Endoscopy and Endoscopic Ultrasound Examination of the Stomach

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Abbreviations

H. pylori	*Helicobacter pylori*
UGI	Upper gastrointestinal
WLE	White light endoscopy
OLGA	Operative link of gastritis assessment
OLGIM	Operative link of gastric intestinal metaplasia
ASGE	American Society of Gastrointestinal Endoscopy
HDGC	Hereditary diffuse gastric cancer
PJS	Peutz-Jeghers syndrome
JPS	Juvenile polyposis syndrome
FAP	Familial adenomatous polyposis
HNPCC	Hereditary nonpolyposis colorectal cancer
FGP	Fundic gland polyp
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
NBI	Narrow band imaging
M-NBI	Magnification NBI
HER2	Human epidermal growth factor receptor 2
ASA	American Society of Anesthesiologists
EUS	Endoscopic ultrasound
FNA	Fine needle aspiration
MDCT	Multidetector computed tomography
MRI	Magnetic resonance imaging
FJP	Familial juvenile polyposis

Introduction

Adenocarcinoma of the stomach accounts for an estimated 7% of total new cancer diagnosis and 9% of total cancer-related deaths worldwide [1]. The role of endoscopy for gastric cancer has over time evolved to include screening, surveillance, diagnosis, staging, and treatment. This chapter will focus on the most recent approaches to endoscopic screening, surveillance, diagnosis, and staging of gastric adenocarcinoma. Endoscopic treatment by endoscopic mucosal resection (EMR) is covered in Chap. 11.

Screening and Surveillance

The incidence of gastric cancer varies considerably worldwide with a predilection for South America, Eastern Europe, Central and Eastern Asia, where some countries have adopted gastric cancer screening programs [1, 2]. In Japan, where the incidence of gastric cancer is among the highest in East Asia at over 50 men per 100,000 persons per year, photofluorography is the recommended population-based and opportunistic screening modality, which has led to a

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significant reduction in gastric cancer mortality [2–4]. A new model of screening incorporating eradication of *Helicobacter pylori (H. pylori)* with upper gastrointestinal (UGI) endoscopy has been suggested [5]. Those under 20 years of age would be tested for *H. pylori* infection and undergo eradication if affected. Individuals older than 50 years who are *H. pylori* infected would receive eradication and endoscopic examination. In Korea, the National Cancer Screening Program recommends individuals over the age of 40 undergo screening UGI endoscopy every other year, which has been shown to be cost effective, and compared to UGI series, has better sensitivity, and a higher positive predictive value [6, 7]. A recent systematic review including studies from Korea, Japan, China, and Singapore concluded endoscopy for gastric cancer in these high incident regions was more cost effective than no screening [8]. In Japan and Korea, as a result of screening, diagnosed gastric cancers are predominantly early stage lesions, which may be amenable to endoscopic treatment and have a more favorable prognosis [6].

In Western Europe and North America, where the incidence among non-Hispanic white males is 7.8 per 100,000 persons, the lower incidence renders screening not cost effective, and no population-based screening recommendations are in place [9]. However, surveillance of chronic atrophic gastritis, gastric intestinal metaplasia, or dysplasia, which represent intermediate states along the intestinal gastric carcinogenesis pathway proposed by Correa, have been suggested [10–12]. Chronic atrophic gastritis and intestinal metaplasia are recognized premalignant conditions that have an estimated annual progression rate to gastric cancer of less than 1% based on a Dutch nationwide cohort study [13]. Although the progression rate is low, worldwide one third of individuals may have chronic atrophic gastritis, while intestinal metaplasia may affect up to one quarter of the population, with more extensive disease reported in regions with higher incidence of gastric cancer [14]. At this time, white light endoscopy (WLE) cannot visually differentiate *H. pylori* gastritis from atrophy or intestinal metaplasia. While antral nodularity has >90% positive predictive value for *H. pylori* infection, the presence of visible vessels and loss of rugae folds are supportive but nonsensitive endoscopic measures of gastric atrophy [11]. Although a classification system using magnification chromoendoscopy with methylene blue had good correlation to histology, and was successfully externally validated, its use in general clinical practice is not yet widely adopted [11, 15]. Therefore, detection of these premalignant intermediates remain primarily through histological review, and when found, gastric mapping by taking at least one biopsy along the lesser and greater curvatures each of the body and antrum (3 cm from the pylorus), and one at the incisura, placed in separate vials, should be performed, as guided by the updated Sydney System [16]. Multiple biopsies are required as for both gastric atrophy and intestinal metaplasia, there is poor correlation between endoscopic and histologic diagnosis. An endoscopic interpretation of gastric atrophy had a sensitivity between 45 and 60%, based on the histological diagnosis, with lower sensitivity in patients younger than 50 years of age [17]. The sensitivity of an endoscopic diagnosis of intestinal metaplasia of the body and antrum, compared to the histological diagnosis, was worse at 24%, in a study of over 1300 patients [18]. Based on the severity and extent of intragastric atrophy or intestinal metaplasia, risk stratification per the operative link of gastritis assessment (OLGA) or operative link of gastric intestinal metaplasia (OLGIM) histological staging system can then be determined, respectively [19]. Greater extent and severity of atrophic gastritis and intestinal metaplasia are associated with an increased risk of gastric neoplasia development [20]. If extensive atrophy or intestinal metaplasia is identified, surveillance endoscopy every 3 years after diagnosis has been recommended by the European Society of Gastrointestinal Endoscopy, although there are no mortality or cost effective results from randomized studies to support these specific surveillance recommendations [11, 21]. The 2006 guidelines from the American Society of Gastrointestinal Endoscopy (ASGE) did not recommend uniform surveillance of gastric intestinal metaplasia in the United States due to weak

level of evidence, though individuals from high risk ethnicity or a family history of gastric cancer may benefit [12].

Low-grade dysplasia of the stomach has been reported to progress to gastric cancer at 5 years follow-up at a rate of 2.8–3.1 %, while high grade dysplasia progression rates are between 7 and 29 %, with differences between Asian and Western studies [13, 22]. In the absence of endoscopically defined lesions, low-grade dysplasia should have surveillance endoscopy within 1 year of diagnosis, while high grade dysplasia should have endoscopic reevaluation with extensive biopsies at 6-month to 1-year intervals [11]. EMR for low-grade dysplasia associated with a visible lesion should be considered, if clinical expertise is available, for more accurate histological staging. Kim et al. highlighted the limitations of gastric mucosal biopsy by forceps, showing that 19 % of low-grade dysplasia diagnoses were upgraded after EMR [23]. *H. pylori,* if detected, should also be eradicated, though its benefits in reversing gastric intestinal metaplasia and more severe histological disease stages are unclear [11, 12].

Other groups at risk for gastric cancer development include pernicious anemia, partial gastrectomy, and genetic syndromes such as hereditary diffuse gastric cancer (HDGC), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), familial adenomatous polyposis (FAP), and hereditary nonpolyposis colon cancer (HNPCC). A recent systematic review and meta-analysis concluded the relative risk of gastric cancer in pernicious anemia was seven times higher compared to the general population, with a gastric cancer incidence rate of 0.27 % per year [24]. These patients are also at risk for development of type I gastric carcinoids. ASGE recommends a single upper endoscopy to identify either gastric cancer or carcinoids at time of diagnosis, but subsequent surveillance interval is unclear [12]. Similarly, surveillance of the gastric remnant in patients with surgeries for peptic ulcer disease is not routinely supported due to insufficient data. If considered, however, it should be performed 15–20 years after time of ulcer surgery, as the risk of gastric cancer development appears highest at this time [12]. Biopsies of the gastric remnant and the anastomosis are suggested [12].

Among the genetic cancer syndromes which make up roughly 5 % of total gastric cancer cases, HDGC confers one of the highest risks, with a cumulative lifetime risk of diffuse gastric cancer of approximately 80 % by 80 years of age [25]. It is characterized by loss of expression of the cell adhesion protein E-cadherin (CDH1) resulting in defective intercellular adhesion, and displays an autosomal dominant inheritance pattern [26]. Lesions usually present submucosally, as scattered microscopic foci of signet cells with intervening normal gastric mucosa. Despite its limitations, surveillance with high-definition WLE every 6 months to 1 year, beginning at 10 years earlier than the youngest affected family member or by 25 years old, is recommended for those with documented CDH1 mutation who are not candidates for total gastrectomy either by choice or fitness [27]. Testing for CDH1 mutation should be performed as recommended by the International Gastric Cancer Linkage Consortium [27]. Any endoscopically visible lesions should be sampled, and six random biopsies each at the fundus, cardia, body, body-antral transition, and antrum, totaling 30 biopsies, are recommended [27]. PJS, which is caused by mutations of the serine threonine kinase STK11, is also an autosomal dominant inherited disorder. Better recognized by the classic pigmented spots on the lips and buccal mucosa, at least 50 % of patients have gastric hamartomas. The lifetime cumulative risk of gastric cancer is estimated to be 29 %, while the relative risk has been reported to be over 200 times compared to the general population [28, 29]. Among those meeting clinical criteria for PJS, baseline upper endoscopy is suggested to start at 8 years old. If significant polyps are found, repeat surveillance endoscopy every 3 years is advised. Conversely if no polyps are detected, the next surveillance endoscopy can be delayed to 18 years of age unless symptoms arise [30]. JPS is defined as the presence of 10 or more juvenile polyps also known as hamartomas. When at least one first-degree relative have similar lesions, the term familial juvenile polyposis (FJP) is used. Germline mutations in three genes (SMAD4, BMPR1A,

and ENG) of the transforming growth factor-beta signaling pathway have been associated with JPS, which manifests as an autosomal dominant disease with high penetrance [31]. In general, upper endoscopy starts at 15 years of age, and is repeated every 1–3 years unless there are interval symptoms [31]. FAP, as a result of loss of the adenomatous polyposis coli tumor suppressor gene, confers increased risk of both colorectal and extra-colonic malignancies. While current FAP recommendations for upper endoscopy, starting at 25–30 years old, or when colectomy is considered, are primarily for surveillance of duodenal/periampullary adenomas and cancers, the stomach should also be evaluated for fundic gland polyps (FGP), adenomas and potentially gastric cancer [11, 32]. In a study of 75 consecutive FAP patients undergoing surveillance upper endoscopy, almost 90% of patients had FGP, nearly half of which were associated with dysplasia, predominantly low-grade dysplasia [33]. Larger polyp size, and more severe duodenal polyposis were associated with an increased risk of dysplasia associated FGP [33]. These authors recommended incorporating presence and degree of dysplasia associated FGP in addition to degree of duodenal polyposis to guide surveillance intervals [33]. The risk of gastric adenomas in FAP has been reported at approximately 10%, but in one study of mostly low-grade dysplastic adenomas, there was no progression to gastric cancer over a 5 year follow-up [34]. The risk of gastric cancer in HNPCC is varied from no higher than the general population to an increased lifetime risk of up to 8%, particularly among MSH1 and MSH2 mutations carriers [35–37]. Since it is the intestinal histological subtype of gastric cancer that is at higher risk of development, recent society guidelines have suggested upper endoscopy among mutation carriers starting at 30–35 years of age to screen for *H. pylori,* and, if found, its eradication with subsequent surveillance at 2–3 years intervals [38, 39]. Table 9.1 provides a summary of the above surveillance recommendations.

Diagnosis

As a result of organized screening programs, up to 50% of diagnosed gastric cancers in countries like Japan are of early stage, defined as those limited to the mucosa or submucosa regardless of lymph node involvement [40, 41]. On WLE,

Table 9.1 Summary of endoscopic surveillance recommendations for conditions associated with an increased risk of gastric cancer

At-risk conditions	Endoscopy surveillance recommendations
Pernicious anemia	At time of diagnosis, UGI WLE for increased risk of gastric cancer and type I carcinoids. Subsequent surveillance interval unclear
Partial gastrectomy	At 15–20 years after surgery, UGI WLE with biopsies of the gastric remnant and anastomosis. Subsequent surveillance interval unclear
Hereditary diffuse gastric cancer	Beginning at 10 years earlier than the youngest affected family member or by 25 years of age, UGI WLE, every 6 months to 1 year, with six random biopsies each at the fundus, cardia, body, body-antral transition, and antrum, and targeted biopsies of any endoscopically visible lesions
Peutz-Jeghers syndrome	Starting at 8 years of age using UGI WLE. If significant polyps are found, repeat surveillance endoscopy every 3 years. If no polyps are detected, next surveillance endoscopy can be delayed to 18 years of age unless symptoms arise
Juvenile polyposis syndrome	Beginning at 15 years of age with UGI WLE. Surveillance every 1–3 years unless there are interval symptoms
Familial adenomatous polyposis	Starting at 25–30 years of age for increased risk of fundic gland polyps, gastric adenomas, gastric cancer, duodenal, and periampullary adenomas and malignancies
Hereditary nonpolyposis colorectal cancer	Commencing at 30–35 years of age with UGI WLE. Subsequent surveillance at 2–3 years intervals unless symptomatic

UGI upper gastrointestinal, *WLE* white light endoscopy

early gastric cancer can be subtle, and therefore gastric contents should be suctioned away, the mucosal surface thoroughly washed of bubbles or debris, and the stomach well insufflated. The endoscopist should be attentive to interruptions of the mucosal folds, differences in mucosal color, mucosal friability, spontaneous bleeding, and changes in submucosal vessel patterns [42]. When a suspected early gastric cancer is identified, its morphology, location, size, and margins should be characterized. Current indications for EMR or endoscopic submucosal dissection (ESD) include a <2 cm nonulcerated, T1a differentiated type adenocarcinoma, with recently proposed expanded criteria [41]. Categorization of lesion morphology has been internationally standardized based on the Paris Endoscopic Classification [43]. Neoplastic lesions can be polypoid, which protrudes above the surrounding mucosa, and may have a narrow base (i.e., pedunculated) or have a base diameter similar to the top (i.e., sessile). Alternatively, nonpolypoid lesions could be slightly elevated, completely flat, or depressed compared to the surrounding mucosa [43] (Fig. 9.1). The surface morphology may also guide T staging. The findings of smooth surface protrusion or depression, slight marginal elevation, and smooth tapering of converging folds have a reported 82% positive predictive value for T1m disease when compared to pathological staging. Conversely, an irregular surface, marked marginal elevation, and abrupt cutting/fusion of converging folds had a 72% positive predictive value for T1sm disease. The overall accuracy of distinguishing T1m from T1sm lesion was 78% [44]. Lesion location can be prognostic in EMR, as those at the fundus, mid/lower body or incisura, versus the antrum, were associated with higher rates of incomplete EMR in a multicenter retrospective review of over 500 EMRs performed in Korea [45]. For advanced disease amenable to gastrectomy, tumor location, particularly in relation to the esophagogastric junction and incisura, also guides the extent of surgical resection. Lesion size is likewise prognostic in EMR, with those smaller than 3 cm achieving a higher complete resection rate than larger lesions [45]. This characteristic however has become less relevant with the advent of ESD, which allows enbloc resection of large lesions, otherwise removed piecemeal by EMR. The lateral margins of relatively flat lesions can be difficult to delineate, raising the possibility of incomplete endoscopic resections. The development of chromoendoscopy and narrow band imaging (NBI), however, has enhanced margin delineation. Chromoendoscopy is a form of enhanced imaging, whereby a dye is sprayed via the working channel on both the suspected lesion and surrounding mucosa. Indigo carmine dye is not absorbed by gastric epithelium, but instead pools in crevices highlighting differences in elevation, and mucosal irregularities.

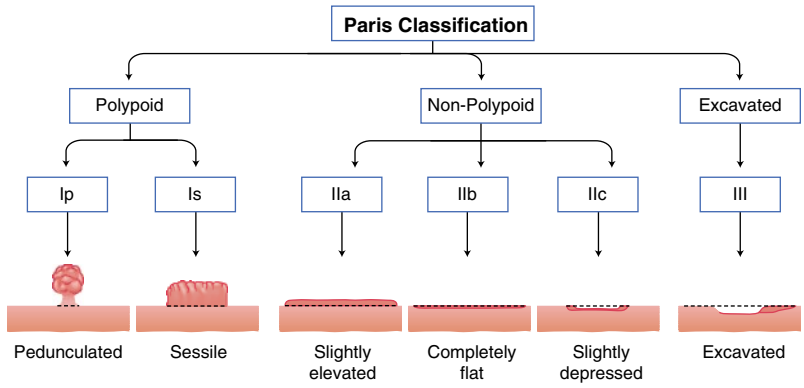

Fig. 9.1 Paris classification for superficial (type 0) neoplastic lesions of the gastrointestinal tract. Based on the endoscopic macroscopic appearance, lesions are categorized as *polypoid*/protruding: *Ip* or *Is,* or *nonpolypoid*/nonprotruding: *IIa, IIb, IIc,* or *III*

Its combined use with acetic acid was superior to either alone, or WLE alone for tumor border recognition, though a more recent study showed improved visualization among well-differentiated cancers only [46, 47]. NBI is an equipment-based form of image-enhanced endoscopy, whereby an optical filter allows light of limited wavelengths, specifically blue and green light, to illuminate the mucosa, highlighting surface and vascular architecture. Use of NBI alone to survey the gastric mucosa in its entirety is impractical due to the darkness of the lumen. Its value lies in further characterizing a lesion once identified. Normal mucosa, *H. pylori*-associated gastric atrophy, and intestinal metaplasia have distinct microsurface and microvascular features enabling differentiation from early gastric cancers [48, 49]. For example, on magnification NBI (M-NBI), the light blue crest sign on the epithelial surface has a sensitivity and specificity of approximately 90% for gastric intestinal metaplasia [50]. And the demarcation line which represents a transition of the microsurface and microvasculature characteristics on M-NBI is most indicative of cancer, and was concluded as useful to determine the lateral extent of early gastric cancer at an Asian-Pacific endoscopy consensus meeting [48, 49]. M-NBI may have better sensitivity and specificity than chromoendoscopy for the diagnosis of gastric cancers less than 5 mm [51]. Of note, however, is that undifferentiated early gastric cancers may spread subepithelially along the lamina propria, and have a normal overlying foveolar epithelium, thus limiting the utility of M-NBI [48]. Hayee et al. recently proposed a diagnostic algorithm for gastric epithelial lesions with WLE and M-NBI [49].

After visual characterization, 8–10 biopsies should be performed of the suspected neoplasia, particularly for ulcerated lesions, with standard size biopsy forceps [52]. Jumbo forceps may increase diagnostic yield, though a recent open-labeled study found for nonulcerated gastric epithelial lesions, four standard forceps (opening diameter 6.8 mm) biopsies and four jumbo forceps (opening diameter 8 mm) biopsies had similar diagnostic concordance rates when compared to the final pathology from ESD [53]. Among those with early gastric cancer likely amenable to endoscopic treatment, if *H. pylori* is detected on biopsy, its eradication may also reduce the risk of metachronous gastric cancer after endoscopic resection [54]. For more advanced cancers eligible for systemic treatment, gastric cancer biopsies should be tested for human epidermal growth factor receptor 2 (HER2) positivity, as the ToGA trial demonstrated for these patients, trastuzumab with chemotherapy resulted in longer overall survival compared to chemotherapy alone [55]. Finally, after a single lesion is identified, careful inspection for synchronous abnormalities is necessary. In one study, preoperative gastroscopy performed by endoscopists with more than 10 years of experience failed to identify 15% of synchronous multifocal gastric cancers found on surgically resected specimens, with the mean size of missed lesions (1.57 cm) significantly smaller than the detected ones (2.14 cm) [56].

The incidence of adverse events from UGI endoscopy is low, with >50% due to sedation and analgesia-related cardiopulmonary complications, reportedly occurring between 1/170 and 1/10,000 [57]. Mild events range from fluctuations in heart rate, blood pressure, and oxygen saturation to serious potentially life threatening aspiration pneumonia with respiratory distress. Risk factors include older age, higher American Society of Anesthesiologists (ASA) class, history of cardiopulmonary disease, prolonged procedure, and prone patient position [57]. The remaining complications relate to perforation, bleeding, and infection. Perforation rates range from 1/2500 to 1/11,000 and are most likely in patients with anatomical variants or abnormalities such as esophageal and duodenal diverticulum, esophageal strictures, or malignancies of the UGI tract [57]. Bleeding rates are likewise low, and the platelet threshold for diagnostic and therapeutic upper endoscopies are >20,000/mL and >50,000/mL, respectively. Preoperative management of antiplatelets and anticoagulants depends on their indications, and the procedure's risk of bleeding [58]. When bleeding from friable tumor is encountered, hemostasis is often refractory to conventional endoscopic tools, though a novel inorganic proprietary agent has shown promise

by causing mechanical tamponade, and activation of the clotting cascade [59]. Finally, infectious complications are either due to improper processing of endoscopy equipment or the procedure itself. Among UGI procedures relating to gastric cancer specifically, antibiotic prophylaxis is recommended when placing percutaneous endoscopic gastrostomies and jejunostomies [60].

Staging

Management decisions of gastric adenocarcinoma depend on accurate tumor staging. The TNM staging model developed by the American Joint Committee on Cancer and the International Union Against Cancer is based on the degree of tumor (T), nodal (N) involvement, and evidence of distant metastasis (M). T staging reflects depth of tumor invasion into the stomach wall. Tumor size does not play a role in T staging, however, is an important factor when deciding suitability of endoscopic treatment in cases of early gastric cancer. N staging describes the number of malignant nodes involved, whereas the location of nodal involvement was considered in earlier TNM classifications. M staging denotes presence or absence of distant metastatic disease. Preoperative clinical staging includes endoscopic ultrasound (EUS), possibly with fine needle aspiration (FNA), for the most accurate noninvasive locoregional T and N staging, while distant metastasis is evaluated by multidetector computed tomography (MDCT) of the chest, abdomen, and pelvis. This approach in turn risk stratifies patients to endoscopic treatment such as EMR, ESD, surgery, or systemic chemotherapy. While both the National Comprehensive Cancer Network of the United States and the European Society of Medical Oncology endorse EUS staging of nonmetastatic lesions possibly treated endoscopically, a recent Asian consensus did not include this modality for routine staging due to its T stage limitations, as discussed below [61].

Staging EUS when performed is preferably with the radial echoendoscope. The circumferential view, which is perpendicular to the shaft axis, permits assessment of wall layer involvement, abnormal lymph nodes, and tumor invasion into adjacent structures. Prior to EUS evaluation, any food contents or bubbles within the stomach should be removed or washed off, and air is suctioned from the stomach. To achieve close acoustic coupling between the echoendoscope tip and the lesion, either 300–400 cc of 0.9% isotonic saline or water can be instilled into the stomach, or a water-filled balloon placed at the echoendoscope tip can be inflated. The endoscopist should be mindful of the risk of aspiration with the patient in the left lateral decubitus position. EUS starts by positioning the probe in the antrum, instillation of water into the stomach/insufflation of the water-filled balloon, and slow withdrawal to the esophagogastric junction. With the 7.5–12-MHz echoendoscope, the normal gastric wall is represented as a 3–4-mm five-layer structure with alternating echogenicity (Fig. 9.2). The first two layers correspond to the superficial and deep mucosal layers. The third layer which is hyperechoic reflects the submucosa, while the fourth hypoechoic layer is the muscularis propria, and the outermost 5th hyperechoic layer represents the subserosal fat and serosa. Higher-frequency (>12 MHz) probes will depict the gastric wall with greater resolution with nine layers, but the depth of penetration is limited, potentially affecting nodal staging. When the lesion of interest is visualized, it is important to position the tip of the echoendoscope perpendicularly to avoid inaccurate staging from tangential views. With fine

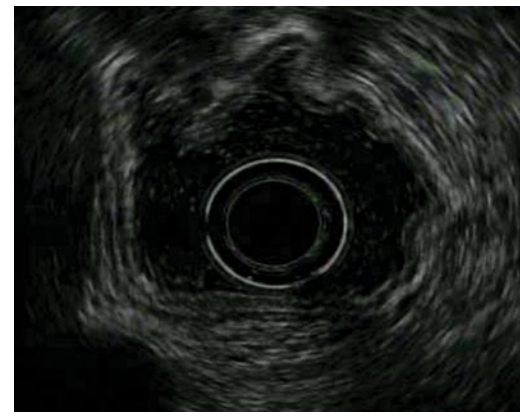

Fig. 9.2 Normal gastric wall represented as a 3–4-mm five-layer structure with alternating echogenicity

movements, the scope can be advanced, withdrawn, and torqued to provide a comprehensive assessment. Clinical T staging by EUS is categorized as:

T1a Tumor limited to the mucosa (first or second layer)

T1b Tumor limited to the submucosa (third layer). The outer margin of the hyperechoic third layer is smooth (Fig. 9.3)

T2 Tumor extends into but not through the muscularis propria (fourth layer). The outer margin of the hypoechoic fourth layer is intact (Fig. 9.4)

T3 Tumor penetrates the subserosa (fifth layer) (Fig. 9.5)

T4 Tumor invades into adjacent vascular structures (aorta or celiac axis) or organs (liver, pancreas, spleen) (Fig. 9.6)

Instead of a discrete mass, gastric cancer can alternatively present as linitis plastica from diffuse tumor infiltration causing a rigid stomach that does not insufflate well with air. On EUS, there is a markedly thickened gastric wall with loss of the normal five-layer pattern (Fig. 9.7).

Once the primary tumor has been T staged, perigastric and regional lymph nodes such as gastrohepatic ligament and celiac axis nodes are assessed. EUS features suggestive of malignant lymph nodes include size greater (vs less) than

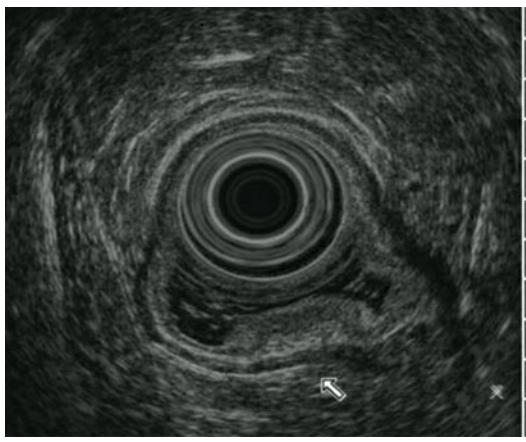

Fig. 9.3 T1b tumor limited to the submucosa (*third layer*)

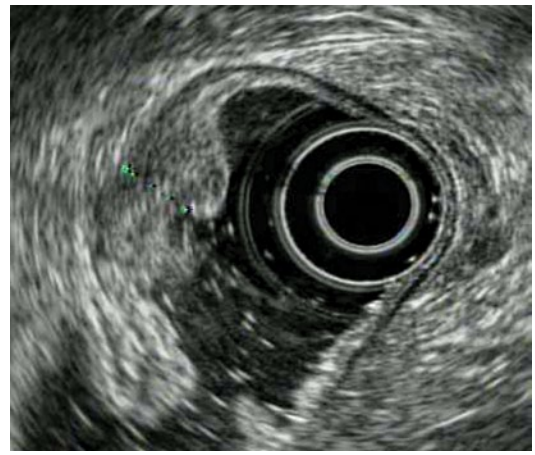

Fig. 9.4 T2 tumor extending into but not through the muscularis propria (*fourth layer*)

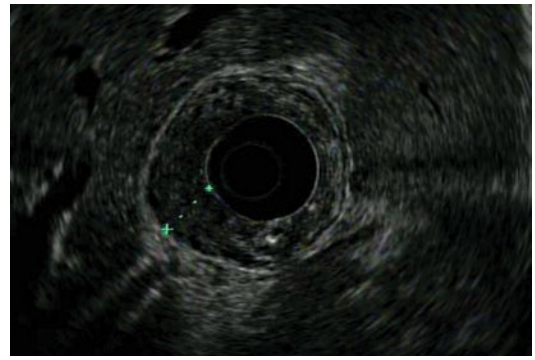

Fig. 9.5 T3 tumor penetrating subserosal connective tissue without invasion of visceral peritoneum or adjacent structures

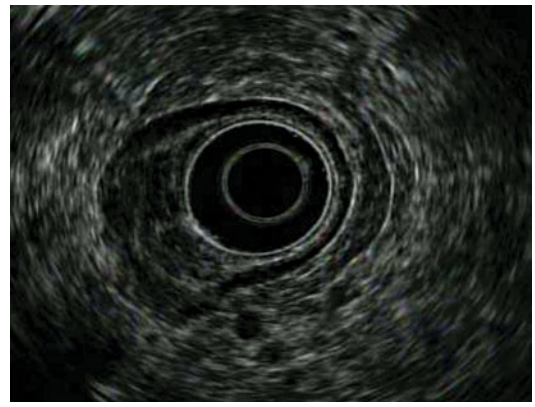

Fig. 9.6 T4a showing tumor invading serosa (visceral peritoneum)

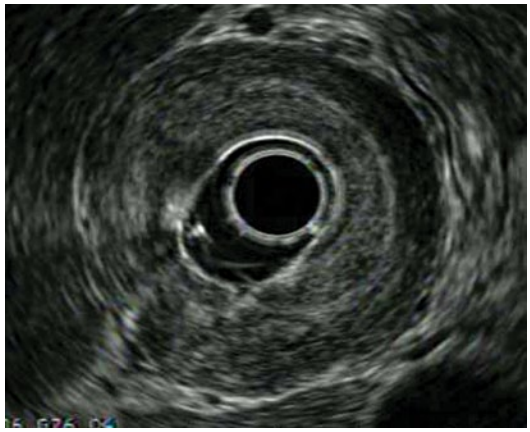

Fig. 9.7 Linitis plastica, represented on EUS as a markedly thickened gastric wall with loss of normal five-layer pattern

1 cm, circular (vs elliptical) shaped, sharp (vs irregular) margins, and hypoechogenicity (vs others). As previously noted, it is the number, not the location or proximity to the primary lesion, which dictate N staging. Cardoso et al. conducted a systematic review and meta-analysis of 22 studies between 1998 and 2009, reporting a pooled accuracy for T staging of 75% with a moderate Kappa of 0.52. EUS T staging was more accurate for T3 and T4 disease, than T1 and T2 disease [62]. Understaging can be due to microscopic infiltration, while peritumoral inflammation may result in overstaging. EUS pooled accuracy for N staging was 64%, with 74% sensitivity and 80% specificity [62]. An earlier meta-analysis likewise noted greater T stage accuracy for more advanced disease, but also demonstrated this for N staging, where the pool sensitivity of N1 disease was 58.2%, and N2 was 64.9% [63]. In comparison to other cross sectional imaging modalities, a systematic review reported the diagnostic accuracy of T staging from EUS (65–92%) was comparable to MDCT (77–88%) and magnetic resonance imaging (MRI) (71–82%) [64]. These three modalities also had similar sensitivities for N staging of between 68% for MRI to 71% for EUS and 80% for MDCT [64]. Site of disease can affect accuracy of T staging, and lesions at the cardia, lesser curvature along the upper body, and the incisura can be challenging to visualize. Further, tumor size greater than 3 cm has been associated with overstaging, while undifferentiated histology correlated to understaging in a retrospective Korean study comparing EUS T staging accuracy with EMR histology [65]. Limitation of EUS for nodal staging is primarily due to the inability to differentiate benign reactive from malignant lymph nodes. The previously described EUS criteria for malignant lymph nodes are found infrequently together. Individually, these features are not specific for cancer involvement. However when all features are present, this can confer an 80% chance of malignancy infiltrating the lymph node [66]. The likelihood of lymph node metastasis also increases with T stage [67]. Lymph nodes beyond the depth of penetration of the echoendoscope will not be detected, and this occurs more commonly for those along the greater curvature than the lesser curvature. EUS's ability to M stage is limited to assessing for disease in the left lobe of the liver, the left adrenal gland, the presence of ascites or pleural effusion, and mediastinal lymphadenopathy. EUS may detect radiographically occult liver metastases, though this is uncommon [68]. For the detection of ascites, EUS has been reported to be more sensitive than either laparoscopy/laparotomy or combined CT and ultrasound in an Asian study [69]. Found between the echoendoscope tip and external to the gastrointestinal tract and visceral organs like the liver, ascites is usually seen as a triangular anechoic space that can change shape with patient position. Finally, EUS guided FNA with a linear echoendoscope has successfully diagnosed malignant ascites, though a negative ascites fluid cytology does not exclude peritoneal carcinomatosis [70]. Endoscopists should be mindful that traversing of the EUS needle across the tumor into ascites fluid can result in false positive cytology, and seeding of the peritoneal cavity.

The type of complications associated with EUS and FNA are similar to UGI endoscopy, and include cardiopulmonary events from sedation and analgesia, perforation, bleeding, and infection [71]. In a systematic review of EUS-FNA studies mostly of pancreatic lesions, perforation, hemorrhage, infections, and post-EUS-FNA pancreatitis were reported to be 0.02% (2/10,941), 0.13% (14/10,941), 0.05% (5/10,941), and

0.44 % (36/8246), respectively [72]. To minimize risk of perforation, endoscopists should be particularly cognizant of the semi-blind nature of the cervical intubation, and the rigidity of the echo-endoscope tip compared to a standard UGI endoscope. Similar to upper endoscopy, preoperative management of antiplatelets and anticoagulants depend on their indications compared to the procedural risk of bleeding.

In summary, gastric cancer is a significant cause of global morbidity and mortality. Gastroenterology's role has expanded to encompass every stage of gastric cancer development, and endoscopists must be cognizant of the most recent evidence-based practice to support the complex multidisciplinary care provided to these patients.

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