Chapter 3
The Role of Endoscopy

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Preneoplastic Changes

In contrast to intestinal-type cancers, diffuse carcinomas do not have a clearly defined precancerous lesion, even those that are associated with *H. pylori* infection. Histologically, among the diffuse types, signet-ring cell carcinoma (SRCC) is dominant (60%) [15]. Commonly, SRCC of the stomach is thought to arise in the mucosa without metaplastic change and is typically confined to the glandular neck region in the original proliferation zone [16]. It is considered, therefore, that early-stage SRCC can be present beneath a flat, intact mucosal surface epithelium and may be very difficult to identify by endoscopy due to its slightly whitish discoloration.

A representative form of *H. pylori*-negative diffuse gastric cancer, hereditary diffuse gastric cancer (HDGC) cases in early stages, when submitted to histologic analysis, has led to a progression model for the disease [2]. In gastrectomy specimens from members of HDGC families, isolated neoplastic SRCC may be seen at the base of glands, representing an "in situ" carcinoma. Neoplastic cells extend within the epithelium in a "pagetoid" fashion and then invade the stroma in multiple foci [3]. These lesions are thought to represent preinvasive lesions.

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Diagnosis

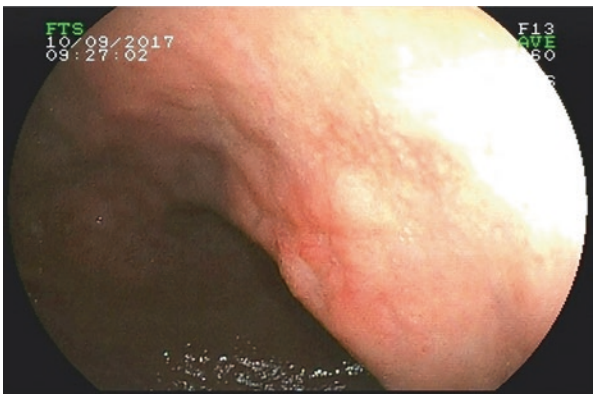
Detecting an early gastric cancer is a real challenge for the endoscopist. Diffuse early gastric cancer is even harder to diagnosis since mucosal alteration may be subtle. A careful and detailed examination, rinsing out any bubbles and mucous, is essential for spotting an early lesion. Japanese experience underscores the systematic inspection of the stomach, with extensive photodocumentation (>24 images). The location of the tumor in the stomach (cardia, fundus, body, antrum, and pylorus) and its relation to the esophagogastric junction (EGJ) for proximal tumors should be carefully recorded to assist with treatment planning and follow-up examinations [1].

What follow are the characteristics of suspicious-appearing gastric lesions that can be found endoscopically:

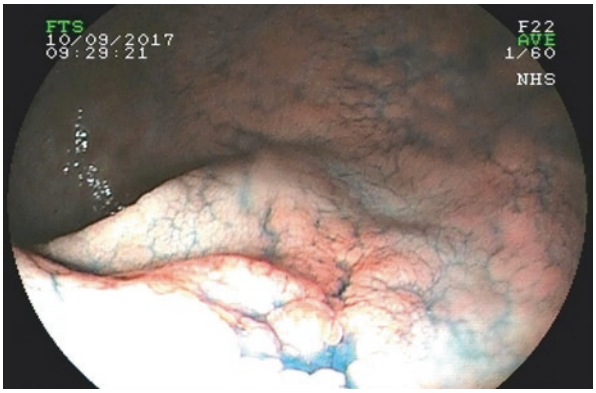
- Protrusion
- Redness
- Depression
- Erosion
- Convergence of folds
- Scar
- Loss of vascular pattern
- Bleeding

It is also important to be aware of the following characteristics in order to perform an adequate description of lesions:

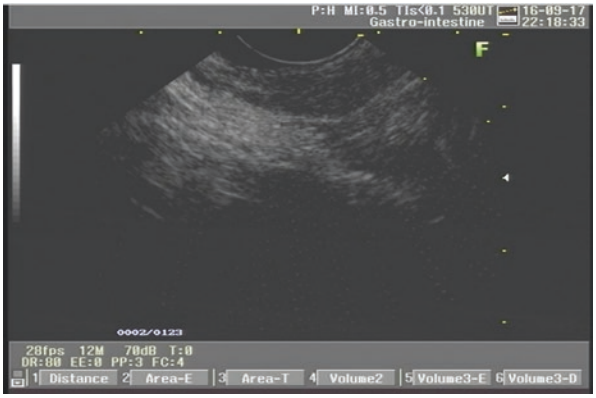
- Size and number
- Location (cardia, fundus, body, antrum, pylorus, EGJ)
- Extension (esophagus and duodenum)
- Macroscopic types/endoscopic classifications



Depressed lesion seen in white light endoscopy.



Indigo carmine chromoscopy.



Endosonography showing the involvement of the mucosa, submucosa, and muscular layers.

Chromoendoscopy (CE) involves the topical application of stains or pigments to improve tissue localization, characterization, or diagnosis during endoscopy. Use of methylene blue CE, particularly with magnification, improves identification of gastric lesions. CE with other dyes, such as indigo carmine, acetic acid, and hematoxylin, has also been shown to accurately differentiate between normal gastric mucosa and dysplastic or malignant gastric lesions [17–19].

A meta-analysis of 7 prospective studies, comprising a total of 429 patients and 465 lesions, showed that CE improves the detection of early gastric cancer ($p < 0.01$) and preneoplastic gastric lesions ($p < 0.01$) compared with standard white light examination [20]

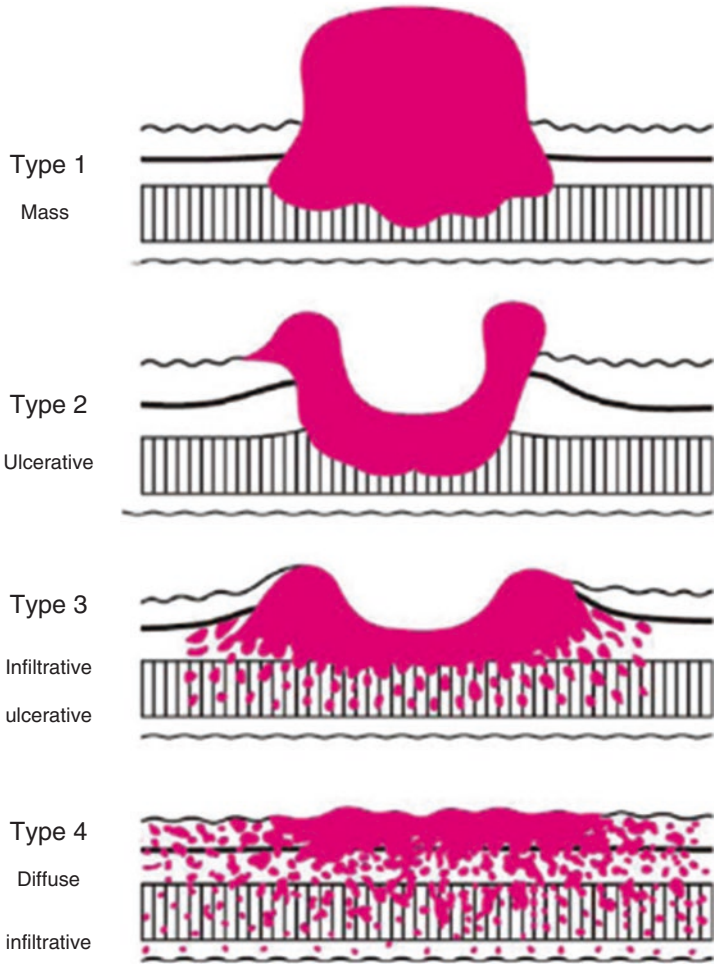
In particular, the diagnosis of early diffuse gastric cancer is hampered by the fact that the tumor cells begin infiltrating the mucosa while preserving a normal surface epithelium, and rarely are any visible lesions spotted endoscopically. To overcome this obstacle, a variety of different endoscopic surveillance protocols have been studied in individuals with *CDH1* mutations [21, 22]. Some of these studies demonstrated

that CE might increase diagnostic accuracy, and thus the researchers suggested that endoscopy may have a role in guiding the timing of total gastrectomy. However, even in these promising studies, endoscopic surveillance yielded false-negative results in a significant proportion of patients [23].

Endoscopic Classifications

Borrmann classification has been used since 1926 to categorize the macroscopic gross appearance of gastric tumors. This system contemplates only advanced gastric tumors, which are divided into four types:

Type 1: polypoid carcinomas, usually attached on a wide base
Type 2: ulcerated carcinomas with sharply demarcated and raised margins
Type 3: ulcerated, infiltrating carcinomas without definite limits
Type 4: nonulcerated, diffusely infiltrating carcinomas (*linitis plastica*)



Type 0 (superficial)	Typical of T1 tumors.
Type 1 (mass)	Polypoid tumors, sharply demarcated from the surrounding mucosa.
Type 2 (ulcerative)	Ulcerated tumors with raised margins surrounded by a thickened gastric wall with clear margins.
Type 3 (infiltrative ulcerative)	Ulcerated tumors with raised margins, surrounded by a thickened gastric wall without clear margins.
Type 4 (diffuse infiltrative)	Tumors without marked ulceration or raised margins, the gastric wall is thickened and indurated and the margin is unclear.
Type 5 (unclassifiable)	Tumors that cannot be classified into any of the above types.

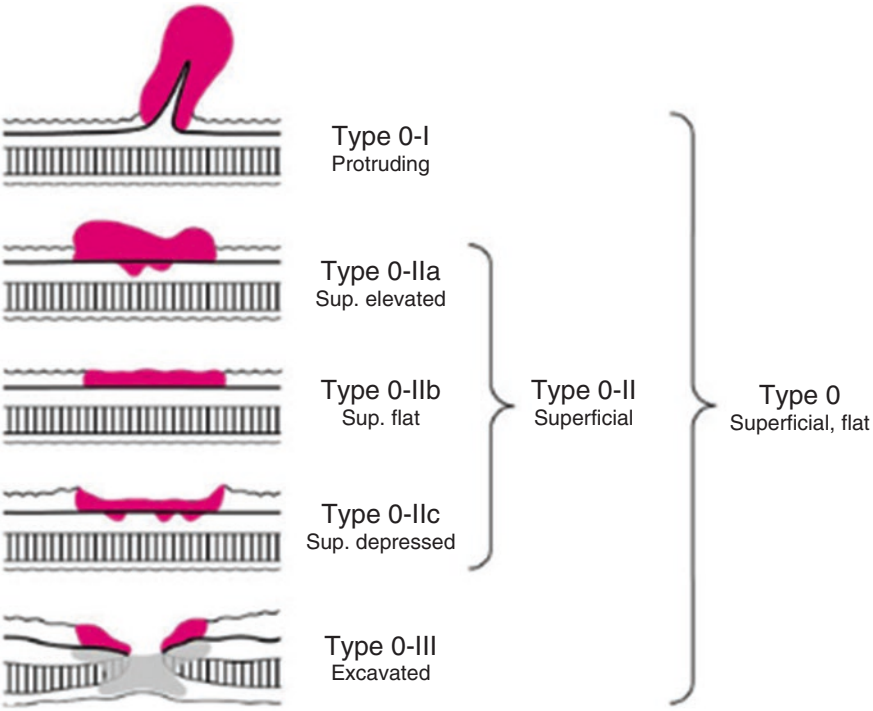
For early gastric cancers, the Japanese classification, as standardized by the Japanese Gastric Cancer Association (JGCA), is more commonly applied:

- Type I lesions are polypoid or protuberant and are subcategorized as follows:
  - Ip – pedunculated
  - Ips/sp – subpedunculated
  - Is – sessile
- Type II lesions are flat and are further subcategorized as follows:
  - IIa – superficial elevated
  - IIb – flat
  - IIc – flat depressed
  - IIc + IIa lesions – elevated area within a depressed lesion
  - IIa + IIc lesions – depressed area within an elevated lesion
- Type III lesions are ulcerated

A newer classification system for superficial lesions was proposed in 2002, at the workshop of Paris, with the participation of occidental and oriental endoscopists, surgeons, and pathologists. The Paris classification is very similar to the Japanese classification. Superficial lesions (type 0) are classified as polypoid, nonpolypoid, or excavated:

- Type 0-I lesions are polypoid and subcategorized as follows:
  - Type 0-Ip – protruded, pedunculated
  - Type 0-Is – protruded, sessile
- Type 0-II lesions are nonpolypoid and subcategorized as follows:
  - Type 0-IIa – slightly elevated
  - Type 0-IIb – flat
  - Type 0-IIc – slightly depressed
- Type 0-III lesions are excavated

Mixed types (e.g., 0-IIa + IIc) are classified similarly to the Japanese system.



Biopsy

Type 0-I (protruding)[a]	Polypoid tumors.
Type 0-II (superficial)[a]	Tumors with or without minimal elevation or depression relative to the surrounding mucosa.
Type 0-IIa (superficial elevated)[a]	Slightly elevated tumors.
Type 0-IIb (superficial flat)	Tumors without elevation or depression.
Type 0-IIc (superficial depressed)	Slightly depressed tumors.
Type 0-III (excavated)	Tumors with deep depression.

[a] Tumors with less than 3 mm elevation are usually classified as 0-IIa, with more elevated tumors being classified as 0-I

A single biopsy has a 70% sensitivity for diagnosing an existing gastric cancer, while performing seven biopsies from the ulcer margin and base increases the sensitivity to greater than 98% [4]. Multiple (six to eight) biopsies using standard size endoscopy forceps should be performed to provide adequate sized material for histologic interpretation, especially in the setting of an ulcerated lesion. Larger forceps may improve the yield [1]. It is important to point out that if endoscopic resection is being considered, the number of biopsies should be reduced as much as possible (one to three fragments); otherwise the inflammatory response and tissue scarring would difficult the endoscopic approach.

The diagnosis of a particularly aggressive form of diffuse-type gastric cancer, so-called linitis plastica, can be difficult endoscopically. Because these tumors tend to infiltrate the submucosa and muscularis propria, superficial mucosal biopsies may be falsely negative [5]. Poor distensibility of the stomach or the classic appearance on barium swallow (described as a leather flask in appearance) may suggest the presence of this disease.

Endoscopic Ultrasonography Staging

Endoscopic ultrasound (EUS) performed prior to any treatment is important in the initial clinical staging of gastric cancer. Careful attention to ultrasound images provides evidence of depth of tumor invasion (T-category), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N-assessment), and occasionally signs of distant spread, such as lesions in surrounding organs (M-category) or the presence of ascites. This is especially important in patients being considered for endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) [1].

Endoscopic ultrasound (EUS) accuracy for locoregional staging was recently calculated in a meta-analysis conducted by Mocellin et al., who found the EUS diagnostic accuracy to be clinically useful, mainly to differentiate T1-2 from T3-4 lesions (sensitivity: 86%, specificity: 91%); however, the researchers warned that for T1a/T1b differentiation and node invasion determination, a certain heterogeneity remained to be elucidated for defining the exact role of EUS in the staging of early and advanced gastric cancer [10].

In comparative studies of preoperative staging, EUS generally provides a more accurate prediction of T stage than does computed tomography (CT) [11, 12], although newer CT techniques (such as three-dimensional multidetector row CT) and magnetic resonance imaging may achieve similar results in terms of diagnostic accuracy in T staging [13]

Mainly, EUS is of value for patients with early gastric cancer because accurate assessment of submucosal invasion is essential before considering EMR. Neoadjuvant chemotherapy or chemoradiotherapy may be recommended for patients with a primary tumor that is considered to invade the muscularis propria (T2 or higher) or with a high suspicion of nodal involvement in pretreatment staging studies.

In light of these considerations, EUS is now recommended for pretreatment evaluation of gastric cancer in patients who have no evidence of metastatic (M1) disease in guidelines from the National Comprehensive Cancer Network [1].

Treatment

Correctly identifying disease limited to the mucosa or submucosa (T1 tumors) is key to selecting patients who are suitable for endoscopic treatment. There are usually two options of management: EMR and ESD.

Early Gastric Cancer

The presence of lymph node metastases is considered one of the most significant prognostic factors for overall and disease-free survival in patients with gastric cancer. Therefore, it is essential to highlight the potential lymph node involvement with appropriate surgery and consequently with extended lymphadenectomy but also to propose postoperative chemotherapy when indicated.

In Europe and the USA, the EORTC St. Gallen International Expert Consensus defines the indications for endoscopic resections of early gastric cancer, largely following JGCA guidelines, except for gastric cancers with diffuse histology for which surgery is considered obligatory [6]. Thus, it is not recommended to perform endoscopic resection for early signet-ring cell gastric cancer in Western countries, whatever the depth of invasion in the gastric walls. In Asia, SRCC that is limited to the mucosa,

nonulcerated, and less than 2 cm in size can be resected by submucosal endoscopic resection, according to the expanded criteria [7]. Ha et al. [8] supported this indication by demonstrating no lymph node metastasis in 77 patients with early gastric cancer confined to the mucosa, less than 2 cm in size, and with no lymphatic involvement.

Incidence of lymph node metastasis (LNM) in early gastric cancer

Depth of invasion	Tumor size	Ulcerated × not ulcerated	Incidence of LNM	Treatment
Mucosal	<2 cm	Not ulcerated	0%	ESD/surgery
		Ulcerated	2%	Surgery
	2–3 cm	Not ulcerated	1.7%	Surgery
		Ulcerated	2.4%	Surgery
	>3 cm		7.3%	Surgery
Submucosal (sm1)	<3 cm		NC	Surgery
	>3 cm		6.5%	Surgery
Submucosal (sm2)	<3 cm		NC	Surgery
	>3 cm		NC	Surgery

According to Gotoda et al. [9]

Advanced Gastric Cancer

Endoscopic resection is not possible for advanced gastric cancer. Surgical resection is then essential to treat these tumors, combined with an adequate lymphadenectomy, in order to assess the patient's prognosis (proper TNM staging), avoid stage migration, and propose the most appropriate therapeutic strategy. The endoscopist must provide detailed information about tumor location and extension (e.g., distance from cardia, fundus involvement, walls involvement, incisura) for proper surgical planning.

Hereditary Screening

The early gastric cancers that develop in individuals with hereditary inheritance are often multifocal and located beneath an intact mucosal surface [14]. Because of the difficulty in early detection and the poor prognosis of these tumors when locoregionally advanced, patients with evidence of a *CDH1* germline mutation in the context of a family history of HDGC are candidates for prophylactic gastrectomy. However, the timing of this operation may vary according to the preferences and age as well as the physical and psychological fitness of the individual.

For individuals with a *CDH1* mutation in whom gastrectomy is not currently being pursued (e.g., through patient choice or existence of physical or psychological comorbidity), regular endoscopy should be offered (annual). However, patients should be aware that delaying surgery can be hazardous [24].

Due to the tiny *foci* of signet-ring cells, which can only be recognized by microscopy, multiple biopsies are required to maximize the likelihood of diagnosing them [26]. Any endoscopically visible lesions should be biopsied, including pale areas. Additionally, random sampling should be performed; this would involve five biopsies taken from each of the following anatomical zones: prepyloric area, antrum, transitional zone, body, fundus, and cardia. A minimum of 30 biopsies is recommended, as described in the Cambridge protocol [24, 25].

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