric cancers being diagnosed at an early stage with excellent outcomes.[8–11] The 5-year overall survival is 60–70% and 90–95% for early gastric cancer compared with 20–30% before the implementation of screening programs.[2,12] In other countries, however, screening endoscopy for OG cancers is not practiced due to lack of cost-effectiveness. Hence, most OG cancers are diagnosed at advanced stages. A new screening strategy to diagnose OG cancers early is highly desirable.

Performing upper endoscopy and colonoscopy at the same setting is a common practice.[13] Currently, patients presenting with iron-deficiency anemia or occult gastrointestinal bleeding are routinely offered double endoscopy.[14,15] To our knowledge, our study was the first report to evaluate the strategy of opportunistic upper endoscopy at the same setting of colonoscopy as a screening strategy for OG cancers in asymptomatic patients. Performing upper endoscopy at the same setting of colonoscopy reduces the need for repetitive services such as sedation and recovery. The convenience and cost-saving may translate to greater acceptance by the patients. The risk of upper endoscopy is minimal with no major adverse events such as bleeding requiring admission or perforation in our study population. For patients who opted for concurrent upper endoscopy, the cost of the procedure is borne by the patents pending prevailing eligible government subsidies.

Previously, two cost-utility studies suggested that this strategy was cost-effective in European countries with intermediate gastric cancer risk and even in the USA where the incidence of gastric cancer is low.[4,5] Areia *et al.* used a Markov model to compare stand-alone upper endoscopy screening, opportunistic upper endoscopy screening at the time of screening colonoscopy, and serologic screening with pepsinogen in Europe.[4] The model showed that combining upper endoscopy with screening colonoscopy was the most cost-effective option. It was found to be cost-effective in countries with age-standardized risk (ASR) of gastric cancer $\geq$ 10 per 100 000.[4] Gupta *et al.* utilized a nation-wide model incorporating a 30-year risk for developing esophageal adenocarcinoma, esophageal squamous cell carcinoma, and gastric adenocarcinoma in the US population.[5] He found that opportunistic upper endoscopy screening at the time of screening colonoscopy was cost-effective and had comparable cost to other established cancer screening interventions.[5]

Table 2 Univariate and multivariate analyses for prognostic variables of pre-neoplastic and neoplastic esophagogastric lesions by using the multivariate logistic regression

Factors	N (n = 1414)	Univariate relative risk (95% CI)	P	Multivariate relative risk (95% CI)	P
Age			< 0.001	1.84 (1.29–2.63)	0.001
≤ 60	685	1.00			
> 60	729	1.82 (1.31–2.51)			
Gender			0.267		
Male	743	1.00			
Female	671	0.84 (0.61–1.15)			
Ethnicity					
Chinese	1144	1.79 (1.12–2.86)	0.014	1.27 (0.77–2.10)	0.354
Malay	66	0.0.81 (0.37–1.81)	0.608		
Indians	57	0.81 (0.34–1.90)	0.622		
Smoker			0.520		
No	1072	1.00			
Current/previous	221	1.15 (0.76–1.74)			
Family history					
Cancer (Any)	542	1.23 (0.87–1.73)	0.234		
First-degree relative with colorectal cancer	199	1.42 (0.93–2.17)	0.105	1.40 (0.91–2.15)	0.125
First-degree relative with gastric cancer	175	1.63 (1.05–2.50)	0.028	1.64 (1.06–2.55)	0.027
Helicobacter pylori[†]			0.026		
No	907	1.00			
Yes	185	1.62 (1.06–2.49)			

[†]Not included into the multivariate model as it is a post-endoscopic finding.

Table 3 Number needed to scope for identification of pre-neoplastic or neoplastic esophagogastric lesions and cost per diagnosis

Indications	Numbers needed to scope (NNS)	Estimated cost in USD (1 OGD–USD$500)
Neoplastic or pre-neoplastic lesions	7.90	3950
Neoplastic or pre-neoplastic lesions with age > 50	7.41	3705
Neoplastic or pre-neoplastic lesions with positive family history of first-degree relative of gastric cancer	5.65	2825
Neoplastic lesions and extensive IM	54.38	27 192
Neoplastic lesions only	282.80	141 400

In our study, opportunistic upper endoscopy detected five (0.35%) neoplastic OG lesions in asymptomatic subjects. Three patients had stage-one gastric cancer, one had high-grade dysplasia, and one had MALT lymphoma. This finding was in contrast to our previous report of 5066 upper endoscopies for symptomatic patients; 26 OG cancers were diagnosed, but early-stage (stages 1 and 2) OG cancer was found in only nine patients (0.18%).[16] Currently, our national cancer registry reveals that only 22% to 28% of new gastric cancer in Singapore was diagnosed as stage 1 disease.[6] Our detection rate was also comparable with the screen-detected cancer rates in countries with gastric cancer screening programs. In Korea, the screen-detected cancer rate using endoscopy was 0.26–0.3% from a population-based screening program.[9,17] In a study from a high incidence region of Japan, screen-detected gastric cancer was 0.87% patients among patients who had no prior upper endoscopy within 2 years.[18] The high yield of screen detected OG lesions for opportunistic upper endoscopy in our study as compared with the general population might be related to the patients' characteristics. Our patients were older

(median age was 60) with 26% of them having first-degree relatives who had gastric or colon cancer.

In terms of cost, opportunistic upper endoscopy is comparable with other cancer screening interventions such as colon cancer. Wong et al. evaluated the screening cost for screening colonoscopy and found that cost of colorectal cancer detection was USD $357 172.[19] In their study, the estimated cost of a colonoscopy was USD$967. In our study, where the cost of an upper endoscopy was USD$500, the cost of detecting an OG neoplasm was USD $141 400. Colorectal cancer screening has the undeniable added benefit of detection and removal of adenomatous polyps that reduces the risk of colorectal cancer. However, these patients will be required to have repeat colonoscopy for surveillance, which adds to the overall long-term cost. Similarly, opportunistic upper endoscopy can lead to the incidental detection of high risk, pre-neoplastic lesions. Such patients may benefit from regular endoscopic surveillance. Understandably, cost effectiveness is expected to vary depending on the geographical incidence of OG neoplasm and the endoscopy cost.

In our study, one in eight patients was found to have pre-neoplastic OG lesions such as AG, IM, and BE. The annual risk of progression of pre-malignant EG lesions is estimated to be 0.1% for patients with AG and 0.25% for patients with IM.[20] Recent guidelines recommend that patients with AG and IM at multiple locations or with a first-degree family history of gastric cancer should undergo surveillance upper endoscopy every 3 years from the initial diagnosis.[21] Opportunistic upper endoscopy allows for identification of this subset of patients within our population who could benefit from regular endoscopic surveillance. In addition, upper endoscopy also detected other incidental OG pathologies such as peptic ulcer and *H. pylori* infection. Treatment of these incidentally diagnosed pre-neoplastic lesions associated with *H. pylori* infection can potentially alter their natural history and reduce the incidence of gastric cancer.

Lastly, we observed that older patients and patients with first-degree relative with gastric cancer had higher yield with opportunistic endoscopy. Age and family history are well-known risk factors for gastric cancer.[2,20–22] In Japan and Korea, individuals aged 40 and above are recommended for gastric cancer screening.[2] As such, we chose 40 as the cut-off age in our study population. Inevitable, our study population is relatively old with a median age of 60.3. With an age cut-off for detection of pre-neoplastic OG lesions at 60 years, we obtained a sensitivity of 64% and specificity of 51%. In Singapore, gastric cancer risk is high in Chinese men above the age of 50 with an age standardized rate of 25.9 per 100 000.[23] This rises to an ASR of 42.8 with the presence of *H. pylori* infection.[23] In our study population, Chinese ethnicity and *H. pylori* were significant risk factors on univariate analysis. However, Chinese ethnicity failed to achieve significance in multivariate analysis. Detection of *H. pylori* was based on post-endoscopy findings and was not evaluated on multivariate analysis. Future study can aim to identify asymptomatic high-risk population who would benefit most from this screening strategy.

Nevertheless, our study has several limitations. It is a retrospective study with its inherited bias. In order to limit selection bias, all consecutive cases were enrolled, and the resultant study population reflects the population encountered in clinical practice. Secondly, the number of patients with OG neoplasm was small, and a study with larger sample size is required to validate our findings. In addition, we did not perform a systematic biopsy such as using the Operative Link on Gastritis/Intestinal-Metaplasia Assessment (OLGIM) to classify IM into focal and extensive IM.[24] While the risk of progression for focal IM is generally acknowledged to be low, extensive IM carries a significantly higher risk of progression to cancer. Hence, it is likely that the rate of extensive IM in our study population was under-reported and the yield of opportunistic upper endoscopy may possibly be higher. Lastly, opportunistic upper endoscopy was only offered for selected patients in this study as there is currently no established gastric screening protocol. The real diagnostic yield of this strategy in the general population is still unknown and warrants further evaluation.

In conclusion, for countries with intermediate gastric cancer risk, opportunistic upper endoscopy at the same setting of colonoscopy may be an alternative strategy for screening of OG malignancies, especially in selected patient population such as age older than 60 years old and patients with first-degree relative with gastric cancer. Prospective trials are warranted to validate its performance.

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