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Review Article

How to manage gastric polyps

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ABSTRACT

Gastric cancer is the second leading cause of cancer related death in the world. In United States, gastric polyps are found in approximately 6% of upper endoscopy. The incidence of gastric polyps increased with widespread use of esophagogastroduodenoscopy and more liberal use of proton pump inhibitors. They are usually asymptomatic, but infrequently cause symptoms of bleeding, pain and gastric outlet obstruction. It is important to distinguish premalignant conditions and mimickers of malignancy. *Helicobacter pylori* eradication therapy leads to regression of hyperplastic polyps but it is not clear for adenoma. Endoscopy plays key role not only in diagnosis but also in surveillance. With narrow band imaging and chromo endoscopy, we are much better today in detecting and discerning these. Also, with endoscopic mucosal resection and endoscopic submucosal dissection, we can manage these better. In this review article we will discuss the various diagnostic tools and therapeutic options for hyperplastic polyp, fundic gland polyp, gastrointestinal stromal tumor, adenoma, neuroendocrine tumor, linitis plastica, and intestinal metaplasia.

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Keywords: Carcinoid tumor; Endosonography; *Helicobacter pylori*; Narrow band imaging; Proton pump inhibitors

Introduction

Gastric polyps are found incidentally for an unrelated condition with increasing use of upper gastrointestinal endoscopy. Gastric polyps are either mucosal or submucosal and benign or malignant. They rarely cause symptoms. Management of gastric polyps is quite challenging. Early and accurate diagnosis and effective management may prevent the malignant transformation of these lesions, thus resulting in improved survival in some cases. This manuscript encompasses all types of gastric polyps we encounter in gastroenterology practice, providing the invaluable information regarding how to promptly make the diagnosis and manage them.

Proton Pump Inhibitors and Gastric Mucosa

Proton pump inhibitors (PPI) are used more often than indicated, and there is concern about long term effects.¹ They are overused because of over the counter availability and affordable cost. There is no consensus on the definition of duration of chronic use and while most agree that 4 to 12 months is considered a long term use.² Both microscopic and macroscopic changes

from proliferation in the mucosa of fundus and gastric body were described secondary to chronic PPI use. Microscopic changes like cystic gland formation, parietal cell hyperplasia, protrusion of parietal cells in to the oxyntic glands and macroscopic changes like formation of sporadic fundic polyps were described.¹ In a retrospective study of 599 patients, of which 322 patients used PPI, the authors concluded that a long term use of PPI for 1 to 5 years was associated with fundic gland polyps (FGPs) when compared to less than 1 year (short term) use of PPI.³

Non-Neoplastic polyps (Benign)

Hyperplastic polyp

They are the second most common gastric polyps (Fig. 1). They can be single, multiple, sessile, or pedunculated. They are composed of elongated and distorted pits lined by foveolar epithelium, inflamed and edematous lamina propria.⁴ They have a wide age range distribution and increases between ages of 60 to 80 years.⁵ The patient is commonly asymptomatic, but hyperplastic polyps can cause anemia, bleeding due to ulceration, dyspepsia, and gastric outlet obstruction.^{6,7} Although they are found

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most commonly in the antrum, they can be found anywhere in the stomach. Histologically, it shows dilated, marked elongation of the foveolae with branching, infiltrated by neutrophils, plasma cells, lymphocytes, mast cells, and macrophages resulting in corkscrew appearance.⁴ The stimuli for hyperplastic gastric polyps is not known but they are thought to arise from mucosal damage due to chronic inflammatory conditions leading to hyper regenerative epithelium. They are commonly encountered in the setting of *Helicobacter pylori*, pernicious anemia, chronic atrophic gastritis, adjacent to ulcers and at sites of gastroenterostomies.^{8,9} Development of hyperplastic gastric polyps is also associated with argon plasma coagulation (APC) treatment of gastric antral vascular ectasia as a result of mucosal reaction from thermal injury.¹⁰ In approximately 2% of the gastric hyperplastic polyps malignant transformation occurs¹¹ and the mechanism of carcinogenesis is unknown. It is hypothesized that they arise either in dysplastic lesion or adjacent to dysplastic lesion. There is a high prevalence of

immunoreactivity found in dysplasia, and p53 overexpression is associated with early carcinogenesis.¹²

Neoplastic Polyps (Malignant)

Fundic gland polyps

They occur predominantly in gastric fundus composed of normal gastric cell types (small glandular cell islands with parietal and chief cells) arranged in a disorderly or microcystic configuration (Fig. 2).¹³ They are more commonly seen in western countries because of the low prevalence of *H. pylori* and more liberal use of PPI. They are sporadic but can occur as polyposis syndromes like familial adenomatous polyposis (FAP), MUTYH-associated polyposis, gastric adenocarcinoma, and proximal polyposis of the stomach.¹⁴ A long term use of PPI (more than 1 year) is associated with FGP.³ Regression of FGPs is seen after discontinuation

Fig. 1. (A) Hyperplastic polyp. (B) Hyperplastic polyp shows superficial ulceration with elongated foveolar epithelium and edematous stroma (H&E stain, ×4).

Fig. 2. (A) Fundic gland polyp. (B) Fundic gland polyp with dilated oxyntic glands and low grade foveolar epithelial dysplasia (H&E stain, ×10).

of PPI.¹⁵ Sporadic FGPs are more commonly seen in females than in males and the patients are middle aged. In FAP, males and females are equally affected and the patients are affected at early age. They are usually asymptomatic but can cause symptoms of obstruction like nausea, vomiting, and abdominal pain if they are large. Alteration in beta-catenin mutation is seen in sporadic FGP while germ line APC mutation and subsequent somatic mutation are seen in syndromic FGP.^{16,17} Endoscopically, they are seen in fundus and upper body of stomach as small (less than 1 cm), hyperemic, multiple, and sessile with smooth contour. Microscopically, they are seen as dilated cystic glands lined by fundic epithelium. A long-term treatment of PPI is associated with hypertrophy and hyperplasia of parietal cells with protrusion in to the lumen of the pits. Management of FGPs usually involves biopsy of the polyps. Polyps which are ulcerated or located in antrum, greater than 1 cm should be resected and dysplasia or neoplasia should be ruled out. In sporadic FGPs attributed to PPI, discontinuation of PPI is encouraged. FAP should be ruled out if FGP are seen in a multitude (20 or greater), located in the antrum, at an early age (younger than 40 years), or concurrent duodenal adenoma is present, colonoscopy should be recommended. Surveillance with esophagogastroduodenoscopy (EGD) is not recommended in sporadic FGP as gastric cancer is rare, but in FAP, it is recommended because 30% to 50% of them may be associated with low grade dysplasia.^{18,19}

Gastrointestinal stromal tumors

These are mesenchymal tumors which arise from the subepithelial layers (muscularis mucosa or muscularis propria) of the gastrointestinal tract (Fig. 3). The etiology is not clear. The phenotypic resemblance to interstitial cells of cajal (ICCs) suggests that the origin is from ICCs.²⁰ They can arise anywhere in the Gastrointestinal tract but the most common location is the stomach.²¹ They are more common in middle age and older individuals.²² Both familial and sporadic gastrointestinal stromal tumors (GISTs) are seen. Although familial and sporadic GISTs are indistinguishable both in phenotype and molecular features,²³ familial GISTs are more predisposed to development of multiple gastric and small intestinal GIST. In GIST, there is an over-expression of c-KIT, a growth factor tyrosine-kinase receptor that is normally expressed

Fig. 3. Gastrointestinal stromal tumor.

in myenteric plexus of adult gastrointestinal tract, melanocytes, and hematopoietic stem cells.²⁴ Conversely, in about 50% of GISTs, c-KIT is not expressed; however, mutation in platelet derived growth factor receptor-alpha (PDGFRA) is seen.²⁵ Prognostic factors include size, location, and mitotic rate.^{26,27} Size less than 2 cm and origin in the stomach are favorable prognostic factors as the risk of malignancy is extremely low.^{28,29} Clinical symptoms depend on size and location of the tumor. Iron deficiency anemia, melena, and hematemesis are seen with ulcerated lesions. In larger tumors, abdominal pain and early satiety²⁷ are present. The liver and peritoneum are the most common metastatic sites.

Histologically, they are spindle cells with elongated nuclei and eosinophilic cytoplasm arranged in whorls or short fascicles.³⁰ Epithelioid type is seen in KIT negative GIST tumors that harbor PDGFRA mutation.³¹ Radiological features of GIST tumors vary depending on their size. Tumors larger than 2 cm develop focal ulceration of the underlying mucosa because of pressure necrosis which is referred to "bull's eye" on radiology.³² They tend to invade adjacent structures like the pancreas, colon and diaphragm with increase in size. Differential diagnosis for GIST includes schwannoma, leiomyoma, type 1 carcinoid, metastasis to the stomach from breast cancer and melanoma. Computed tomography (CT) with oral and intravenous contrast is the initial imaging of choice to characterize the mass, evaluate the extent and spread of tumor. It appears as smoothly contoured solid mass that enhances with intravenous contrast. On upper endoscopy both GIST and leiomyoma appear as a subepithelial mass with smooth margins and occasional ulceration. Endoscopic ultrasonography (EUS) can help differentiate subepithelial lesions based on the layer of origin and also in obtaining biopsy for cytological analysis and immunohistochemistry. Treatment for localized GIST is surgical resection if feasible. Although there are no clear guidelines, NCCN (National Comprehensive Cancer Network) recommends a follow-up with CT abdomen and pelvis, every 3 to 6 months for 3 to 5 years and then annually, for completely resected GIST tumors. For locally advanced or metastatic GIST tumors receiving imatinib, the patients should have a CT abdomen and pelvis every 3 to 6 months. Adjuvant therapy with imatinib is recommended for tumors greater than 3 cm in size or if the margins are positive after surgical resection. In addition, neoadjuvant therapy with imatinib is recommended for tumors that are unresectable, borderline resectable with locally advanced or tumors that require extensive organ disruption. The goal of neoadjuvant therapy is to reduce the tumor size thereby making it potentially resectable with organ preservation.

Gastric adenoma (raised intraepithelial neoplasia)

They are polypoid, circumscribed lesions lined by dysplastic epithelium composed of either tubular and or villous structures (Fig. 4). They account for 6% to 10% of gastric polyps in western populations.³³ Atrophic gastritis and intestinal metaplasia are associated with the development of gastric adenoma.³⁴ They may occur in individuals with familial adenomatous polyps and their incidence increases with age.³⁵ They are frequently solitary and commonly found in the antrum. Histologically, they are classified into tubular, villous, or tubulovillous. Polyps that have villous histology and size greater than 2 cm have a 28% to 40% increased risk of malignancy.³⁶ High grade dysplasia predisposes to invasive cancer, not only within the polyp but also in synchronous areas of the stomach.³⁷ Differentiating between low and high dysplasia of gastric adenoma is based on degree of mitotic activity, cytoplasmic differentiation, nuclear crowding, hyperchroma-

sia, stratification, and architectural distortion.³⁸ Gastric adenomas may have combined gastric and intestinal features³⁹ and minority of them contain foveolar or pyloric gland epithelium. The pyloric adenoma is more common in older patients (women > men) and carries a 30% risk of malignant transformation.⁴⁰

Gastric neuroendocrine tumors (carcinoids)

Gastric neuroendocrine tumors (NETs) formerly known as carcinoids are well differentiated arising in the oxyntic mucosa of corpus or fundus composed of nonfunctioning enterochromaffin cells (Fig. 5). There are three types of carcinoid in the stomach. Type 1 carcinoids are most common and usually found in middle-aged women with autoimmune gastritis. The pathogenesis involves autoimmune destruction of parietal cells which leads to loss of feedback inhibition of gastrin and enterochromaffin cell proliferation appearing as small nodules in the body of the stomach.⁴¹ Type 2 carcinoids are rare and they occur in multiple

endocrine neoplasia type 1 (MEN1), Zollinger-Ellison syndrome, or gastrin secreting tumors. They metastasize in approximately 30%⁴² of cases and have a worse prognosis compared to type 1 carcinoids. Treatment for type 2 involves evaluation for metastasis, resection of local tumor, and removal of gastrin secreting tumor. Type 3 carcinoids are usually solitary arising anywhere in the stomach and are sporadic. Lymph node metastasis is found in approximately 71% of cases measuring more than 2 cm and the treatment involves surgical resection.⁴³

Symptoms include nonspecific epigastric pain or carcinoid syndrome caused by the release of histamine and tachykinin (flushing, lacrimation, facial edema, lacrimation, bronchoconstriction, and headache). A barium contrast study helps in identifying polypoid lesions and abdominal CT can assist in identifying lymph node spread and liver metastasis.⁴⁴ Radiolabeled somatostatin analogues like pentatreotide are helpful in identifying local vs metastatic foci of carcinoid tumors having somatostatin receptors.⁴⁵ Histopathologically, they contain variety of cell

Fig. 4. (A) Gastric adenoma. (B) Gastric tubular adenoma with intestinal metaplasia (H&E stain, ×10).

Fig. 5. (A) Gastric carcinoid. (B) Gastric submucosal carcinoid with nests of bland neuroendocrine cells (H&E stain, ×10).

types which include enterochromaffin like, enterochromaffin, and X cells.⁴⁶ They are immunoreactive for synaptophysin, neuron specific enolase, and chromogranin; exhibit different growth patterns like trabecular, solid, rosette or combination of these types. Antrectomy is recommended for multiple lesions and for recurrence after removal since it decreases the stimulus for growth by removing hypergastrinemia.⁴⁷ For sporadic lesions, *en bloc* surgical resection with lymph node dissection is recommended.⁴⁸ Hepatic metastasis can be treated by hepatic artery ligation or embolization, which decreases the symptoms and improves survival. Octreotide that is a somatostatin analogue is used to decrease the symptoms of carcinoid syndrome. Metastatic carcinoids are treated with chemotherapeutic agents like streptozocin, fluorouracil, doxorubicin and cyclophosphamide which produce tumor response in 20% to 40% of patients.⁴⁹

Gastric linitis plastica

It is a diffuse type of gastric cancer characterized by diffuse thickening and it accounts for 3% to 19% of gastric adenocarcinoma (Fig. 6).⁵⁰ Most are asymptomatic but symptoms arise at an advanced stage.⁵¹ Metastasis from breast should be excluded as infiltrative lobular cancer of breast tends to metastasize to the stomach, mimicking gastric linitis plastica (GLP).⁵² Common symptoms when present include early satiety, abdominal discomfort, weight loss, dysphagia, dyspepsia and vomiting.⁵³ Often there is regurgitation of food into the esophagus because of infiltration of tumor cells decreasing the volume of stomach and hence interfering with peristalsis. Linitis plastica usually involves the lower third of the mucosa; thus and biopsy of mucosa can be negative because the mucosa is not infiltrated. Multiple biopsy samples from the same site or using diathermic snare can increase the yield of diagnosing GLP. Preoperative staging is important in the diagnosis and treatment. CT scan and gastroscopy are the two important tools in evaluating the extent of cancer. Histopathologically, GLP consists of atypical cells which often has a signet ring cell appearance and are diffusely infiltrating.⁵⁴ CT scan findings include thickened stomach wall, diffuse gastric wall thickening, perigastric stranding, lung nodules, mediastinal lymphadenopathy, local lymphadenopathy and liver metastasis. Primary gastric

adenocarcinoma has a low fluorodeoxyglucose (FDG) uptake because of non-intestinal type, signet ring cells, high mucous content, and low cellularity.⁵⁵ For distant metastasis, the sensitivity and specificity of positron emission tomography (PET) are 35% to 74% and 74% to 99%, respectively.⁵⁶ PET FDG activity of standardized uptake value less than 4 was reported not associated with esophagogastric neoplasia⁵⁷ but associated with physiologic smooth muscle activity or non-neoplastic inflammation in the stomach. A complete preoperative staging is composed of diagnostic laparoscopy, CT, endoscopy, endoscopic ultrasound, and ultrasound abdomen. Serum tumor markers such as carcinoembryonic antigen, CA 19-9 and CA 72-4 are frequently done before treatment. Elevated CA 19-9 is elevated in patients with peritoneal spread and lymph node involvement and associated with a poor prognosis.⁵⁸ Treatment is a complete resection, but only 20% of them benefit from total gastrectomy⁵⁹ because peritoneal seeding, extension to surrounding organs and metastasis to lymph nodes is common. A role of postoperative radiation with or without chemotherapy should be further evaluated in future studies since complete resection is not possible in the majority of cases.

Gastric intestinal metaplasia

It is the most frequently encountered precancerous lesion of the stomach (Fig. 7).⁶⁰ The sequence of gastric adenocarcinoma of intestinal type includes nonatrophic gastritis, multifocal atrophic gastritis, metaplasia, and dysplasia.⁶¹ It is more common in populations at high risk for gastric cancer, as in Eastern Asia, Eastern Europe, and Andean Latin America. In United States, high-risk populations include African Americans, Native Americans, and immigrants from Asia and Latin America.⁶² Risk factors for gastric intestinal metaplasia (GIM) include *H. pylori* infection, high salt intake, smoking, alcohol consumption, and chronic bile reflux.⁶³ It is classified histopathologically into complete and incomplete based on the presence of small intestinal enzymes.⁶⁴ Complete type intestinal metaplasia (IM) contains the enzymes resembling the small intestinal epithelium with presence of the eosinophil enterocytes, goblet cells, and paneth cells. Incomplete IM contains either a small amount or none of the enzymes resembling the colonic epithelium with absent brush border. Filipe et al⁶⁵ proposed

Fig. 6. (A) Gastric linitis plastica. (B) Diffuse type gastric carcinoma with signet ring cells (H&E stain, ×10).

Fig. 7. (A) Gastric intestinal metaplasia. (B) Antral type gastric mucosa with intestinal metaplasia (H&E stain, $\times 10$).

another classification based on the type of mucins. In IM, acid mucins replace original gastric mucins. In type 1 (incomplete), it is sialomucins; type 2 (incomplete) contains mixed gastrin and intestinal mucins; type 3 (complete) contains sulphomucins. Samloff et al⁶⁶ proposed that the extent of gastric atrophy and intestinal metaplasia could be assessed by the measurement of the serum pepsinogen levels. Pepsinogen levels reflect the morphology and functional status of the gastric mucosa.^{66,67} As precancerous focus starts from the antral- corpus region and advances to the antrum and corpus, the serum levels of pepsinogen decrease from the atrophy of the corpus. If the pepsinogen levels are not affected, it is probably because only the antrum is affected and not the corpus.

In gastric cancer screening of high risk patients, pepsinogen was found to be useful as it is cost effective, less invasive, and provides faster results.⁶⁸ *H. pylori* colonization is seen in incomplete IM and areas adjacent to nonmetaplastic gastric mucosa of complete IM.⁶⁹ False negative test with rapid urease test for *H. pylori* can be seen in IM patients taking PPI, and hence other tests, such as serology, stool antigen and C13 urea breath test should be considered. Eradicating *H. pylori* will attenuate the precancerous process of gastric adenocarcinoma since *H. pylori* plays a role in IM.⁷⁰ It is still unclear whether eradicating *H. pylori* infection will prevent cancer if IM has already developed.⁷¹

Diagnostic Tools and Endoscopic Management

Computed tomography

It is helpful in preoperative staging of gastric cancer and also detection of both benign and malignant tumors. When compared to gastroscopy, it provides additional information not only about the gastric wall but also the entire abdomen.⁷² Multidetector CT allows three dimensional images and creates thinner or thicker sections in a shorter acquisition time.⁷³ CT manifestation of gastric cancer can be a polypoid lesion, focal or diffuse (linitis plastica) mural thickening with or without ulceration. D'Elia et al⁷⁴ evaluated the diagnostic accuracy of CT in preoperative staging of gastric cancer when compared to pathology. The diagnostic accuracy was 80% and 99% in an early and advanced gastric cancer respectively. Diagnostic accuracy of tumor stage was 78%; depth of invasion was 20% in early and 87% in advanced cancer. The

sensitivity and specificity of liver metastasis were 87.5% and 99%, respectively.

In another prospective study by Kim et al,⁷⁵ they evaluated the diagnostic accuracy of multiplanar CT in preoperative staging of gastric cancer when compared to pathology. Both virtual endoscopy (volumetric CT) and transverse CT is used. Volumetric images give added advantage of endoluminal perspective when compared to transverse CT. For tumor stage, diagnostic accuracy for transverse CT vs volumetric CT were 77% vs 84%; for lymph node detection 62% vs 64%; and for metastasis 86% for both respectively.⁷⁵ Kwee and Kwee⁷⁶ reviewed five multidetector row CT studies for staging of gastric cancer and the overall accuracy for T-staging was 77.1% to 88.9%. Sensitivity and specificity for the serosa involvement were 82.8% to 100% and 80% to 96.8%, respectively.⁷⁶

Binstock et al⁷⁷ evaluated the radiologic features of carcinoid tumors in CT. Carcinoids can be detected as small submucosal or mucosal polyp in patients with history of chronic atrophic gastritis and hypergastrinemia. In patients with MEN1, they can be identified as multiple gastric polypoid masses and diffuse gastric wall thickening. In type 3 carcinoids, it can be seen with metastatic lymph node involvement of the liver, spleen, and perigastric region, and localized thickening of posterior gastric wall.⁷⁷

Hyperplastic polyps on CT can be detected as multiple small, round, sessile polyps in fundus or gastric body and they usually range in 5 to 10 mm size. Gastric adenomas are usually solitary, found adjacent to the antrum; they are sessile or pedunculated and are lobulated in appearance, sometimes with size > 2 cm.

Magnetic resonance imaging

It is preferred over CT in renally compromised patients as gadolinium contrast is not nephrotoxic. It also has the advantage of no radiation. In a study of 189 patients, Jang et al⁷⁸ compared the diagnostic accuracy of magnetic resonance imaging (MRI) vs two-dimensional CT for gastric cancer. They showed that the diagnostic accuracy and sensitivity of MRI (combined conventional, diffusion weighted) vs CT were 77.8% to 78.3% vs 67.7% to 71.4% and 75.3% to 75.9% vs 64.1% to 68.2%, respectively. The diagnostic accuracy and sensitivity for conventional MRI alone were 72% to 73% and 68.8% to 70%, respectively.⁷⁸ In another

study by Kim et al,⁷⁹ the authors looked at 20 patients with gastric cancer and they compared MRI vs pathology to determine the accuracy of T-staging and N-staging. The accuracy of T-staging and N-staging for gastric cancer with MRI vs pathology were 74% and 47%, respectively.⁷⁹ MRI has certain limitations stemming from its high cost, motion artifacts, and lack of stable contrast medium.⁸⁰ Use of abdominal binders, antiperistaltic agents, phased-coil arrays, and breath-hold imaging techniques can reduce motion artifacts and improve the quality of images.⁸¹

In a prospective study involving 64 patients, Dromain et al⁸² evaluated the sensitivity of CT, MRI and somatostatin receptor scintigraphy (SRS) for the detection of liver metastasis from well differentiated gastroenteropancreatic tumors; the sensitivity of SRS, CT, and MRI were 49.3%, 78.5%, and 95.2%, respectively.⁸²

Positron emission tomography

18F-FDG PET is sensitive for NETs with high proliferation index when compared to low proliferation index.⁸³ In a prospective study of 96 patients, Binderup et al⁸⁴ compared the sensitivity of SRS with 111 In-Diethylenetriaminepentaacetic acid-octreotide, scintigraphy with 123I-metaiodobenzylguanidine (MIBG) and 18F-FDG PET for diagnosing NETs. The sensitivity of SRS, 123I-MIBG scintigraphy, and 18F-FDG PET were 89%, 52%, and 58%, respectively.⁸⁴ In a study of 124 patients investigating the sensitivity and positive predictive value of 18F-FDG PET for screening early gastric cancer (EGC) in Japan, the authors found the sensitivity 37.9% and specificity 33.6%.⁸⁵

Probe-based confocal laser microscopy

Probe-based confocal laser microscopy (pCLE) has an advantage over high definition white light endoscopy (WLE) and chromo endoscopy in identifying mucosal dysplasia and EGC by direct histological visualization of the tissue, thus allowing targeted biopsy.⁸⁶ There are 2 types of CLE, endoscopy-based CLE (eCLE) and pCLE. While pCLE is convenient to use through the endoscopes, eCLE may provide a higher resolution and deeper depth penetration when compared to pCLE. In a prospective study of 46 patients, the authors reported that the accuracy of pCLE, conventional endoscopic biopsy, combined pCLE and conventional endoscopic biopsy for diagnosis of early gastric adenocarcinoma were 91.7%, 85.2%, and 98.1%, respectively.⁸⁷ In another prospective study of 182 patients, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CLE for detection of superficial gastric cancer when compared to white-light endoscopy were found to be 88.9% vs 72.2%, 99.3% vs 95.1%, 85.3% vs 41.6%, 99.5% vs 98.6%, and 98.1% vs 94.1%, respectively.⁸⁸

Narrow band imaging

Narrow band imaging (NBI) provides clear images of micro-vasculature and gastrointestinal mucosa and can enhance early detection of gastric cancer. In a retrospective study of 51 patients, Horiuchi et al⁸⁹ looked at the sensitivity and specificity of detection of coexistence of gastric cancer in hyperplastic gastric polyps with WLE and magnifying endoscopy-NBI (ME-NBI). The sensitivity and specificity for WLE were 66.7% and 96.2%, respectively. The sensitivity and specificity of ME-NBI were 83.3% and 84.6% for fine mucosal structure, and 54.5% and 92.3% for irregularity of micro vessels, respectively.⁸⁹ In a retrospective study of 99 patients, the sensitivity, specificity, diagnostic accuracy of

NBI vs chromoendoscopy for gastric cancer smaller than 5 mm in size were found to be 78% vs 43.7%, 92.9% vs 81.6%, 88.3% vs 69.9%, respectively.⁹⁰

Chromo-endoscopy

It enhances tumor localization and characterization by application of various dyes. Absorptive, contrast, and reactive stains are different types of stains used. Absorptive stains include methylene blue and Lugol's iodine that are useful in detecting gastric metaplasia and EGC. Reactive stains like congo red and phenol help in detection of gastric cancer and *H. pylori* infection. Contrast stains like Indigo carmine are used to detect EGC and delineate the margins of gastric cancer before endoscopic submucosal dissection (ESD).⁹¹ In a prospective study of 104 patients by Kawahara et al,⁹² the diagnostic accuracy of white light, indigo carmine, and acetic acid-indigo carmine mixture for detecting EGC were 50.0%, 75.9%, and 90.7%, respectively.⁹² Dye based chromo endoscopy is limited by uneven staining of the mucosal areas resulting in overstraining or under staining of lesions thereby affecting the diagnosis and treatment. Dye-less chromo endoscopy is introduced to overcome this limitation, which includes Fujifilm Intelligent Color Enhancement (FICE; Fujifilm, Tokyo, Japan) and I-scan (Pentax, Tokyo, Japan). Mouri et al prospectively studied 100 patients with EGC and they showed that flexible spectral imaging color enhancement improved visualization of EGC in 46% of cases.⁹³

Esophagogastroduodenoscopy

Hyperplastic polyps are usually less than 1 cm, smooth, dome-shaped, or stalked. Endoscopic finding of white opaque substance in a gastric hyperplastic polyp is suggestive of neoplastic transformation.⁹⁴ There are no endoscopic guidelines for follow up of hyperplastic gastric polyp without dysplasia, but, if polyp persists or dysplasia is present, polypectomy is recommended with repeat EGD in one year.⁴¹ Whenever hyperplastic polyps are seen, examination of the whole stomach should be made to look for mucosal abnormalities and biopsy should be done to look for a synchronous cancer.⁹⁵ There are no standard guidelines for endoscopic removal of hyperplastic polyps. Although polyps greater than 2 cm should be removed,⁹⁶ carcinoma can arise in polyps smaller than 2 cm.⁹⁷ When hyperplastic polyps arise from chronic atrophic gastritis, the severity should be assessed based on the Operative Link for Gastritis Assessment (OLGA) or the Operative Link on Gastritis/Intestinal Metaplasia Assessment staging systems.⁹⁸ In general, 5 to 7 biopsy specimens (3 from the antrum, 2 from the lesser curvature of corpus and 2 from the greater curvature of the corpus) should be obtained to assess the severity of atrophic gastritis. Endoscopic surveillance should be considered for stage 3 or stage 4 OLGA but the guidelines are not standardized.

Gastric adenomas range in size from few millimeters to 4 cm in size⁹⁹ and are flat or sessile. Endoscopic follow-up for gastric adenoma should be done 6 months after incomplete polypectomy or for high grade dysplasia and 1 year for all other polyps.⁴¹ High grade dysplasia predisposes to invasive cancer not only within the polyp but also in synchronous areas of the stomach.³⁷ Operative resection should be considered for those not amenable for endoscopic resection.

Gastric NETs on upper gastrointestinal endoscopy are visible as submucosal masses that have yellow color, small, and rounded.¹⁰⁰ For type 1 and type 2 carcinoids measuring less than 1 cm and fewer than 3 to 5 in number, endoscopic polypectomy with

follow-up every 6 months is recommended.¹⁰¹

Endoscopic features of GLP include prominent gastric folds, thickened area of irregular gastric mucosa at greater curvature, circumferential thickening of the proximal stomach, fungating lesion extending from the esophagogastric junction to the antrum and diffuse gastric mucosal inflammation with normal biopsy.

As aforementioned, GIM is classified histologically into complete and incomplete intestinal types. Incomplete IM should undergo endoscopic mapping to identify multifocal areas of IM because several studies showed progression of IM to gastric adenocarcinoma.¹⁰² Typically, biopsies are obtained from the antrum, corpus, incisura angularis, and any visible lesions.¹⁰³ For complete IM, endoscopic surveillance is not indicated unless there are other risk factors for gastric cancer.

Endoscopic ultrasonography

EUS can help in differentiating submucosal and mucosal gastric polyps.¹⁰⁴ It also helps in determining the feasibility of endoscopic resection by assessing the depth of involvement. In general, endoscopic resection is not indicated if it involves muscularis propria.^{105,106} EUS can further differentiate submucosal tumors from extrinsic compressions and cystic from solid masses.¹⁰⁷ Carcinoids usually arise from deep mucosal or submucosal layers and spread deeper to submucosal area. While performing endoscopy, resection can be performed for type 1 and type 2 gastric carcinoids measuring 1 to 2 cm and confined within the mucosa and submucosal layers.¹⁰⁸ However, for gastric carcinoids > 2 cm, surgical resection should be considered^{109–113} rather than endoscopic attempt. EUS can also help in identifying the blood vessel near the carcinoid, which can potentially help prevent bleeding during endoscopic resection.¹¹⁴

Endoscopic mucosal resection and endoscopic submucosal dissection

One of the indications for endoscopic mucosal resection (EMR) and ESD is curative resection of the EGC. Gastric lesions confined to the mucosa, papillary or tubular (differentiated) adenocarcinoma, less than 2 cm for elevated lesions, less than 1 cm for flat or depressed lesions, no venous or lymph node involvement, no ulcer or ulcer scar are ideal candidates for EMR.¹¹⁵ Identifying lymph node metastasis is important prior to attempting EMR or ESD. Paris and Kudo classifications describe shape and pit-pattern of the lesions. Paris 1 includes protruded lesions; Paris 2 is subdivided into 2a slightly elevated, 2b completely flat, 2c depressed lesions; and Paris 3 lesions have ulceration in the mucosa.¹¹⁶ According to pit-patterns, Kudos classification is subdivided into type 1 (round), type 2 (stellate or papillary) which are nonneoplastic, type 3 (tubular or small roundish), type 4 (branch-like or gyrus-like), and type 5 (irregular or nonstructural pits) neoplastic.¹¹⁷ Type 5 usually involves the submucosal layer and portends higher lymph node metastasis.¹¹⁸ ESD has the advantage of *en bloc* resection and better histological assessment of lymphovascular invasion compared to EMR which employs a piece-meal resection.¹¹⁹ Catalano et al¹²⁰ compared EMR and ESD for EGC in 45 patients. *En bloc* resection for EMR vs ESD was reported in 26/32 patients (76%) and 11/12 patients (92%), respectively. Curative resection for EMR vs ESD was 20/36 patients (56%) vs 11/12 patients (92%), respectively. Complications of EMR vs ESD included bleeding (8% vs 8%), stenosis (3% vs 0%) and perforation (0% vs 8%), respectively.¹²⁰

EMR is recommended for both type 1 and type 2 gastric carcinoids associated with hypergastrinemia, less than 1 cm in

diameter and presence of 3 to 5 tumors.¹²¹ EUS is performed before treatment to assess the depth of invasion. Tumors confined to submucosa are treated endoscopically (EMR) and with deeper invasion are treated surgically. Endoscopic surveillance with biopsy at 6 months interval is performed after complete resection to evaluate for recurrence.

Gastric adenoma (low grade dysplasia and high grade dysplasia) can progress to invasive carcinoma¹²² or advanced cancer¹²³ at the time of follow-up. Treatment for gastric adenoma is endoscopic *en bloc* resection and complete resection. ESD is preferred than EMR because of the advantage of *en bloc* resection and complete resection regardless of lesion size.¹²⁴ In a retrospective study done by Kim et al,¹²⁵ they evaluated 252 patients with low grade dysplasia who have undergone EMR (77.8%) and ESD (22.2%), respectively. They concluded that *en bloc* resection was significantly lower in the EMR group (31.1%) when compared to ESD group (75%) ($P < 0.001$) and no significant difference in prevalence of remnant lesions or recurrence rate ($P = 0.911$) of gastric adenoma.¹²⁵

Perforation with ESD (1.2%–5.2%) usually occurs in the upper and middle parts of the stomach because of the thin wall and retro flexion position of the endoscope. The risk for perforation further increases with increasing size of the lesion and ulceration.¹²⁶ Submucosal injection is paramount of importance in creating a safety net in ESD by providing an adequate space for dissection between the mucosa and muscularis propria layers. Single-closure and omental patch using endoclips are utilized in endoscopic closure. Single-closure is used for smaller defects and omental patch is used for larger defects.¹²⁷ Bleeding can be immediate (intraoperative) or delayed (within 24 hours of procedure). For the control of bleeding, there are many in the armamentarium, electric cautery, injection therapy, placement of hemoclips, or combinations thereof. However, delayed bleeding can be prevented by carefully inspecting the resection bed and applying coagulation to the visible vessels while performing EMR or ESD.¹²⁸ Stenosis usually occurs when the mucosal defect is greater than 75% of the circumference and/or longitudinal defect is more than 5 cm; a serial dilation with balloon inflation is often required to treat the stenosis.

Conclusion

With increasing incidence of gastric lesions detected, the prompt differentiation between benign from malignant gastric lesions is essential to successful, efficient, and cost-effective management. Careful inspection and biopsy of the lesion and perhaps the surrounding mucosa will prevent missing hidden cancers. Clearly, accurate diagnosis and staging, complete resection, and meticulous follow-up are the principles in preventing invasive surgery and potentially improving survival. Good judgment of endoscopists and close collaboration with pathologists are priceless in this challenging endeavor.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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