

The role of endoscopy in the management of premalignant and malignant conditions of the stomach

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This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature was performed by using PubMed from January 1980 through March 2014 by using the keyword(s) "gastric tumor," "gastric cancer," "gastric lymphoma," "gastric and adenocarcinoma," "gastrointestinal stromal tumor," "gastrointestinal endoscopy," "endoscopy," "endoscopic procedures," and "procedures." The search was supplemented by accessing the "related articles" feature of PubMed, with articles identified on PubMed as the references. Pertinent studies published in English were reviewed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. Guidelines for the appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time that the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence by using the GRADE criteria (Table 1).¹

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard

of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines.

This revision of the 2006 document "The Role of Endoscopy in the Surveillance of Premalignant Conditions of the Upper GI Tract" has been expanded to include discussion of malignant conditions of the stomach.² ASGE documents addressing the role of endoscopy in malignant and premalignant conditions of the esophagus have been recently published.^{3,4}

PREMALIGNANT CONDITIONS OF THE STOMACH

Gastric polyps

Sporadic gastric epithelial polyps. Gastric polyp histology cannot be reliably distinguished by endoscopic appearance; therefore, biopsy or polypectomy is warranted when polyps are detected.⁵ The majority (70%-90%) of gastric epithelial polyps are fundic gland polyps (FGPs) or hyperplastic polyps and are often incidental findings on endoscopy. Sporadic FGPs may develop in association with long-term proton pump inhibitor use and are not associated with an increased risk of cancer in the absence of familial adenomatous polyposis syndrome (FAP).⁶⁻⁸ In contrast, hyperplastic polyps are associated with an increased risk of gastric cancer. Dysplastic elements and focal cancer have been found in 5% to 19% of hyperplastic polyps,⁹⁻¹² and some national guidelines recommend polypectomy of all gastric hyperplastic polyps greater than 0.5 cm to 1 cm.¹³ Size greater than 1 cm and pedunculated morphology have been identified as risk factors for dysplasia in hyperplastic polyps.⁹ Adenomatous polyps also have

TABLE 1. GRADE system for rating the quality of evidence for guidelines¹

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕○
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕○○
Very low quality	Any estimate of effect is very uncertain.	⊕○○○

malignant potential.¹⁴⁻¹⁶ Adenomatous polyps of the stomach should be endoscopically removed when possible, but recurrence has been reported in up to 2.6% after complete endoscopic excision,¹⁷ and gastric cancer has been found in 1.3% of patients during follow-up.¹⁸ Compared with EMR, endoscopic submucosal resection reduces tumor recurrences, yet increases the risk of procedural adverse events.¹⁹ Endoscopy is recommended 1 year after adenomatous polyp resection, followed by surveillance endoscopy every 3 to 5 years, although this strategy has not been extensively studied. Hyperplastic and adenomatous polyps may occur in the presence of *Helicobacter pylori* (*H pylori*) infection and environmental metaplastic atrophic gastritis, and polypectomy should be performed.

Gastric polyps in FAP and Lynch syndrome.

Gastric polyps are common in individuals with FAP.²⁰⁻³⁰ These are most often FGPs and are found in up to 88% of children and adults with FAP.^{23,31} Adenomas also occur in the stomach of individuals with FAP.³²⁻³⁵ When present, they are usually solitary and sessile and located in the antrum.³⁰ Cases of gastric adenocarcinoma associated with FGP have been described in patients with familial polyposis syndromes.^{36,37} The risk of gastric cancer in FAP is incompletely characterized. Several multinational series have shown a higher incidence of gastric cancer in FAP patients,³⁷⁻³⁹ whereas a U.S. study concluded that the risk was not significantly increased.²⁸

There are also conflicting data regarding the risk of gastric cancer in individuals with Lynch syndrome.^{38,39} In a Korean cohort of patients, the relative risk of the development of gastric cancer was 2.1-fold higher than in the general population.⁴⁰ Conversely, a Finnish cohort of Lynch syndrome patients did not have a higher prevalence of gastric cancer relative to the general population.⁴¹ A recent prospective cohort study demonstrated a standardized incidence ratio of 9.78 (95% confidence interval [CI], 1.18-35.3) for the development of gastric cancer in subjects with a mismatch repair gene mutation over sex- and age-matched unaffected relatives.⁴²

Gastric intestinal metaplasia and dysplasia

Patients with gastric intestinal metaplasia (GIM) may have a greater than 10-fold increased risk of gastric cancer than the general population.⁴³ GIM is recognized as a

pre-malignant condition that may be the result of an adaptive response to environmental stimuli such as *H pylori* infection, smoking, and high salt intake.⁴³ The potential benefits of surveillance were evaluated in 2 retrospective studies from the United Kingdom.^{44,45} The incidence of gastric cancer was reported to be as high as 11%.⁴⁵ Endoscopic surveillance was associated with earlier stage cancer detection and improved survival.^{44,45} Additionally, patients with GIM and high-grade dysplasia (HGD) were at significant risk of harboring a prevalent or incident cancer.⁴⁵ In both retrospective^{46,47} and prospective⁴⁸⁻⁵⁰ European studies of patients with GIM and HGD, the cancer detection rate with endoscopic surveillance ranged from 33% to 85%. A review of the management of patients with GIM suggests that for most U.S. patients, the risk of progression to cancer is low, and surveillance is not clinically indicated unless other risk factors for gastric cancer are present, such as a family history of gastric cancer and Asian heritage.⁵¹ A recent European consensus statement suggested that if low-grade dysplasia is detected in a patient with GIM, a repeat surveillance EGD with a topographic mapping biopsy strategy should be performed within 1 year.⁵² The optimal frequency of subsequent endoscopic evaluation is not known. Surveillance may be suspended when 2 consecutive endoscopies are negative for dysplasia. Patients with confirmed HGD should undergo surgical or endoscopic resection due to the high probability of coexisting invasive adenocarcinoma. Twenty-five percent of patients with HGD will progress to adenocarcinoma within a year.⁵³ If *H pylori* infection is identified, eradication should be performed. It remains controversial whether empiric *H pylori* treatment should be administered when GIM is diagnosed.

Pernicious anemia

The prevalence of gastric adenocarcinoma in patients with pernicious anemia, now considered to be associated with type A atrophic gastritis,⁵⁴ is reported to be 1% to 3%.⁵⁵ Most studies have shown a 2- to 3-fold increased incidence of gastric cancer in patients with pernicious anemia,⁵⁶⁻⁶¹ although a large U.S. population-based cohort study found an incidence of gastric cancer of 1.2%, similar to that of the general population.⁶² The risk seems to be highest within the first year of diagnosis.^{56,58} The benefits of endoscopic surveillance in patients with pernicious

anemia have not been established.^{55,63-65} Gastric carcinoma, in addition to gastric carcinoid, has been found in prospective series of patients undergoing surveillance endoscopy.^{55,64} A series from Italy found no gastric carcinoma after an initial follow-up of either 2 or 4 years.⁶⁵ These data have prompted the recommendations to perform endoscopy soon after the diagnosis of pernicious anemia and/or to perform endoscopy on patients with pernicious anemia in whom upper GI symptoms develop.^{55,57,62-64}

Gastric carcinoid tumors

Gastric carcinoid tumors can be classified as type 1 (multifocal, well differentiated, associated with type A chronic atrophic gastritis), type 2 (multifocal, well differentiated, associated with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1), type 3 (solitary, well differentiated, sporadic), and type 4 (solitary, poorly differentiated). Endoscopic evaluation should include a description of carcinoid size, number, and anatomic distribution. Gastric fluid aspiration for pH testing and a fasting serum gastrin level can assist in the classification of gastric carcinoid tumors, particularly if the individual is not taking medications that affect the gastrin level (ie, proton pump inhibitors). Management options include endoscopic surveillance alone, endoscopic removal of smaller lesions (<1 cm) if few (3-5 lesions) in number, and surgical excision. Once diagnosed via endoscopy, EUS may be useful to determine the depth of invasion if EMR is considered.^{66,67}

Type 1 gastric carcinoids are the most common type encountered in clinical practice^{68,69} and usually have a benign clinical course. Five- and 10-year survival of patients with type 1 gastric carcinoid is no different from that of the general population,⁷⁰ and clinical management is not well defined because both endoscopic surveillance alone and polypectomy with surveillance have been advocated.^{68,69,71} Type 2 gastric carcinoids affect men and women equally, and lymph node metastases are found in 10% to 30% of patients at the time of discovery.⁷⁰ The 5-year survival associated with type 2 gastric carcinoid tumors is 60% to 75%.⁷⁰ Worldwide, therapeutic approaches for both type 1 and 2 gastric carcinoid tumors vary. Type 3 carcinoids are often found in advanced stages. The 5-year survival rate is 50% or worse. All type 3 gastric carcinoids should be considered for surgical removal based on a high incidence of lymph node invasion, and only very small (<1 cm), well-differentiated lesions should be considered for endoscopic removal.⁷⁰ Type 4 gastric carcinoids are associated with a poor outcome with a 50% survival rate at 1 year after the diagnosis. Surgery should be considered for all type 4 gastric carcinoids as well as all other carcinoids (regardless of size), with indicators of more aggressive pathology such as angioinvasion, muscular wall invasion, high proliferative index, and metastatic disease.⁷⁰ Surveillance after surgical or endoscopic resection may be indicated, although the optimal surveillance frequency and

intervals are unknown. Some expert opinions suggest every 1 to 2 years.⁷⁰

Post-gastric surgery

There may be an increased risk of gastric cancer in patients who have undergone partial gastrectomy for benign gastric or duodenal ulcer. Reported frequencies of gastric remnant carcinoma range from 0.8% to 8.9%.⁷²⁻⁸³ Endoscopic follow-up studies have detected gastric cancer in 4% to 6% of these patients, and a dysplasia-to-carcinoma sequence has been described.^{73,74,78,80,81} However, other population-based studies have not confirmed an increased risk.^{78,83} Studies that have demonstrated an increased risk of gastric carcinoma suggest that the risk appears to increase 15 to 20 years after the initial surgery.^{72,73,76,77,82-85}

MALIGNANT CONDITIONS OF THE STOMACH

Adenocarcinoma

Diagnosis. Adenocarcinoma, the most common form of gastric malignancy, typically presents as a mass lesion, but may present as a nonhealing gastric ulcer or as a diffuse infiltrative form known as linitis plastica. The criterion standard for diagnosing gastric cancer is endoscopic mucosal biopsy. Generally, the mass or abnormal mucosa is targeted for biopsy, although in the case of a malignant gastric ulcer, at least 7 biopsies of the heaped up edges of the ulcer and base should be performed.⁸⁶ Diagnosing linitis plastica can be more difficult because this condition is associated with infiltration of the submucosa and/or muscularis propria of the stomach, reducing the yield of mucosal biopsies. Other means of sampling include "tunnel biopsies" in which a mucosal defect is created by mucosal biopsy so that deeper tissue can then be sampled with biopsy forceps. Large mucosal and submucosal biopsy samples may be taken with snare resection. EUS-FNA or core sampling may be necessary, although histopathology is generally preferable to cytology for diagnosis.

Staging. Once a diagnosis of gastric cancer is confirmed, cross-sectional imaging should be performed to facilitate staging. In the absence of metastatic disease, EUS with or without FNA is indicated for local-regional staging. EUS staging of gastric cancer conforms to the TNM staging of the American Joint Committee on Cancer. Staging EUS should first focus on identifying metastatic (M) disease, such as liver lesions or other solid organ involvement. Whenever possible, these lesions should be sampled with FNA. In the absence of metastatic disease, staging EUS should focus on regional and nonregional lymph node (N) staging and primary tumor (T) staging. A recent meta-analysis summarized the available evidence on the staging performance of EUS for gastric cancer.⁸⁷ The analysis determined that EUS can differentiate T1-2 from T3-4 gastric cancer with high accuracy (sensitivity, 86%; specificity, 91%), but was less accurate for lymph

node staging (sensitivity, 69%; specificity, 84%) by using EUS features suggestive of a malignant lymph node (size >8 mm, distinct margins, round shape, and hypoechogenicity). When EUS-FNA is used to sample abnormal-appearing lymph nodes and suspected metastatic lesions, the results can change patient management in up to 15% of cases.⁸⁸ Furthermore, ascites seen on EUS staging of a known GE junction cancer is an independent predictor of inoperability.⁸⁹

Endoscopic treatment. Gastric cancer screening in countries with high-risk populations is effective in identifying early gastric cancer (EGC), which can be treated endoscopically. Accurate pretreatment staging is critical in identifying EGC patients with disease that is limited to the mucosa and submucosa (stage T1) and who are candidates for EMR or endoscopic submucosal dissection (ESD). A discussion on EMR and ESD techniques and equipment can be found in the ASGE Technology Status Evaluation Report entitled "Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection."⁹⁰ ESD permits en bloc resection of most lesions and is the preferred technique for resecting EGC in Asia.⁹¹ A recent review of 1000 ESDs for EGC showed a complete en bloc resection rate of 87.7%, a significant bleeding rate of 0.6%, and a perforation rate of 1.2%.⁹² A meta-analysis and systematic review of ESD compared with EMR identified 12 studies (9 Japanese, 2 Korean, and 1 Italian), 3 of which were cohort studies comparing a prospective treatment group with a past group and 9 were retrospective cohort studies.⁹³ ESD outperformed EMR for en bloc resection (odds ratio 8.43; 95% CI, 5.20–13.67), complete resection (odds ratio 14.11; 95% CI, 10.85–18.35), curative resection (odds ratio 3.28; 95% CI, 1.95–5.54), and local recurrence (risk ratio 0.13; 95% CI, 0.04–0.41). Adverse events were more common with ESD than EMR including intraoperative bleeding (risk ratio 2.16; 95% CI, 1.14–4.09) and perforation (risk ratio 3.58; 95% CI, 1.95–6.55). Overall bleeding risk was not significantly different, nor was all-cause mortality. The procedure time was longer with ESD than EMR (standard mean difference, 1.55; 95% CI, 0.74–2.37). In the United States, ESD is rarely performed outside referral centers with expertise in this technique.

Palliation. Malignant gastric outlet obstruction may complicate gastric, duodenal, and pancreaticobiliary malignancy and can dramatically affect quality of life and nutritional status. Endoscopic stent (ES) placement has been shown to be safe and effective for palliation of malignant gastric outlet obstruction. Two small randomized, controlled trials of ES placement versus laparoscopic gastrojejunostomy demonstrated efficacy of both techniques, with fewer adverse events and shorter hospital stay for patients who underwent enteral stenting.^{94,95} A systematic review of studies comparing ES placement with open gastrojejunostomy (OGJ) concluded that ES placement was associated with improved clinical outcomes (shorter hospital stay and shorter time to resumption of oral diet) than

OGJ.⁹⁶ However, other investigators demonstrated that although food intake occurred sooner in patients treated with ES placement, gastrojejunostomy was superior to ES placement for achieving long-term relief in patients surviving more than 2 months.⁹⁷ When stent occlusion was considered a major adverse event, gastrojejunostomy-treated patients also had lower adverse event rates than patients treated with ES placement in this same trial. Small case series have described the use of argon plasma coagulation for re-establishment of luminal patency and treatment of tumor ingrowth of ES in patients with gastric cancers, but this technique has not been compared with ES, laparoscopic gastrojejunostomy, or OGJ.^{98,99} Gastric cancers are often complicated by GI bleeding, which may persist after systemic chemotherapy. There are no randomized, controlled trials to support endoscopic therapy of bleeding gastric cancers; however, a recent report of endoscopic spray application of an absorbable hemostatic powder showed promising results.¹⁰⁰

Mucosa-associated lymphoid tissue lymphoma

Extranodal marginal zone B-cell lymphoma is a low-grade B-cell lymphoma occurring in mucosa-associated lymphoid tissue (MALT) of the stomach, lung, small bowel, and other organs. MALT lymphoma of the stomach is pathologically distinct from gastric adenocarcinoma, but may present with similar symptoms of dyspepsia, weight loss, or GI bleeding. On endoscopy, findings range from subtle erosions to nodular masses. Diagnosis is confirmed with mucosal sampling. Nearly all patients with gastric MALT lymphoma also have *H pylori* infection. Chronic inflammation associated with *H pylori* infection may trigger B-cell clonal expansion leading to MALT lymphoma. *H pylori* eradication is the treatment of choice for patients with low-grade MALT lymphoma and is effective in achieving clinical remission in up to 80%.¹⁰¹ Extended follow-up and surveillance with both endoscopy and tissue sampling are recommended after successful *H pylori* eradication in the setting of MALT lymphoma because complete regression may require a prolonged period of time and there is also a risk of recurrence, with or without *H pylori* reinfection. The optimal surveillance interval has not been defined, but 1 large international series reported low rates of progression identified with endoscopy and mucosal sampling every 3 to 6 months for the first 2 years after *H pylori* eradication with extension to every 6 to 12 months thereafter with a median follow-up of 42.2 months (range 2–144).¹⁰² EUS may be used to gather prognostic information by permitting accurate assessment of the degree of infiltration of lymphoma in the gastric wall as well as regional lymph node involvement.^{103–105}

GI stromal tumors

GI stromal tumors (GISTs) are the most common type of mesenchymal tumor of the stomach. National Institutes of Health guidelines use size and the mitotic index

(number of mitoses per high-power field) to categorize GISTs for malignant potential; however, the mitotic index can only be reliably determined from resected lesions. EUS with or without FNA is the preferred imaging technique used to further characterize subepithelial gastric lesions. EUS features of GISTs that have been shown to predict malignant potential include size greater than 2 cm, lobulated or irregular borders, invasion of adjacent structures, and heterogeneity.^{106,107} EUS-directed sampling can be helpful in distinguishing GISTs from other subepithelial lesions, but is poor at predicting malignant potential. Cytology specimens from EUS-FNA of a GIST may demonstrate spindle cells, and if cellularity is adequate, immunohistochemical staining for specific markers (eg, CD117 [KIT], DOG-1) can confirm the diagnosis. However, cytology specimens from EUS-FNA are often suboptimal. An EUS-guided core biopsy may be used to obtain specimens from suspected GISTs and has been demonstrated to be an acceptable alternative to FNA.^{108,109} Case series of an “unroofing” technique to access lesions in the muscularis propria for diagnostic tissue have shown this technique to be safe and effective.¹¹⁰

Generally, any symptomatic lesion should be surgically resected, particularly if the lesion is a source of bleeding. Patients with asymptomatic GISTs larger than 2 cm or with EUS features associated with malignant potential should also be considered for resection.¹⁰⁶ Patients with asymptomatic subepithelial tumors smaller than 2 cm and without EUS features associated with malignant potential can be placed into an EUS surveillance program to be monitored for changes in size or imaging features associated with malignancy. The optimal surveillance interval for small (<2 cm) GISTs without high-risk features has not been established; however, annual surveillance is commonly practiced.¹¹¹

Recent advances in ESD techniques have demonstrated that small subepithelial lesions originating from the muscularis propria can be safely removed. However, these techniques should be performed only in select patients by practitioners with dedicated training and skill.^{112,113}

RECOMMENDATIONS

1. We recommend solitary gastric polyps undergo biopsy or be resected when possible. ⊕⊕⊕⊕
2. We suggest polypectomy of fundic gland polyps 1 cm or larger, hyperplastic polyps 0.5 cm or larger, and adenomatous polyps of any size when possible. ⊕⊕⊕⊕
3. We suggest surveillance endoscopy 1 year after removing adenomatous gastric polyps. ⊕⊕⊕⊕
4. In the setting of multiple polyps, we recommend biopsy or resection of the largest polyps and representative biopsy specimens be taken from others. ⊕⊕⊕⊕
5. In the setting of multiple hyperplastic or adenomatous polyps, we suggest systematic sampling of the

- surrounding nonpolypoid gastric mucosa to assess for *H pylori* and metaplastic atrophic gastritis. ⊕⊕⊕⊕
6. We suggest sampling and, when feasible, resection of large gastric polyps in patients with FAP to confirm histology and to assess for dysplasia. ⊕⊕⊕⊕
7. We suggest surveillance endoscopy for patients with GIM who are at increased risk of gastric cancer due to ethnic background or family history. Optimal surveillance intervals have not been extensively studied and should be individualized. ⊕⊕⊕⊕
8. We recommend endoscopic resection and surveillance endoscopy for patients with confirmed GIM with HGD when feasible. ⊕⊕⊕⊕
9. We suggest endoscopy within 6 months of the diagnosis of pernicious anemia or the development of upper GI symptoms in patients with pernicious anemia. ⊕⊕⊕⊕
10. We recommend EUS for local staging of gastric carcinoids. ⊕⊕⊕⊕
11. We suggest endoscopic resection of small (<1 cm) type 1 and type 2 gastric carcinoids that do not demonstrate aggressive features such as angioinvasion, muscular wall invasion, high proliferative index, and/or metastatic disease and endoscopic surveillance thereafter every 1 to 2 years. We suggest endoscopic removal for type 3 and 4 gastric carcinoids (isolated and <1 cm in diameter) ⊕⊕⊕⊕
12. We recommend at least 7 biopsy samples be obtained of gastric masses or the heaped-up edges of ulcers suspicious for gastric adenocarcinoma. ⊕⊕⊕⊕
13. We recommend EUS and when applicable, EUS-FNA to locally stage gastric cancer. ⊕⊕⊕⊕
14. We recommend endoscopically placed self-expanding metal stents for the palliation of malignant gastric outlet obstruction due to gastric cancer in patients with poor performance status or nonoperable anatomy. ⊕⊕⊕⊕
15. We recommend EUS with or without FNA in the evaluation of gastric submucosal lesions. ⊕⊕⊕⊕
16. We suggest annual EUS surveillance of GISTs smaller than 2 cm if surgical resection is not performed to determine progression of size or change in echo features. ⊕⊕⊕⊕

DISCLOSURE

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Abbreviations: CI, confidence interval; EGC, early gastric cancer; ES, endoscopic stent; FAP, familial adenomatous polyposis; FGP, fundic gland polyp; GIM, gastric intestinal metaplasia; HDG, high-grade dysplasia; MALT, mucosa-associated lymphoid tissue; OGJ, open gastrojejunostomy.

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