

Academy of Medicine, Singapore clinical guideline on endoscopic surveillance and management of gastric premalignant lesions

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ABSTRACT

Gastric cancer (GC) has a good prognosis, if detected at an early stage. The intestinal subtype of GC follows a stepwise progression to carcinoma, which is treatable with early detection and intervention using high-quality endoscopy. Premalignant lesions and gastric epithelial polyps are commonly encountered in clinical practice. Surveillance of patients with premalignant gastric lesions may aid in early diagnosis of GC, and thus improve chances of survival. An expert professional workgroup was formed to summarise the current evidence and provide recommendations on the management of patients with gastric premalignant lesions in Singapore. Twenty-five recommendations were made to address screening and surveillance, strategies for detection and management of gastric premalignant lesions, management of gastric epithelial polyps, and pathological reporting of gastric premalignant lesions.

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INTRODUCTION

Gastric cancer (GC) is the 7th most common cancer in men and the 9th most common cancer in women in Singapore. More than two-thirds of patients with GC are diagnosed at stage III or IV, when the 5-year survival rate is <5%.¹ In contrast, early GC (EGC) is associated with good prognosis. While Japan and South Korea have a high incidence of GC, survival outcomes have improved with population-based screening programmes,^{2,3}

Singapore has an intermediate incidence level of GC. This requires interventions to be directed at population subgroups with the highest risk of developing GC.³ A rational strategy for identifying the target group is to use known risk factors such as age, *Helicobacter pylori* infection, current or past history of smoking, family history of GC, as well as the presence of premalignant lesions such as intestinal metaplasia (IM), atrophic gastritis (AG) and dysplasia.

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CLINICAL IMPACT

What is New

- This guideline provides recommendations on the management of gastric premalignant lesions and gastric epithelial polyps in Singapore.

Clinical Implications

- A high-quality oesophago-gastro-duodenoscopy identifies at-risk patients who require surveillance and those with early gastric neoplasia (EGN) who require endoscopic intervention.
- The detection of EGN enables endoscopic treatment, which may obviate the need for surgery.
- In patients with intestinal metaplasia, risk stratification may guide decisions on endoscopic surveillance for gastric cancer.
- The finding of dysplasia should prompt a careful examination for an endoscopically resectable lesion for definitive diagnosis.

The majority of GCs are adenocarcinomas with 2 distinct subtypes—intestinal and diffuse, both of which have different aetiologies, clinical pathways and genetic backgrounds.^{4,5} Diffuse type GC is more common in young patients, and behaves more aggressively than the intestinal type.^{5,6} Intestinal subtype, which accounts for the vast majority of GCs, is associated with *H. pylori* infection and develops through a stepwise progression of premalignant lesions: gastritis, atrophy, IM and dysplasia.⁷ This lends itself to early detection and intervention with high-quality endoscopy. GC is thought to arise from increased genetic instability of gastric stem cells, rather than by a direct transition from metaplasia. IM therefore represents a high-risk lesion in the background mucosa that shares the same pathogenesis with intestinal-type adenocarcinoma, although it is not a direct precursor of GC.^{8,9} IM is commonly encountered in the upper gastrointestinal (GI) endoscopy. A recent report from the Gastric Cancer Epidemiology and Molecular Genetics Programme (GCEP) has further clarified the natural history of these lesions in the Singapore population.¹⁰

Hence it is timely to review the current evidence and provide recommendations on the management of patients with gastric premalignant lesions in Singapore. It is recognised that epithelial gastric polyps (EGPs), either sessile or pedunculated, are common incidental findings on endoscopy that encompass a spectrum of

neoplastic potential (Table 1). There is thus a need to provide clinical guidance for the management of EGPs.

This guideline focuses on the gastric premalignant lesions such as IM, and EGP. The management of diffuse type GC and non-epithelial lesions such as neuroendocrine tumours and sub-epithelial lesions will not be addressed in this guideline. This guideline does not define a standard of care but are written to improve endoscopic practice standards. In clinical practice, it is recognised that variations from this guideline may occur depending on the individual patient's needs, clinical scenarios and availability of expertise. The decision to screen and survey for GC should be individualised, taking into consideration the patient's overall health and preferences.

METHODS

The Chapter of Gastroenterologists of the College of Physicians, Academy of Medicine, Singapore (AMS) initiated the formation of a workgroup to formulate guidelines for the endoscopic surveillance of gastric premalignant lesions.

Six main sections and framing questions were first defined by the co-chairs of the workgroup (KGY, VN and CJK) in October 2020. Doctors comprising gastroenterologists, surgeons and pathologists from the Singapore public hospitals, private hospitals, the Chapter of Gastroenterologists of the College of Physicians (AMS) and Chapter of General Surgeons of the College of Surgeons (AMS) were invited to be part of the workgroup. Each doctor was assigned to 1 or 2 sections based on their expertise (Table 2). The co-chairs first identified recent relevant guidelines published by international professional societies pertaining to the issue of endoscopic surveillance and management of gastric malignant lesions. A set of draft statements together with the initial references was circulated to members of the workgroup who then conducted further literature search in PubMed pertinent to their assigned section up to December 2020, and further revised the statements. Examples of PubMed search terms used were: “endoscopic surveillance”, “gastric cancer”, “gastric polyps”, “gastric dysplasia”, “gastric atrophy”, “gastric intestinal metaplasia” and “gastric cancer precursors”. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to evaluate the quality of evidence and assess the strength of recommendations.¹¹ Consensus level was predefined as $\geq 80\%$ agreement.

The formal consensus process used the modified Delphi technique. The first round of voting was

performed online from 21 to 25 January 2021. All members were asked to indicate their agreement (agree or disagree), levels of recommendation strength (strong or weak), levels of quality of evidence (high, moderate or low), and comments for each statement. The statements were further revised after discussion. In the second round, members of the workgroup met in person to discuss the revised statements, level of evidence and recommendations on 27 January 2021. Statements that failed to reach $\geq 80\%$ of agreement during the first vote were revised and polled again, in order to achieve consensus. The final statements are summarised in Table 3. Each section of the workgroup drafted the initial explanatory text that follows each statement. The co-chairs and corresponding authors (VN, CJK, KGY, TLA) then compiled and edited the drafted guideline, which was circulated to all workgroup

members for vetting. The completed guideline was reviewed and endorsed by the Board of the Chapter of Gastroenterologists, and by the governing Council of AMS.

Table 1. Epithelial gastric polyps

Fundic gland polyp
Hyperplastic polyp
Adenomatous polyp
Hamartomatous polyps
Juvenile polyp
Peutz-Jeghers syndrome
Cowden's syndrome
Polyposis syndromes (non-hamartomatous)
Juvenile polyposis
Familial adenomatous polyposis

Table 2. Clinical questions

Clinical questions	Section members
Section A. Pathogenesis, who is at risk and who needs surveillance - Who is at risk of gastric cancer? - Should <i>H. pylori</i> eradication be recommended in all patients with <i>H. pylori</i> infection? - Should endoscopic screening be recommended? - What are the biomarkers which are useful in surveillance and management of gastric neoplasia?	Khay Guan Yeoh, Jonathan Lee, James Weiquan Li, Aung Myint Oo
Section B. Strategies to increase detection of gastric intestinal metaplasia, dysplasia and neoplasia - What constitutes a high-quality oesophago-gastro-duodenoscopy? - What is the utility of chromoendoscopy and virtual chromoendoscopy for the detection of gastric neoplasia?	Vikneswaran Namasivayam, Khoon Lin Ling, Benjamin CH Yip, Ming Teh
Section C. Strategies for managing dysplasia and early gastric neoplasia - How should indefinite for dysplasia be managed? - How should dysplasia detected on random biopsies be managed? - How should dysplastic lesions be managed? - How should early gastric neoplasia be managed?	Stephen Tsao, Christopher Khor, Jimmy BY So, Tony Lim
Section D. Surveillance guidelines for gastric intestinal metaplasia, dysplasia and neoplasia - What are the appropriate surveillance intervals - for gastric intestinal metaplasia - for resected low grade dysplasia, high grade dysplasia, early gastric cancer - for random biopsies of low grade dysplasia without lesion to resect - for indefinite for dysplasia - How should surveillance oesophago-gastro-duodenoscopy be performed (high-quality, chromoendoscopy, etc.?) - When do we stop surveillance?	Stephen Tsao, Calvin J Koh, Ikram Hussain, Jonathan Lee, Tju Siang Chua
Section E. Gastric polyps - How should "non-dysplastic" polyps be managed? - Role of biopsy - Role of resection - Role of surveillance	Tiing Leong Ang, Bin Chet Toh, Hock Soo Ong, Lai Mun Wang
Section F. Pathology section - What constitutes a robust diagnosis of dysplasia? - What would be an adequate resection specimen? - How should resection specimens be prepared? - What are the features consistent with curative resection?	Ming Teh, Tony Lim, Lai Mun Wang

Table 3. Summary of statements

	Statements	Quality of evidence	Strength of recommendation	Final vote
Section A. Pathogenesis, who is at risk and who needs surveillance				
1.	We recommend eradication of <i>H. pylori</i> when it is detected during routine clinical care, for the primary prevention of gastric adenocarcinoma.	High	Strong	100%
2.	We recommend eradication of <i>H. pylori</i> in patients with gastric cancer undergoing endoscopic or surgical resection with curative intent to reduce the risk of metachronous gastric cancer.	High	Strong	100%
3.	Patients with chronic atrophic gastritis, intestinal metaplasia and dysplasia are at increased risk for gastric adenocarcinoma.	High	Not applicable	95%
4.	In Singapore, given the intermediate incidence of gastric cancer, we suggest targeted endoscopic screening for gastric cancer in individuals with increased risk.	Moderate	Weak	89%
5.	Serum biomarkers, such as pepsinogen levels and microRNA, may be useful for the identification of individuals at high risk for gastric cancer.	Low	Weak	89%
Section B. Strategies to increase detection of gastric intestinal metaplasia, dysplasia and neoplasia				
6.	High-quality examination of the stomach should be performed to increase detection of gastric neoplasia. High-quality examination would involve systematic mapping of the stomach with adequate examination time and photo documentation. Mucosal visualisation may be enhanced with the use of mucolytic/defoaming agents and antispasmodics.	Moderate	Strong	100%
7.	High-resolution, image-enhanced endoscopy (IEE) should be used for the diagnosis of gastric precancerous conditions and early gastric neoplasia. The presence of a suspicious focal gastric lesion on white light endoscopy should be further characterised with IEE, preferably with magnification, to determine whether it is a gastric neoplasia.	Moderate	Strong	100%
8.	The presence of atrophic gastritis and intestinal metaplasia should be documented and prompt a diligent examination for the presence of gastric neoplasia.	Moderate	Strong	95%
9.	Where risk stratification of progression to gastric cancer is required, we recommend the use of histopathological staging (e.g. Operative Link on Gastric Intestinal Metaplasia [OLGIM]).	Moderate	Strong	95%
Section C. Strategies for managing dysplasia and early gastric neoplasia				
10.	Patients with any degree of dysplasia found on random biopsy should undergo a repeat examination with image-enhanced endoscopy to increase the chances of identifying and diagnosing a potentially resectable lesion.	Low	Strong	95%
11.	When a directed biopsy is reported as showing low grade dysplasia or indefinite for dysplasia, endoscopic evaluation should be repeated. If a focal lesion is identified, consideration should be given to endoscopic resection for more accurate histological assessment as well as for therapy.	Moderate	Strong	100%
12.	Early gastric neoplasia (visible lesion with either high grade dysplasia or early stage adenocarcinoma) should be resected en bloc if possible. When lesions are <15mm, endoscopic mucosal resection is sufficient to achieve en bloc resection. When lesions are >15mm, endoscopic submucosal dissection is the method of choice to achieve en bloc resection.	Moderate	Strong	95%
Section D. Surveillance guidelines for gastric intestinal metaplasia, dysplasia and neoplasia				
13.	Patients with OLGIM stage I intestinal metaplasia have an increased risk of gastric cancer. However, this increased risk does not justify surveillance in most cases.	Moderate	Strong	100%
14.	Patients with OLGIM stage I intestinal metaplasia, with additional risk factors such as significant smoking history (20 pack-years), age >50 years, incomplete intestinal metaplasia, persistent <i>H. pylori</i> infection and first-degree family history of gastric cancer should have surveillance every 3 years.	Low	Strong	95%

Table 3. Summary of statements (Cont'd)

	Statements	Quality of evidence	Strength of recommendation	Final vote
15.	We recommend endoscopic surveillance every 3 years for patients with advanced stage of atrophic gastritis or intestinal metaplasia (OLGIM stage III–IV). Patients with ≥ 2 risk factors (smoking, age > 50 years, incomplete intestinal metaplasia, persistent <i>H. pylori</i> infection, first-degree family history of gastric cancer) may be offered a surveillance endoscopy in 2 years.	Low	Strong	84%
16.	We suggest endoscopic surveillance every 5 years for patients with intermediate stage of intestinal metaplasia (OLGIM stage II).	Low	Weak	100%
17.	We suggest patients with autoimmune gastritis to undergo endoscopy with biopsies at the time of diagnosis and subsequently, every 3–5 years.	Low	Weak	89%
18.	In cases of high grade dysplasia and low grade dysplasia detected incidentally from random biopsies, when there is still no focal lesion(s) identified on repeat endoscopy, a surveillance endoscopy should be carried out once every 6 months in the case of high grade dysplasia and annually for low grade dysplasia, both for a minimum period of 5 years.	Low	Strong	84%
Section E. Gastric polyps				
19.	We recommend polypectomy for fundic gland polyps ≥ 1 cm, hyperplastic polyps ≥ 0.5 cm, and adenomatous polyps of any size when possible.	Moderate	Strong	100%
20.	We recommend that in the setting of multiple hyperplastic polyps or adenomatous polyps, surrounding gastric mucosa should be assessed for synchronous neoplasia, and biopsies taken for the assessment of <i>H. pylori</i> infection, atrophic gastritis and intestinal metaplasia.	Moderate	Strong	89%
21.	We suggest surveillance endoscopy 1 year after complete endoscopic excision of dysplastic or adenomatous polyps.	Low	Weak	95%
Section F. Pathology section				
22.	We recommend pathology reports to standardise the description of intestinal metaplasia: intestinal metaplasia to be quantified for each site as mild (0–30% involvement of mucosa), moderate (31–60% involvement of mucosa) and marked ($> 60\%$ involvement of mucosa). The presence of gastric atrophy in oxyntic mucosa should be assessed where feasible.	High	Strong	100%
23.	Dysplasia should be graded on a 2-tiered system as recommended in the WHO Classification of Tumours, 5th Edition, Volume 1 for digestive system tumours.	High	Strong	100%
24.	We recommend that the handling and reporting of endoscopic resected specimens (endoscopic mucosal resection and endoscopic submucosal dissection) be performed as described by the Japanese Gastric Cancer Association. The en bloc resection specimen is pinned out on a flat board in the fresh state, serially sliced after adequate fixation, placed into cassettes in sequential order and entirely submitted for histological examination.	Moderate	Strong	95%
25.	When resected en bloc and lymphovascular invasion is absent on histology, complete (R0) endoscopic resection of gastric dysplasia and early gastric adenocarcinoma should be considered as curative if the lesion meets one of the following criteria: i. Dysplasia: low or high grade ii. Well or moderately differentiated intramucosal carcinoma (IMC) (pT1a) irrespective of size and without ulceration iii. Well or moderately differentiated IMC (pT1a), < 3 cm in size if ulcerated iv. Well or moderately differentiated adenocarcinoma with superficial submucosal invasion (pT1b and $< 500 \mu\text{m}$ in depth measured in a straight line from the deepest fibre of the muscularis mucosae), < 3 cm in size v. Poorly differentiated IMC (pT1a), ≤ 2 cm in size	Moderate	Strong	95%

Table 4. Summary of surveillance recommendations for intestinal metaplasia by Operative Link on Gastric Intestinal Metaplasia (OLGIM) stage

OLGIM stage	Additional risk factors (smoking, age >50 years, persistent <i>H. pylori</i> infection, incomplete intestinal metaplasia, first-degree family history of gastric cancer)	Recommended surveillance endoscopy, years
I	Absent	Nil
	Present	3
II	Absent	5
	Present	3
III and IV	Absent	3
	Present	2

H. pylori: *Helicobacter pylori*

Table 5. Pathology reporting on biopsies sent for the evaluation of gastric intestinal metaplasia

Characteristics	Remarks
Site	Indicate anatomical site (i.e. antrum, corpus or cardia) ^a where intestinal metaplasia is observed.
Severity	Assess the severity of intestinal metaplasia based on the estimated percentage of mucosal involvement: mild (0–30%), moderate (31–60%) and marked (>60%).
OLGIM stage	OLGIM stage I/II/III/IV or insufficient biopsies for OLGIM staging. ^b

OLGIM: Operative Link on Gastric Intestinal Metaplasia

^a Only possible if specimen site is specified by endoscopist. When the gastric anatomical site is not provided, a general overview assessment will be done.

^b This scoring will not be routinely done. When required, the clinician/endoscopist needs to request specifically for OLGIM assessment.

RESULTS

Statements with explanation

Section A. Pathogenesis, who is at risk and who needs surveillance

Statement 1: We recommend eradication of *H. pylori* when it is detected during routine clinical care, for the primary prevention of gastric adenocarcinoma.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

Although the aetiology of GC is heterogeneous, it is estimated that 89% of non-cardia GC is attributable to *H. pylori* infection.¹² *H. pylori* eradication is effective in reducing the incidence of GC in healthy individuals.^{13,14} Meta-analysis of 7 randomised clinical trials^{13,15–19} with a total of 8,834 individuals without premalignant lesions, demonstrated a reduction in the risk of GC (relative risk [RR] 0.55, 95% confidence interval [CI] 0.42–0.74). The magnitude of the effect

of *H. pylori* eradication varied with the baseline GC incidence.²⁰

The evidence of *H. pylori* eradication in reducing the risk of GC in patients with premalignant conditions is less convincing. Meta-analysis showed that patients with gastric atrophy benefited from *H. pylori* eradication through the reduced risk of GC but the same effect was not seen in patients with IM or dysplasia.²¹ The Taipei global consensus on screening and eradication of *H. pylori* for GC prevention recommended *H. pylori* eradication before the development of AG and IM.²² Patients with premalignant conditions may benefit from *H. pylori* eradication due to reduced severity of inflammation and AG.

In Singapore, where the incidence rate of GC is at intermediate level,^{3,10} screening and eradication of *H. pylori* at population level is not recommended. Treatment of *H. pylori* should be considered and offered when it is detected in the course of clinical care.

Statement 2: We recommend eradication of *H. pylori* in patients with gastric cancer undergoing

endoscopic or surgical resection with curative intent to reduce the risk of metachronous gastric cancer.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

Eradication of *H. pylori* is effective in the prevention of metachronous GC. A meta-analysis of 3 randomised controlled trials of 1,841 patients with GC undergoing curative endoscopic resection demonstrated that *H. pylori* eradication was superior to placebo or no treatment in reducing the risk of metachronous GC (RR 0.49, 95% CI 0.34–0.70).¹³ Another meta-analysis of 10 cohort studies similarly demonstrated that eradication therapy reduced the risk of metachronous GC after curative resection (RR 0.44, 95% CI 0.33–0.58).²³ In patients with GC undergoing endoscopic or surgical resection with curative intent, we recommend eradication of *H. pylori* to reduce the risk of metachronous GC.

Statement 3: Patients with chronic atrophic gastritis, intestinal metaplasia and dysplasia are at increased risk for gastric adenocarcinoma.

Quality of evidence: High

Strength of recommendation: Not applicable

Agreement: 95%

The intestinal subtype of GC develops through a sequence of well-recognised stages: inflammation, atrophy, IM, dysplasia and subsequent carcinoma.²³ In a Japanese cohort of 1,246 patients followed for 7.8 years, patients with gastric IM were at 6-fold increased risk of GC.²⁴ Similarly, a Korean study of 541 patients reported that moderate-to-severe IM at the antrum and corpus lesser curvature (odds ratio [OR] 7.52 and OR 9.25, respectively) were associated with GC risk.²⁵ In Singapore, findings from the GCEP study published in 2021 showed that patients with gastric IM had a 5.36-fold increased risk of early gastric neoplasia (EGN).¹⁰ EGN referred to visible lesions with either high grade dysplasia (HGD) or early stage adenocarcinoma.

Statement 4: In Singapore, given the intermediate incidence of gastric cancer, we suggest targeted endoscopic screening for gastric cancer in individuals with increased risk.

Quality of evidence: Moderate

Strength of recommendation: Weak

Agreement: 89%

Population screening for GC has been associated with improved survival of patients with GC in high-prevalence populations such as Japan and South Korea. Both of these countries have national endoscopic screening programmes and low mortality-to-incidence ratios (0.43 and 0.35, respectively), reflecting the benefit of endoscopic screening for early detection of GC.²⁶ In Singapore, where risk of GC is intermediate, screening of the average risk population would not be cost-effective. A study showed that 2-yearly oesophago-gastro-duodenoscopy is cost-effective in the high-risk subgroup of 50–70-year-old Chinese men with or without *H. pylori* infection.³ We suggest that targeted endoscopic screening be considered in high-risk individuals ≥ 50 years, with 3 or more of the following risk factors: Chinese, male, history of *H. pylori* infection, heavy smoker, first-degree family history of GC, or pernicious anaemia.^{27–31}

Statement 5: Serum biomarkers, such as pepsinogen levels and microRNA, may be useful for the identification of individuals at high risk for gastric cancer.

Quality of evidence: Low

Strength of recommendation: Weak

Agreement: 89%

Pepsinogen (PG) and microRNA (miRNA) have been reported as useful serum biomarkers for the detection of GC.^{32–35} The ABC method using a combined assay for serum anti-*H. pylori* immunoglobulin G (IgG) antibody and serum PG levels was shown to have superior cost benefit and GC detection rate compared to conventional X-ray mass screening in Japan.^{32–34} In the meta-analysis of 31 studies with a total of 3,785 patients (1,520 GC patients and 2,265 AG patients), the area under the curve (AUC), sensitivity and specificity for GC diagnosis using PG was 0.76 (95% CI 0.72–0.80), 0.69 (95% CI 0.60–0.76) and 0.73 (95% CI 0.62–0.82), respectively.³⁶

A recent study reported a novel 12-miRNA assay (validated in a prospective cohort of 4,566 Asian patients) to have a sensitivity of 87% (95% CI 79.4–92.5) and specificity of 68.4% (95% CI 67.0–69.8) for the detection of GC.³⁵ The AUC of the 12-miRNA assay was 0.848 (95% CI 0.81–0.88), which is significantly higher than the ABC method (0.647). The assay performance further improved with the AUC of 0.884, by including patient's age, *H. pylori* serology and PG1/PG2 ratio. The study also reported that the number needed to screen is 489 and proposed the assay can be used as a risk assessment tool for GC before endoscopy. Cost-effectiveness analysis showed the miRNA blood test

as the primary screening test for GC in high-risk population (Chinese males, 50–75 years). This would be cost-effective compared to the current practice of no screening, with an incremental cost-effectiveness ratio of USD40,971/quality-adjusted life-year.³⁷ The test has received regulatory approval from the Health Sciences Authority of Singapore to be used in adults who are ≥ 40 years at average risk of having GC. However, the role of miRNA test in clinical management has yet to be determined. More studies are needed to clarify its performance in different clinical settings, before a recommendation can be made for its use in the screening of average-risk population.

Section B. Strategies to increase detection of gastric intestinal metaplasia, dysplasia and neoplasia

Statement 6: High-quality examination of the stomach should be performed to increase detection of gastric neoplasia. High-quality examination would involve systematic mapping of the stomach with adequate examination time and photo documentation. Mucosal visualisation may be enhanced with the use of mucolytic/defoaming agents and antispasmodics.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

EGC may be missed on endoscopy as they are challenging to detect.³⁸ They present as subtle morphological changes in the mucosa, may be located in blind areas in the stomach such as the incisura, high lesser curve and posterior wall, and may be obscured by adherent mucus. The following strategies are recommended to improve the quality of endoscopic examination.

Systematic examination and photo documentation

Systematic endoscopic mapping and photo documentation of the stomach is recommended to ensure that blind areas are not missed. The systematic screening protocol proposed by Yao³⁹ is well accepted internationally.⁴⁰ There is significant variation among existing guidelines on the recommended number of photos to be taken for an adequate examination,⁴¹ with no well-designed studies that address this question. Endoscopic photo-documentation also provides a useful mechanism for review of challenging cases.

Examination time

Several observational studies have demonstrated that an adequate duration of examination is associated with increased detection of gastric neoplasia. A

Singapore study reported that endoscopists with a mean examination time ≥ 7 min were more likely to uncover premalignant and neoplastic lesions during diagnostic endoscopies.⁴² The time taken encompasses the effort to clean the gastric mucosal surface, and to meticulously examine the mucosa to detect subtle abnormalities. Other studies have suggested a different cut-off for examination time.^{43,44} However, the effect of a longer examination time may be reduced with very experienced endoscopists who are able to readily recognise a neoplastic lesion.⁴⁵ While there is no consensus on what should be the minimum time for a quality endoscopic examination, evidence suggests that a longer examination time results in higher endoscopic yield.

Mucolytic/defoaming agents (N-acetylcysteine, simethicone) and antispasmodics

Pronase and N-acetylcysteine are mucolytic agents whereas simethicone is a defoaming agent. Pronase is currently not available for clinical use in Singapore and hence will not be further discussed. All these agents have been investigated in randomised controlled trials.⁴⁰ While mucolytic/defoaming agents have not been shown to increase the detection of EGC, they improve endoscopic visualisation. Premedication with simethicone alone, or simethicone and N-acetylcysteine have been demonstrated to improve visualisation in the oesophagus and stomach.^{46–48} Endoscope manufacturers have advised against the use of simethicone through an irrigation pump due to concerns of retained simethicone residue and bacterial contamination. Simethicone administered through the working channel or by oral ingestion before the procedure is a reasonable option.

The use of antispasmodics (e.g. hyoscine and glucagon) may be considered in instances where peristalsis interferes with mucosal visualisation. However, no study has demonstrated that their routine use improves EGC detection, and caution is advised in view of their potential adverse effects.

Statement 7: High-resolution, image-enhanced endoscopy (IEE) should be used for the diagnosis of gastric precancerous conditions and early gastric neoplasia. The presence of a suspicious focal gastric lesion on white light endoscopy should be further characterised with IEE, preferably with magnification, to determine whether it is a gastric neoplasia.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

Multiple studies have demonstrated that IEE increases the detection of premalignant changes in the stomach, such as IM and atrophy.⁴⁹ Atrophic mucosa is seen as increased visibility of vessels, low height or pale colour mucosa.⁵⁰ While IM is diagnosed by systematic biopsies, it is reliably detected by the presence of light blue crests on IEE.^{51,52} Narrow band imaging (NBI) is superior to white light and may be sufficiently accurate to either target biopsy or grade IM endoscopically without biopsies.⁵³ The detection of IM or atrophy in the background mucosa should prompt a more meticulous search for neoplastic lesions.⁵⁴

The detection of neoplastic lesions during upper GI endoscopy requires a careful white light examination (WLE). However, WLE has limited sensitivity in the detection of EGC. Neoplastic lesions present as subtle changes in mucosal colour (e.g. erythema or pallor) or morphology (elevation or depression), spontaneous bleeding, a focal change in the vascular pattern or interrupted mucosal folds. These focal areas of subtle change require further characterisation to differentiate the benign lesions (e.g. focal gastritis) from EGC.

IEE has not been demonstrated to increase the detection of EGC over conventional WLE.⁵⁵ However, IEE, especially with magnification endoscopy (ME), is more accurate than WLE in characterising focal gastric lesions.^{56,57} The vessels plus surface (VS) classification system using NBI-ME and based on microvascular and microsurface patterns, provides a useful framework for the endoscopic diagnosis of neoplastic lesions. The presence of a demarcation line in combination with either an irregular microsurface or microvascular pattern is consistent with an endoscopic diagnosis of gastric neoplasia.⁵⁷ The use of IEE with magnification to characterise focal gastric lesions may reduce the need for biopsies, which can then be limited to instances where the endoscopic features are inconclusive.⁵⁸ Endoscopic detection of gastric neoplasia entails a meticulous WLE examination coupled with characterisation of focal lesions using IEE, preferably with magnification.

Statement 8: The presence of atrophic gastritis and intestinal metaplasia should be documented and prompt a diligent examination for the presence of gastric neoplasia.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

AG and IM are associated with an increased risk of GC. Hence the presence of either finding should prompt a more careful examination for the presence of concomitant gastric neoplasia. While AG and IM are diagnosed on histological evaluation of gastric biopsies, characteristic features may be present on endoscopic appearance of the gastric mucosa. Flattening of the gastric rugal folds and visible submucosal vessels are features suggestive of AG. Gastric IM has the appearance of small grey-white, slightly elevated plaques surrounded by mixed patchy pink and pale areas of mucosa causing an irregular, uneven surface. IEE, combined with magnification, improves detection of IM. The light blue crest pattern on NBI-ME is consistent with a diagnosis of IM.⁵¹

Statement 9: Where risk stratification of progression to gastric cancer is required, we recommend the use of histopathological staging (e.g. Operative Link on Gastric Intestinal Metaplasia [OLGIM]).

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

Intestinal type GC progresses through a series of histologically recognisable premalignant stages, and patients with these premalignant lesions are at increased risk of developing GC.^{24,25} Histological staging of AG and IM found on index endoscopy stratifies the risk of subsequent EGC. This may be a useful risk stratification tool in patients who are suitable and willing to undergo GC surveillance.^{10,59}

Histological staging of gastric atrophy and IM may be performed using the Operative Link on Gastritis Assessment (OLGA)⁶⁰ and OLGIM, respectively.⁶¹ While multiple studies have shown OLGA to reliably identify a subpopulation of patients with high risk of GC (i.e. OLGA stage III/IV), OLGIM is preferred as it has a high level of interobserver concordance, and categorises fewer patients to high-risk stages of OLGIM III–IV.^{59,61–63}

OLGIM staging is performed during the index endoscopy with gastric biopsies obtained as follows. Non-targeted gastric biopsies are obtained from a minimum of 5 sites (the lesser and greater curvatures of the antrum and body, and the incisura), with 1 or 2 biopsies per site.⁶⁴ Specimens are placed in a minimum of 2 bottles (1 for the body and 1 for the antrum with incisura).⁶⁵ The value of repeat OLGIM staging, and time interval needed for such restaging are uncertain.

Section C. Strategies for managing dysplasia and early gastric neoplasia

Statement 10: Patients with any degree of dysplasia found on random biopsy should undergo a repeat examination with image-enhanced endoscopy to increase the chances of identifying and diagnosing a potentially resectable lesion.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 95%

The statement refers to careful re-examination to detect discrete, focal lesions that were missed endoscopically during prior endoscopy where random mucosal biopsies were taken. Well-demarcated, discrete lesion can then be subjected to endoscopic resection. Gastric dysplasia varies in reported prevalence from 0.5–3.7% in Western countries, and in areas with high incidence of gastric carcinoma, it can be as high as 9–20%.³¹ The presence of gastric dysplasia is a clinically significant finding and should prompt careful examination of the rest of the stomach as it is associated with a risk of synchronous GC in 10% of cases,⁶⁶ as well as an increased risk of progression to subsequent GC. In some cases, the dysplastic lesion may already harbour a GC.⁶⁷ Therefore, the presence of gastric dysplasia alerts the endoscopist to the possibility of synchronous GC. Patients with HGD had a rate of malignant progression or synchronous cancer of 60–85% over a median interval of 4–48 months.³¹ The risk of progression in individuals with low grade dysplasia (LGD) is less clear. Evidence shows that 19–50% of LGD persists over time, and the risk of malignant transformation may range from 0–23% over 10–48 months.⁶⁸ In addition, visible LGD following resection is upstaged in 25–30% of lesions, including those of <1cm, with an adenocarcinoma rate of 6.9%. The natural history of non-visible LGD is unclear, but evidence suggests an increased rate of progression. For these reasons, if dysplasia is discovered on random biopsies, it is vital to repeat a high-quality IEE in a systematic manner to increase the likelihood of finding a subtle but discrete, visible lesion. Following this, assessment can be made to predict the grade of dysplasia of the lesion, and endoscopic resection can be performed.

Statement 11: When a directed biopsy is reported as showing low grade dysplasia or indefinite for dysplasia, endoscopic evaluation should be repeated. If a focal lesion is identified, consideration should be given to endoscopic resection for more accurate

histological assessment as well as for therapy.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

There are concerns regarding the diagnostic accuracy of gastric dysplasia from forceps biopsies. Significant discrepancies can be found between histology based on forceps biopsy and resected specimens. A meta-analysis of 16 studies involving 3,303 patients with gastric LGD lesions confirmed with forceps biopsy showed that 25% were subsequently diagnosed as more advanced lesions (16.7% gastric HGD and 6.9% gastric carcinoma) following histopathological examination of the endoscopic resection specimen.⁶⁷ Therefore, endoscopic resection of visible lesions in which biopsies have shown LGD is recommended for definitive histological assessment, and potentially for cure if the histopathology is indeed upstaged.

Statement 12: Early gastric neoplasia (visible lesion with either high grade dysplasia or early stage adenocarcinoma) should be resected en bloc if possible. When lesions are <15mm, endoscopic mucosal resection is sufficient to achieve en bloc resection. When lesions are >15mm, endoscopic submucosal dissection is the method of choice to achieve en bloc resection.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

EGN carries an excellent prognosis if it is resected completely.⁶⁹ En bloc resection is recommended as it allows for accurate histological assessment and is associated with a reduced risk of recurrence. EGN may be resected surgically or endoscopically. Endoscopic resection is organ preserving and less invasive for patients. It is potentially curative if the histopathological findings from the resected specimen meet the criteria for curative resection as specified in the Japanese guidelines.⁷⁰

In general, gastric mucosal lesions are not as amenable to lift-and-cut endoscopic mucosal resection (EMR) compared to lesions in the colon. This is because gastric mucosa is thicker. Therefore, it is harder to control the resection margins during snare closure. For lesions <15mm, cap-assisted EMR is feasible and is relatively simple to perform.⁷¹ However, studies have shown that when target lesions are >15mm, cap-assisted EMR is associated with a lower en bloc resection rate

and higher recurrence rate.⁷²⁻⁷⁴ Hence, endoscopic submucosal dissection (ESD) is the preferred method of resection for lesions that are >15mm.⁷⁵ ESD achieves a higher rate of en bloc resection and histologically complete resection rate, compared to EMR. However, ESD is technically demanding, and is associated with a higher risk of complications such as delayed bleeding and perforation.⁷⁶ A discussion between the patient and the relevant experts is important. Patients should be aware of the risks and benefits of endoscopic resection and surgery before any decision-making.³¹

Section D. Surveillance guidelines for gastric intestinal metaplasia, dysplasia and neoplasia

Statement 13: Patients with OLGIM stage I intestinal metaplasia have an increased risk of gastric cancer. However, this increased risk does not justify surveillance in most cases.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

Statement 14: Patients with OLGIM stage I intestinal metaplasia, with additional risk factors such as significant smoking history (20 pack-years), age >50 years, incomplete intestinal metaplasia, persistent *H. pylori* infection and first-degree family history of gastric cancer should have surveillance every 3 years.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 95%

Statement 15: We recommend endoscopic surveillance every 3 years for patients with advanced stage of atrophic gastritis or intestinal metaplasia (OLGIM stage III–IV). Patients with ≥2 risk factors (smoking, age >50 years, incomplete intestinal metaplasia, persistent *H. pylori* infection, first-degree family history of gastric cancer) may be offered a surveillance endoscopy in 2 years.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 84%

Statement 16: We suggest endoscopic surveillance every 5 years for patients with intermediate stage of intestinal metaplasia (OLGIM stage II).

Quality of evidence: Low

Strength of recommendation: Weak

Agreement: 100%

Explanation (for statements 13 to 16): IM is a common finding in patients undergoing endoscopy, with a prevalence of 25% in pooled estimates of 107 studies,⁷⁷ and 44% in a Singapore GC surveillance cohort GCEP.¹⁰ Patients with IM are at an increased risk for GC. The annual incidence rate was 0.12–0.4% as reported in a systematic review.⁷⁸ Non-selective population surveillance of this group would impose a considerable strain on limited healthcare resources. OLGIM is recommended as a risk stratification tool in IM patients. In one longitudinal study, individuals with OLGIM high-risk stages were 38 times more likely to develop GC compared to those with low-risk stages.⁷⁹ Meta-analysis of cohort studies that examined high versus low OLGIM stage suggested a risk ratio of 27.7 (95% CI 0.80–327.53) for developing GC.^{59,61,62} The GCEP cohort, which is the largest prospective cohort study to analyse this association, has also shown that OLGIM stage III/IV was associated with increased risk of EGN (GC or HGD) with adjusted hazard ratio (HR) of 20.77 (95% CI 5.04–85.61, $P<0.01$).¹⁰ The median time to develop EGN for patients with OLGIM stage III/IV was 22.7 months (range 12.7–44.8). The participants of the GCEP study were Chinese aged ≥50 years, who were at high risk for GC. Recommendations are a combination of progression risk based on available information as well as what is feasible in the Singapore context. Therefore, we recommend endoscopic surveillance every 3 years for patients with advanced stages of IM (OLGIM stage III–IV), consistent with international guidelines.^{31,80}

Patients with OLGIM stage II were found to be at intermediate risk of EGN (adjusted HR 7.34, 95% CI 1.60–33.7, $P=0.02$) in GCEP study and the median time to develop EGN was 50.7 months (range 28.5–73.3).¹⁰ We suggest endoscopic surveillance every 5 years for patients with OLGIM stage II (Table 4). Existing international guidelines do not recommend surveillance in patient with IM limited to antrum site (OLGIM stage I–II) as there was paucity of evidence on progression prior to GCEP.

We do not recommend endoscopic surveillance in patient with OLGIM I, which is consistent with other professional guidelines.^{31,80} The risk of developing early gastric neoplasia among patient with OLGIM I was low as observed in the GCEP study (adjusted HR of 1.95 with 95% CI 0.39–9.74, $P=0.417$).¹⁰ It is crucial to appreciate the nuance of the use of OLGIM in that it implies systematic mapping of the histology of the gastric mucosa. For a patient who only had random biopsy of the gastric antrum that revealed focal IM, the risk for disease progression cannot be dismissed or

quantified, and the role of future interval endoscopy for full mapping and risk stratification should be considered.

Additional risk factors increase the risk of progression to GC in IM patients. A shorter surveillance interval is recommended for patients with additional risk factors, such as *H. pylori* infection, family history of GC, and smoking. For OLGIM stage I with no risk factors, no surveillance recommendations are proposed. For OLGIM stage I with additional risk factors, a surveillance of 3 years is recommended. For OLGIM stage II, with no risk factors, a surveillance interval of 5 years is recommended, and with additional risk factors, this interval decreases to 3 years. For OLGIM stage III and IV, with no additional risk factors, a surveillance interval of 3 years is recommended, and with additional risk factors, this interval decreased to 2 years. Table 4 summarises these recommendations.

H. pylori infection plays a pivotal role in GC pathogenesis and progression. It was classified as a type 1 carcinogen in 1994 by the World Health Organization (WHO).⁸¹ The risk of GC in *H. pylori* eradication group was much lower compared to the persistent group who had not had *H. pylori* eradication or the eradication had failed (HR 0.24, 95% CI 0.09–0.60).⁸² Family history of GC is one of the strong risk factors that have been consistently shown in many epidemiologic studies across different geographic regions and ethnicities. A meta-analysis of 26 studies showed an RR of 2.71 (95% CI 2.08–3.53).²⁹ Smoking contributes to the risk of developing GC with an estimated OR of 1.33 for a smoker of 20 cigarettes per day in a large epidemiologic database.⁸³

IM is heterogeneous and can be described as complete when the brush border is well formed, the goblet cells are regular and intestinal enzymes are secreted. IM is classified as incomplete when the mucin droplets are irregular and of variable size, the brush border is absent, and the intestinal enzymes are absent or partially expressed.⁸⁴ A review of available cross-sectional and cohort studies where subtyping of IM was available revealed that incomplete subtypes had 4–11 times increased risk of GC compared to the complete subtypes.⁸⁵ It is hoped that improvements in testing and reporting methodologies will allow better histologic risk stratification in this field.

The issue of when to stop endoscopic surveillance is clinically relevant. However, rather than predefining a specific age cut-off to stop surveillance, the decision should be made based on benefit-risk considerations, and need to be individualised according to patient comorbidities and preferences.

Statement 17: We suggest patients with autoimmune gastritis to undergo endoscopy with biopsies at the time of diagnosis and subsequently, every 3–5 years.

Level of evidence: Low

Strength of recommendation: Weak

Agreement: 89%

Autoimmune gastritis is characterised by chronic inflammation of the oxyntic mucosa that results in parietal cell atrophy, reduced acid production, loss of intrinsic factor, vitamin B12 deficiency and gastritis of the gastric corpus. While multiple case-control and cohort studies link pernicious anaemia with GC, a meta-analysis of 27 studies pooling 22,417 patients yielded a GC incidence rate of 0.27% per person-year,⁸⁶ many of these individual studies used low levels of vitamin B12 as the basis of autoimmune gastritis, which might not reflect the true incidence rate of this condition. This limits the quality of the evidence, as many patients may have had other conditions apart from autoimmune gastritis.

The observed risk of GC is highest within the first year of follow-up,⁸⁷ and of the cohorts that examined subsequent follow-up, one found GC in 3.6% of patients over 3 years, while 2 found no GC in periods ranging from 4–6 years.^{88,89} We suggest endoscopy with biopsies at the time of diagnosis and every 3–5 years subsequently.⁸⁰ The timing for ending endoscopic surveillance need to be individualised according to patient comorbidities and preferences.

Statement 18: In cases of high grade dysplasia and low grade dysplasia detected incidentally from random biopsies, when there is still no focal lesion(s) identified on repeat endoscopy, a surveillance endoscopy should be carried out once every 6 months in the case of high grade dysplasia, and annually for low grade dysplasia, both for a minimum period of 5 years.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 84%

A repeat high-quality endoscopy is the key recommendation for incidental dysplasia detected on random biopsies, as up to 90% of lesions can be identified and successfully treated at repeat endoscopy.⁹⁰ IEE or chromoendoscopy may be helpful in this regard. However, where no discrete focal lesion can be identified and targeted for endoscopic resection, unresected dysplasia will confer a longitudinal risk of progression to GC. The best available evidence comes

from a large nationwide cohort study of more than 8,000 patients followed up with dysplasia, which estimates for the first 5 years of follow-up, an annual incidence of 0.6% for mild-to-moderate dysplasia, and 6% for severe dysplasia.⁹¹ Hence, surveillance endoscopy should be carried out once every 6 months for HGD and annually for LGD, and that surveillance should be continued for at least 5 years.^{31,80}

Section E. Gastric polyps

Statement 19: We recommend polypectomy for fundic gland polyps ≥ 1 cm, hyperplastic polyps ≥ 0.5 cm, and adenomatous polyps of any size when possible.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

In the setting of a solitary polyp, unless it is clearly a small fundic gland polyp (FGP) < 1 cm, biopsies or resection is recommended. In the case of multiple polyps, we recommend biopsy or resection of the largest polyps, and for representative biopsy specimens to be taken from the other polyps. The only exception would be small FGP < 1 cm. Unlike non-protruding lesions, which require advanced endoscopic resection techniques (EMR/ESD), hot snare polypectomy is generally sufficient for resection of the majority of EGP.

FGPs have round mucosa pit patterns similar to the normal corpus mucosa. Hyperplastic polyps tend to appear hyperaemic and have a heterogeneous mucosa surface pattern. When larger, these polyps may also ulcerate. It may be difficult to differentiate between hyperplastic and adenomatous gastric polyps without histology. Dysplasia is rare in sporadic FGPs, but common in syndromic FGPs. Dysplasia and malignant transformation can occur in hyperplastic polyps. These dysplastic changes may be microscopic and not obvious during endoscopy. For both FGPs and hyperplastic polyps, a larger size increases the risk for dysplasia. Hence biopsies, especially of larger polyps, are recommended even in the presence of characteristic endoscopic appearance to differentiate the types of gastric polyps and exclude higher grade histology.⁹²⁻⁹⁴ Horiuchi et al. examined the use of NBI-ME to predict neoplasia coexisting with gastric hyperplastic polyps. The sensitivity and specificity of micrification of fine mucosal structures on NBI-ME were 100% and 85.2%, respectively. The sensitivity and specificity of NBI-ME diagnosis of coexisting neoplasia using irregular

microvessels in hyperplastic polyps were 54.5% and 92.3%, respectively.⁹⁵ Mankaney et al. developed endoscopic criteria to distinguish between high- and low-risk polyps associated with GC in familial adenomatous polyposis (FAP). Using the criteria, endoscopists distinguished high- from low-risk polyps with a mean sensitivity and specificity of 79% and 78.8%, respectively. The kappa coefficient was 0.45, indicating moderate agreement.⁹⁶ Hence, it is clear that endoscopic diagnosis cannot replace the role of histology.

Dysplasia is exceedingly rare in sporadic FGPs with malignancy potential $< 1\%$.⁹⁷ Dysplastic changes typically affect only polyps > 1 cm, and no cases of sporadic FGPs progressing to cancer have been reported.⁹⁸⁻¹⁰⁰ The risk of dysplasia for FAP-associated FGPs is higher but even then, progression to cancer is rare.¹⁰¹ Hence, we recommend polypectomy of FGP ≥ 1 cm. In contrast, there is a low but real risk of gastric hyperplastic polyps progressing to malignancy, with an estimated 5–37% having focal IM, 2–20% having focal dysplasia, and 2–6% harbouring adenocarcinoma.¹⁰² Gastric hyperplastic polyps are associated with *H. pylori*, and eradication of *H. pylori* would lead to regression in 80% of hyperplastic polyps before endoscopic removal.¹⁰³ Gastric hyperplastic polyps, unlike colonic hyperplastic polyps, have neoplastic potential, even when ≥ 1 cm.^{104,105} Hence, we suggest polypectomy for hyperplastic polyps ≥ 0.5 cm. Adenomatous gastric polyps are precursors to GC and thus, considered to have a true malignant risk, with estimated 8–59% associated with synchronous and metachronous GC.^{106,107} Adenomatous gastric polyps are frequently solitary and found mostly in the antrum with background of atrophic gastritis and IM.¹⁰⁸ Hence, we recommend resection of all adenomatous gastric polyps regardless of size.

Statement 20: We recommend that in the setting of multiple hyperplastic polyps or adenomatous polyps, surrounding gastric mucosa should be assessed for synchronous neoplasia, and biopsies taken for the assessment of *H. pylori* infection, atrophic gastritis and intestinal metaplasia.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 89%

Hyperplastic polyps are often associated with *H. pylori* gastritis, gastric atrophy and IM.^{103,109-111} Regression of hyperplastic polyps has been shown to occur after

successful *H. pylori* eradication in retrospective studies and small randomised control trials.^{111–116} There is also an increased risk (approximately 6%) of synchronous neoplasia in the surrounding mucosa if dysplasia is identified in a hyperplastic polyp.^{104,117,118} Adenomatous gastric polyps are also known to be associated with gastric atrophy, IM and synchronous adenocarcinoma. We therefore recommend for biopsies to be taken to assess the background mucosa.

Statement 21: We suggest surveillance endoscopy 1 year after complete endoscopic excision of dysplastic or adenomatous polyps.

Quality of evidence: Low

Strength of recommendation: Weak

Agreement: 95%

The need and frequency of surveillance is guided by the histology, completeness of excision, background mucosa characteristics and association with familial polyposis/cancer syndromes. In the absence of the aforementioned adverse factors, we suggest surveillance endoscopy at 1 year after complete endoscopic excision of dysplastic or adenomatous polyps. Presence of other associated adverse features may modify the surveillance schedule. Sporadic FGPs may develop with long-term use of proton-pump inhibitors (PPIs) and is not associated with an increased risk of cancer. Surveillance oesophago-gastro-duodenoscopy is not recommended for sporadic FGPs without dysplasia. Consideration should be given to stop PPI use. However, endoscopy is recommended every 2–3 years in patients with FAP and multiple FGPs without dysplasia, because of the higher risk of GC in FAP patients.¹¹⁹

Hyperplastic polyp is associated with *H. pylori* infection, gastric IM/dysplasia and AG. Hyperplastic polyps may harbour dysplastic elements and focal cancer in 5–19% of cases.¹⁰² Size >1cm and pedunculated morphology are risk factors for dysplasia. *H. pylori* infection should be treated and surveillance scope should be repeated at 1 year. Further need of surveillance of hyperplastic polyps will depend on the histology findings and underlying background mucosa and risk factors. An adenomatous gastric polyp is a precursor to GC. Incompletely excised adenomatous polyps should undergo repeat endoscopy and endoscopic resection. After complete endoscopic resection, surveillance endoscopy at 1 year is recommended because of a high rate of metachronous GC in this group of patients.¹²⁰ Further need of surveillance will depend on the histology findings and underlying background

mucosa and risk factors. In particular, patients with resected EGC arising from either a hyperplastic or adenomatous polyps should undergo long-term annual endoscopic surveillance.⁷⁰

Section F. Pathology section

Statement 22: We recommend pathology reports to standardise the description of intestinal metaplasia: intestinal metaplasia to be quantified for each site as mild (0–30% involvement of mucosa), moderate (31–60% involvement of mucosa) and marked (>60% involvement of mucosa). The presence of gastric atrophy in oxyntic mucosa should be assessed where feasible.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

Phrases used to quantify IM as currently employed can be a source of confusion for clinicians. The OLGIM system has been found to be of prognostic value, and following the guidelines can help to stratify patients with IM into different risk categories leading to more effective surveillance strategies.^{61,121} Pathology reporting on biopsies sent for the evaluation of gastric IM is summarised in Table 5.

While there are literature reports that highlight incomplete IM—especially type III IM (where the columnar cells secrete sulfomucins, and the goblet cells secrete sialomucins and sulfomucins)—is associated with increased risk of GC, routine subclassification of IM can be histologically challenging. Due to its technical complexity, the non-routine nature of this classification, and the expectations of non-GI pathologists doing routine reporting, we suggest IM remain unclassified at present.

Statement 23: Dysplasia should be graded on a 2-tiered system as recommended in the WHO Classification of Tumours, 5th Edition, Volume 1 for digestive system tumours.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

This is the internationally accepted practice.^{122,123}

Statement 24: We recommend that the handling and reporting of endoscopic resected specimens (endoscopic mucosal resection and endoscopic submucosal dissection) be performed as described by the Japanese

Gastric Cancer Association. The en bloc resection specimen is pinned out on a flat board in the fresh state, serially sliced after adequate fixation, placed into cassettes in sequential order and entirely submitted for histological examination.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

This is a widely adopted standard of practice for en bloc endoscopic resection specimen since its first introduction by the Japanese.¹²⁴ Pinning of the specimen in the fresh state by endoscopists prevents curling and shrinkage, thus allowing proper orientation during sectioning for optimal evaluation of the horizontal and vertical margins.⁷²⁻⁷⁴ Further practical technical issues on EMR/ESD specimen handling for pathologists are also covered by a document published by representatives of the Rodger C. Haggitt and Australasian Gastrointestinal Pathology Societies.¹²⁴

The pathology report of endoscopic resection for EGC should include the following:

- (i) Size and number of specimens
- (ii) Size of tumour
- (iii) Histological type
- (iv) Depth of invasion (pT1a/pT1b)
 - a. For pT1b tumour, the depth of submucosal invasion (μm) from the lower border of the muscularis mucosae is recorded. If muscularis mucosae is obscured by ulceration, the depth is measured from the virtual line based on the adjacent intact muscularis mucosae.
- (v) Presence/absence of intratumoural ulcer or ulcer scar
- (vi) Lymphovascular invasion
- (vii) Horizontal margin involvement
- (viii) Vertical margin involvement

Statement 25: When resected en bloc and lymphovascular invasion is absent on histology, complete (R0) endoscopic resection of gastric dysplasia and early gastric adenocarcinoma should be considered as curative if the lesion meets one of the following criteria:

- (i) **Dysplasia: low or high grade**
- (ii) **Well or moderately differentiated intramucosal carcinoma (IMC) (pT1a), irrespective of size and without ulceration**
- (iii) **Well or moderately differentiated IMC (pT1a), <3cm in size if ulcerated**

(iv) Well or moderately differentiated adenocarcinoma with superficial submucosal invasion (pT1b and <500 μm in depth measured in a straight line from the deepest fibre of the muscularis mucosae), <3cm in size

(v) Poorly differentiated IMC (pT1a), $\leq 2\text{cm}$ in size

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 95%

The curative status of an EMR/ESD specimen depends on adequacy of resection and the risk of lymph node metastasis. Margin involvement is associated with residual disease and local recurrence. For non-invasive dysplastic lesions, comment on the horizontal margin is appropriate as complete resection is curative. The pathology report should state when carcinoma is present at the vertical or horizontal margins (unequivocal positive margin status). Currently, there is no consensus or evidence-based data on the definition of clear vertical margin on endoscopic resections.¹²⁴ We suggest the clearance distance between invasive cancer front and vertical margin to be measured in micrometres (μm), and clinicopathological correlation about margin status is advised in challenging cases.

For EGC, the risk of lymph node metastasis is linked to the depth of invasion, 0–3% and 19% for mucosa and submucosa invasion, respectively.¹²⁵ Histological features such as poorly differentiated invasive submucosal component (irrespective of depth below the muscularis mucosae), signet ring cell morphology, lymphovascular invasion and submucosal invasion $\geq 500\mu\text{m}$ (measured in a straight line from the deepest fibre of the muscularis mucosae) are associated with higher risk of lymph node metastasis.^{4,31,126-128} Two large series by Gotoda et al.¹²⁹ and Hirasawa et al.¹³⁰ on surgically resected EGC demonstrated that the risk of lymph node metastasis is <1% if the aforementioned criteria (ii)–(iv) are met. Although long-term survival data are currently lacking on endoscopic resection performed as an expanded indication based on these criteria, the resection can be considered curative if the following are also fulfilled: en bloc resection, negative horizontal margin, negative vertical margin and no lymphovascular invasion. It is also important to note that if mucinous adenocarcinoma is identified in the submucosa, it is considered non-curative.^{31,70,131}

Accurate histological examination of the EMR/ESD resection specimen is required to determine the curative status of the endoscopic resection procedure performed for gastric dysplasia and EGC.

CONCLUSION

We have summarised the current evidence and provided recommendations on the management of patients with gastric premalignant lesions in Singapore. These guidelines do not define a standard of care but are written in the spirit of improving endoscopic practice standards. In clinical practice, it is recognised that variations may be needed according to patient's needs and characteristics, and available expertise. The decision to screen and survey for GC should ultimately be individualised, taking into consideration the patient's overall health and preferences. Similarly, the decision to stop surveillance should be individualised, based on consideration of benefit and risk to the individual. Much of the existing evidence is retrospective and evidence gaps remain on many key questions in the surveillance and diagnosis of gastric premalignant lesions. Clinical practice should be tempered by new evidence as it emerges and contextualised to our unique patient population.

Disclosure

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