Endoscopy in Early Gastrointestinal Cancers, Volume 1

Diagnosis

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Foreword

I am very much pleased to introduce this book entitled *Endoscopy in Early Gastrointestinal Cancers* from Springer. This book consists of two parts, that is, Volume I focuses on "Diagnosis" and Volume II focuses on "Treatment." All of the contributors of this book are the members of ANBIIG (Asian Novel Bio-Imaging and Intervention Group). I would like to provide introductory remarks for Volume 2—Treatment in the preface here.

The history of endoscopy over the past three decades has been marked by steady and rapid progress in endoscopic treatment, starting from the development of the video endoscope in 1983, which led to more progress in the subsequent years. The period during the 1980s was characterized by improvements in endoscopic treatment of early gastrointestinal cancers using endoscopic mucosal resection (EMR). In the 2000s, the rapid dissemination of endoscopic submucosal dissection (ESD) has led to further advances in endoscopic treatment, while the introduction of the HDTV endoscope to the market in 2002, together with more recent innovations such as image-enhanced endoscopy (IEE) and magnifying endoscopy, has provided the basis for a new diagnostic study.

Historically, ANBIIG was founded as a nongovernmental organization (NGO) in 2013. At first, in the first four years, more than 45 workshops have been conducted, and more than 2000 young doctors received comprehensive trainings. Throughout all those trainings, we came to realize the necessity to establish an actual consensus on how much Asian practitioners have common knowledge of endoscopic diagnosis related to IEE.

"ANBIIG Consensus Meeting" was started in January 2016, aiming to figure out consensus on the present situation of Asia in the field of endoscopic diagnosis of early gastrointestinal cancers. The policies of ANBIIG activities comprise the aim, the means, and also the performers taking part in healthcare practices. These policies were "**ORIGINATED IN ASIA**," "**DEVELOPED BY ASIA**," and "**OPTIMIZED FOR ASIA**." We set our destination to be most suitably optimized and implemented in Asia. In reality, there is a big difference between Asian and Western countries in many ways, such as frequency of disease and ways of thinking and practices.

We, in charge of clinical practices in Asia, are striving to provide meaningful results from our research by Asian endoscopists, widely. Back in the day, we used to learn most of medicine from Western countries. However, I believe that we have now reached "**Asian Endoscopic Revolution**."

I would like to emphasize the importance and benefits of ANBIIG Consensus in Asia, which is being realized now. For example, IEE diagnosis was unified as Asian Guideline, which is to deliver consistent diagnostic procedures as daily practices with the same contexts, to prevent any deviations at teaching and learning procedures, skills, and knowledge on IEE, and also to optimize IEE practices in Asia. It is important to lift up the level of standard in the field of Asian endoscopic diagnosis, which will lead to early diagnosis and treatment. Also it is expected that Asian endoscopic medicine will develop and expand globally from now.

I regard this Consensus as the best compass for the journey on "**ASIAN IEE OCEAN**," which certainly guides young and ambitious Asian practitioners to master IEE diagnosis. And it will increase the number of IEE practitioners in Asia for sure.

In this book, based on the above background, indications for endoscopic resection of early GI cancers, real procedure of EMR, real procedure of ESD, management of noncurative resection and local recurrence after endoscopic resection, complications of endoscopic resection, and management for each organ are stated by experts as easy to understand and in detail. In the last chapter, special ESD cases illustrations are mentioned for every country as in Japan, China, Korea, and Hong Kong SAR, which makes it educational and fascinating.

I hope that doctors who are about to start ESD, those who are confronted with difficulties during conducting ESD in real, and also those who are at the side to direct ESD would read this book of practices widely in Asia. And then, all those doctors can enter the matured world of endoscopic resection of early GI cancers and perform their value at an advanced level. It would be grateful for me if those who read this book could heal as many patients as they could as one of skillful practitioners of Asia-Pacific Society for Digestive Endoscopy.

I believe that the contents covered by this book will give our readers the confidence to take on the unity of clinical medicine in the field of endoscopic diagnosis, which has surmounted the problems associated with conventional manners and advanced new functional studies.

Finally, I would like to express my deepest gratitude to the many doctors and compiling staffs who contributed to this book even though they were very busy.

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Foreword

I wish to congratulate the success of experts from the Asian Novel Bio-Imaging and Intervention Group (ANBIIG) to publish these important books on diagnostic and therapeutic for early gastrointestinal cancers. Gastrointestinal cancers are among the commonest cancers worldwide with significant risks in cancer-related mortality. Gastric and esophageal cancers had been an important cause of cancer mortality in Asia, with 70% of patients with gastric cancers coming from Asia. Recently, there is an increase in the number of patients diagnosed to have colorectal cancers worldwide which incurs concerns from gastroenterologists, surgeons, oncologists as well as the government in diagnosis and treatment of these cancers. To impact on the prognosis, it is essential to diagnose these gastrointestinal cancers at an early stage.

Image-enhanced endoscopy had been tremendously advanced over the past decade, with the clinical application of technologies including narrow band imaging and magnifying endoscopy demonstrating the effect of improving recognition and characterization of early gastrointestinal cancers. The mission of ANBIIG is to provide a learning platform for education and training of novel endoscopic imaging and therapeutic technologies for Asian endoscopists. I must congratulate the success of ANBIIG in achieving this goal, as more than 110 workshops in Asia, providing training for more than 7,000 healthcare professionals. Moreover, two consensus papers were published on standards and quality of endoscopy for diagnosis of early gastrointestinal cancers.

One of the important initiatives for education and training of ANBIIG is to publish two books focusing on the diagnosis and endoscopic treatments. These books served as important educational material to propagate exchange of knowledge in these areas. Serving as an advisor for ANBIIG, I am delighted to see these books published with high quality in the content.

With the current advances in artificial intelligence and robotics, I look forward to future technological advances in diagnosis and treatment of early gastrointestinal cancers as well as additional chapters on these topics in the second edition of these books.

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1 Esophago-Gastrointestinal Pathology on Early Carcinoma for Endoscopists

Takahiro Fujimori

1.1 Introduction

General rules for treatment of early carcinoma have been determined in cooperation by clinicians, pathologists, and radiologists belonging to the Japan Esophageal Society (JES) [1], the Japanese Research Society for Gastric Cancer (JRSGC) [2], and the Japanese Society for Cancer of the Colon and Rectum (JSCCR) [3, 4], with repeated revision from the 1960s to the 1990s in Japan. One of the purposes of this chapter is to introduce the latest information on them.

We describe the items regarding histopathological diagnosis to introduce topics in Japan by extracting these rules in this chapter.

1.2 Developments and Normal Structure

Gastrointestinal tract, which is originally a simple tube, forms different organs with the development. Formation of the gastrointestinal tract starts with tubulation of endoderm by folding of early embryo. As a result of craniocaudal folding, saclike foregut and hindgut are formed in the head and tail of the embryo. The midgut in between is widely in contact with the yolk sac at first, and subsequently becomes tubular being in contact with yolk sac only through yolk duct.

For gastrointestinal tract, the part from pharynx to around opening of duodenal common bile duct originates in foregut, and the part from the remaining of duodenum to right two-third of transverse colon and the part from light one-third of transverse colon to the upper anus originates in in midgut and hindgut, respectively. In addition, generally, while endoderm lining of intestinal tract differentiates into epithelium controlling digestive and absorptive function, splanchnic mesoderm around endoderm differentiates into lamina propria, submucosal tissue, muscularis mucosae, and muscle layer. Neural crest cells entering into the bowel wall by cell migration differentiates into ganglion cell to form plexuses beneath the mucous membrane or in between muscle layers

1.2.1 Esophagus

The length of esophagus is approximately 25 cm with tube from the pharynx with height at the level of Sixth cervical vertebra to the esophagogastric junction with height at the level of 11th thoracic vertebra. There are sphincters in pharyngoesophageal junction and gastroesophageal junction to prevent inhalation of air from phar-

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ynx and reflux from stomach to esophagus by closing lumen at any other time but swallowing movement. In adults, the depth from the incisors to the upper esophageal sphincter is 15–18 cm, and to lower esophageal sphincter is 37–40 cm. The diameter of esophagus is 1.5–2.5 cm with a tendency of the lower half of lumen being larger and the largest part being above the diaphragm (esophageal hiatus). The lumen of esophagus is covered by stratified squamous epithelium having a sufficient protective function. The lymphocyte population exists in the lamina propria underneath the epithelium. There are small mucous glands in submucosal tissue under the muscularis mucosae. The inner circular layer is clearly distinguished from the outer longitudinal layer in the muscle layer. It is said that the first stage of swallowing movement is voluntarily adjustable with striated muscle in muscle layer of the upper one-third part of esophagus.

At the outside of muscle layer, blood vessel rich adventitia extends to the surrounding connective tissues. The upper esophageal sphincter includes the cricopharyngeal muscle constituting the lowest part of hypopharyngeal sphincter. The lower esophageal sphincter is called LES with specific function and response for various stimulus. This lower esophageal sphincter causes the formation of high-pressure zone by tonic contraction even during non-active stage to separate esophageal lumen from gastric lumen. Normal pressure of lower esophageal sphincter is 15–35 mm Hg.

1.2.2 Stomach

Stomach can be anatomically divided into cardia, fundus, corpus, pyloric antrum, and pylorus. It is histologically divided into three areas containing cardiac gland, fundic gland, and pyloric gland. There are boundaries between each area, which is readily modified by age and inflammation. The gastric glands consisting of units of secretory part and the opening part as gastric pits (foveola, crypt, pit) are recognized as groove or depression from the mucosal surface gathering to form atypical mucosal elevation, which is called gastric area.

The surfaces of gastric mucosa and gastric pits (foveola, crypt, pit) are covered by columnar epithelium. This cell is called surface mucus cell because of the secretory ability of special mucus with the secretion fluid which is insoluble in hydrochloric acid to protect mucous membrane from hydrochloric acid. Surface mucus cells accompanied by goblet cells or cilia represents metaplasia.

The lamina propria of corpus is occupied by fundic glands including a few fundic glands producing opening into gastric pits (foveola, crypt, pit). Fundic glands consist of three types of cells as principal cell, parietal cell, and mucous neck cell. Principal cells exist in the deepest part to produce pepsinogen, a precursor of pepsin. Parietal cells are disseminated throughout the intermediate layer to secrete hydrochloric acid. Mucous neck cells exist at the side of gastric pit (foveola, crypt, pit) to secrete mucus. Cardiac glands and pyloric glands are both mucous glands.

Fundic gland and pyloric gland include cells having endocrine factor other than the above exocrine cells. Especially in pyloric gland, endocrine cells are substantially observed including 50% of G cells (gastrin-secreting), 30% of enterochromaffin cells (EC cell, serotonin-secreting), 15% of D cells (somatostatin-secreting). The main endocrine cells in fundic glands are EC-like (ECL) cells to secrete histamine and also include EC cells and a small amount of X cells (secretion is unspecified). The layer of gastric wall consists of surface epithelium, lamina propria, muscularis mucosae, submucosa, and muscle layer.

1.2.3 Colon and Rectum

Large intestine is an organ with the total length of approximately 1.5 m consisting of vermiform appendix, caecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. Unlike small intestine, large intestine has no plicae circulares or villi with formation of lam-

ina propria by crypts formed by simple tubular glands. Large intestine wall underneath consists of submucosa, muscle layer, and serosa. The surface of crypt is covered by absorptive epithelial cells with a number of goblet cells. Although absorptive epithelial cells are similar to absorptive epithelial cells of the villi in the small intestine, the microvilli of the brush border have a length of a half of that in the small intestine. The function of this cells is to absorb large volumes of water and electrolytes.

Observation by electron microscope demonstrates existence of secretory granule with very small diameter around the upper end of absorptive epithelium, indicating an opening into the upper surface of cells. Acid mucopolysaccharide detected in this granule is considered to secrete sugar coating components on the surface of microvilli. In addition, presence of IgA in the upper part of nucleus has been confirmed, indicating that secretory IgA are aggregated in this granule to be released.

Goblet cells are observed in crypt more than surface epithelium, especially in the lateral wall. Mucus of goblet cells show positive for alcian blue staining, suggesting intestinal type mucus and also, intestinal type mucus shows positive for high iron diamine (HID) staining.

Many basal granulated cells appear on the crypt epithelium with several types of cells other than enterochromaffin cell (EC cells, serotonin secreting), although hormonal secretion is unknown.

Table 1.1 Mucin staining requiring diagnosis and the location

Core protein	Secretion Membrane binding	Region
MUC 1	Membrane	Pancreatic acinus, mammary gland
MUC 2	Secretion	Small intestine, large intestine goblet cell respiratory tract
MUC 3	Membrane	Small intestine, large intestine, gallbladder
MUC 4	Membrane	Large intestine, respiratory tract
MUC5AC	Secretion	Gastric surface epithelium
MUC5B	Secretion	Esophageal glands, respiratory tract, salivary glands
MUC 6	Secretion	Pyloric gland, cardiac glands, mucous neck cell of stomach, duodenal Brunner's glands, esophageal cardiac gland
MUC 7	Secretion	Salivary glands

Table 1.2 Macroscopic classification

Type 0: Superficial type
Type 1: Protruding type
Type 2: Ulcerative and localized type
Type 3: Ulcerative and infiltrative type
Type 4: Diffusely infiltrative type
Type 5: Unclassifiable type
Type 5a: Unclassifiable type without treatment
Type 5b: Unclassifiable type after treatment

1.3 Definitions of Early Carcinoma in Japan and Macroscopic Type Classification in Esophago-Gastrointestinal Tracts (EGI) [1] (Tables 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6)

Principles of Tumor Type Classification

The tumor type classification is based on the macroscopic findings. Radiological and endo-

Table 1.3 Subclassification of superficial type (type 0)

Type 0-Ip: Superficial and protruding type
Type 0-Ip: Pedunculated type
Type 0-Is: Sessile (broad based) type
Type 0-II: Superficial and flat type
Type 0-IIa: Slightly elevated type
Type 0-IIb: Flat type
Type 0-IIc: Slightly depressed type
Type 0-III: Superficial and excavated type

Combined type: When multiple macroscopic tumor types are mixed in one lesion, it is called a combined type. The wider type is described first and types are connected with +

Table 1.4 Esophagus: depth of tumor invasion (T)

TX: Depth of tumor invasion cannot be assessed
T0: No evidence of primary tumor
T1a: Tumor invaded mucosa *Note 1*
T1a-EP: Carcinoma in situ (Tis: M1)
T1a-LPM: Tumor invades lamina propria mucosa (LPM: M2)
T1a-MM: Tumor invades muscularis mucosa (MM: M3)
T1b: Tumor invades submucosa (SM)
SM1: Tumor invades the upper third of the submucosal layer
SM2: Tumor invades the middle third of the submucosal layer
SM3: Tumor invades the lower third of the submucosal layer
T2: Tumor invades muscularis propria (MP)
T3: Tumor invades adventitia (AD)
T4: Tumor invades adjacent structures (AI)

In endoscopically resected specimens, a tumor invading the submucosa to a depth of 200 μm or less from the lamina muscularis mucosa is classified as SM1, while a tumor extending more than 200 μm is classified as SM2

Table 1.6 Depth of submucosal invasion in T1 (SM) colon carcinomas [3, 5]

1. When it is possible to identify the muscularis mucosae, the depth of submucosal invasion is the distance between the deeper edge of the muscularis mucosae and the deepest invasion
2. When it is not possible to identify the muscularis mucosae, the depth of submucosal invasion is the distance between the surface of the tumor and the deepest invasion
3. In polypoid tumor (Ip) with **disrupted muscularis mucosae**, the depth of submucosal invasion is the distance between the deepest invasion and the **Haggitt level 2 line** being defined as the boundary between the tumor head and the pedicle
When cancer does not invade beyond the level 2 line, it is defined as **head invasion** Migration of adenomatous glands (pseudocarcinomatous invasion or submucosal misplacement) should be differentiated from true submucosal invasion

Table 1.5 Comparison of Japanese classification in early carcinoma of EGI tracts with UICC

	Esophagus		Stomach		Colon	
	UICC	JES	UICC	JRSGC	UICC	JSCCR
Tis	Carcinoma in situ (CIS)/ high grade dysplasia	CIS(Tis)	Carcinoma in situ (CIS)		CIS and invasion of lamina propria	Tis M
T1	M/SM	M/SM	M/SM	M/SM	SM	SM
T1a	Tumor invades mucosa and muscularis mucosa	T1a-LPM(M2) or T1a-MM(M3)	Tumor invades mucosa and muscularis mucosa	M		T1a (SM_1) < 1 mm
T1b	Tumor invades submucosa	T1b SM1 SM2 SM3 (SM1 ≦ 0.2 mm)	Tumor invades submucosa	SM T1b1 < 0.5 mm T1b2 ≧ 0.5 mm		T1b (SM_2) ≧ 1 mm
		Japan Esophageal Society (JES)		Japanese research Society for Gastric Cancer (JRSGC)		Japanese Society for Cancer of the colon and Rectum (JSCCR)

Regardless of the presence of lymph node or distant organ metastasis, T1a can be designated as early esophageal carcinoma and T1 can be designated as early carcinoma of stomach and colorectum in Japan

scopic classifications are based on the macroscopic classification.

Tumors in which invasion is macroscopically diagnosed to be limited to within the submucosa are classified as superficial type (early carcinoma: Tis/T1), while tumors in which invasion is diagnosed to extend to the muscularis propria (MP) or beyond are classified as T2–4.

The superficial type has the prefix "0" and is classified into 0-I, 0-II, or 0-III. The carcinomas of EGI with more than invasion to MP is divided into four categories: 1, 2, 3, or 4. When a tumor cannot be classified into any of the 5 (0–4) categories or their combinations, it is classified as 5.

1.4 Handling of Endoscopic Resected Specimen [1]

Macroscopic Examination and Handling of Endoscopically Resected Specimens

Specimens obtained by complete endoscopic excision (en bloc excision) are handled as follows. Whenever possible, specimens obtained by partial excision should be handled as those obtained by complete endoscopic excision.

1. Stretching and fixation

   When the lesion is sessile type or superficial type, the specimen is stretched lightly, pinned with the mucosal side up to a flat board with stainless steel pins, and then completely immersed with the mucosal side down in a container of formalin solution. Polyps are immersed in formalin solution immediately.
2. Macroscopic examination

   The side of the resected specimen and the following features of the tumor are recorded; side, macroscopic type, length of the stalk, surface appearance, color, and distances from horizontal/lateral and vertical/deep margins.

   It is recommended that the resection margins are marked with ink immediately after endoscopic excision.
3. Sectioning

   Pedunculated polyps with a thick stalk (2 mm or more in diameter): The first cut is made 1 mm from the center of the stalk and the polyp is sectioned at 2 mm intervals. The entire polyp is sectioned and examined histologically.

   Pedunculated polyps with a thin stalk (less than 2 mm in diameter): The stalk is totally embedded in paraffin and thin sections of the paraffin block are cut for examination.

   Sessile lesion and superficial type lesion:

   The specimen if cut at 2 mm intervals to determine the margin of clearance.

   Stereomicroscopic examination can be useful for identifying the extent of the lesion and for proper sectioning.

   In principle, all section lines are made in the same direction. However, sectioning in different directions is permissible when necessary.

   If submucosal invasion is suspected, then the first cut should be made in longitudinal axis 1 mm from site of suspected deepest invasion.
4. Photography

   Photography is performed before and after sectioning.

   To make a histological map of the tumor, it is essential to photograph the tumor with section lines.

   Shallow section lines in the mucosal surface are recommended for photography.

1.5 Topics of Esophago-Gastrointestinal Pathology in Japan

1.5.1 Esophagus: Barrett Adenocarcinoma [1] (Table 1.7)

Barrett adenocarcinoma is an adenocarcinoma arising from Barrett mucosa. Barrett mucosa is

Table 1.7 Barrett esophagus

The esophageal having Barrett mucosa is designated Barrett esophagus
At least one of the following conditions must be satisfied:
1. Esophageal glands in the area of columnar epithelium
2. Squamous islands in the columnar epithelium
3. Double layer structure of muscularis mucosa

defined as columnar epithelium extending from stomach to esophagus in succession. While it must be associated with intestinal metaplasia as the definition in Europe and the United States, presence/absence of intestinal metaplasia is not considered in Japan. Recently, some researchers in Europe and the United States reported that presence/absence of intestinal metaplasia is not taken into account. Circumferential Barrett mucosa with the length of 3 cm or more is defined as long segment Barrett esophagus (LSBE), and Barrett mucosa which is not circumferential with the length of less than 3 cm in some part is defined as short segment Barrett esophagus (SSBE).

Intestinal metaplasia (involvement of CDX2, etc.) is considered to arise from metaplasia of the gastric metaplasia due to abnormality in differentiation of esophageal squamous stem cells or circulating bone marrow stem cells associated with chronic inflammation.

Adenocarcinoma of esophagus may include invasion to esophagus of gastric cardia adenocarcinoma and Barrett adenocarcinoma, those which are difficult to distinguish for progressed cancer. Although there is concern for increase in adenocarcinoma of the esophagogastric junction including Barrett adenocarcinoma with decreasing *H. pylori* infection rate in Japan, the frequency of Barrett adenocarcinoma among esophageal carcinoma in Japan is currently lower compared with that in the EU or the United States (small percent of esophageal carcinoma).

For stage of adenocarcinoma arising in Barrett mucosa, the rule is same as the previously mentioned rules for esophageal carcinoma. For this disease, however, sometimes there is new muscularis mucosa just under the columnar epithelium. In the Japanese classification, the primary muscularis mucosa is called deep muscularis mucosa (DMM), and the new muscularis mucosa is called superficial muscularis mucosa (SMM). The identification of SMM and DMM is occasionally difficult due to fusion of both of the layers, thickness, and irregularity.

When the location of muscularis mucosae and cancer invasion are evaluated, careful evaluation may be required for endoscopic therapy, including evaluation of vessels invasion. This is the issue that does not exist in other EGI together with muscularis mucosae-tangled case of Ip cancer of large intestine.

1.5.2 Stomach: Fundic Gland Type Tumor [6]

Recently, fundic gland type tumor has been a focus of attention as neoplastic change associated with non-Hp, with lesion which is difficult to be diagnosed by biopsy. It is sometimes difficult to distinguish benign tumor from malignant tumor. This disease caught the public's attention in 2010 as low-grade differentiated gastric cancer indicating differentiation to fundic glands with predominantly principal cell. MUC6 (mucous neck cell) or pepsinogen I becomes positive immunohistologically. Parietal cells stained by ATPase are often observed in tumor and this is considered to support the diagnosis. The appearance may be endoscopically similar to carcinoid. It is called oxyntic gland polyp/adenoma in Europe and the United States. This tumor is considered to be *H. pylori* negative; however, it also develops in *H. pylori* positive mucosa of the fundic gland. Therefore, it would catch the public's attention as a target of endoscopic therapy in the future.

1.5.3 Colon and Rectum

1.5.3.1 SSA/P with Cytological Dysplasia

Colorectal serrated lesions are pathologically classified as hyperplastic polyps (HPs), sessile serrated adenoma/polyps (SSA/Ps), or traditional serrated adenomas (TSAs). Of these, SSA/Ps and TSAs are regarded as premalignant lesions in the serrated neoplastic pathway to colorectal carcinoma (CRC). Thus, these serrated polyps have attracted much attention in the study of carcinogenesis [7].

SSA/Ps have molecular feature of activating point mutations in the *braf* and hypermethylation of CpG islands in the promotor of tumor suppressor (i.e., the CpG island methylation phenotype (CIMP)) [8]. Both these features are detected in

colorectal carcinomas with microsatellite instability (MSI), suggesting SSA/Ps are the most potent processor lesions of colorectal carcinomas.

Interval colorectal cancers (post-colonoscopy colorectal cancer: PCCRC) have been demonstrated to be more likely to exhibit CIMP and MSI than non-interval colorectal cancers, indicating SSA/Ps may also be precursor lesions of interval cancers [9]. Some SSA/Ps may be overlooked or incompletely removed because of their subtle, flat morphology, or indistinct borders, which can result in the development of interval cancers.

However, from the general statement of tumor, the problem of SSA/P is whether it is tumor or remains tumor-like lesion. It is currently considered to be tumor-like lesion; however, some consider as tumor because it is genetically monoclonal. Considering the diagnosis for tumor by both of cellular atypia and structural atypia, it may be difficult to make morphological diagnosis. On the other hand, no one would deny that SSA/P with cytological dysplasia is regarded as tumor based on morphological diagnosis [10].

Cytological dysplasia (CD) in the SSA/P was classified into the following four types: (1) conventional adenoma-like dysplasia, (2) serrated dysplasia with eosinophilic cytoplasm, (3) serrated dysplasia without eosinophilic dysplasia, and (4) "cryptal dysplasia (tentative name)." Conventional adenoma-like dysplasia was defined as dysplasia that cytologically looked similar to a conventional tubular or tubulovillous adenoma. Serrated dysplasia was subclassified into two types according to the presence or absence of prominent eosinophilic cytoplasm. Serrated dysplasia with eosinophilic cytoplasm was defined as dysplasia that cytologically looked similar to a TSA with prominent eosinophilic cytoplasm. Serrated dysplasia without eosinophilic cytoplasm was defined as dysplasia that cytologically looked similar to a TSA but exhibited no prominent eosinophilic cytoplasm.

Previously unreported type of CD localized in the crypt base was detected that could neither be classified as conventional adenoma-like dysplasia nor serrated dysplasia in some cases. Such cryptal dysplasia shows high Ki-67 index occasionally associated with abnormality in p53.

These diseases also may be a target of endoscopic therapy as second or third carcinoma in the aging society in the future. Lesions with over 10 mm of hyperplastic polyp-like appearance (IIa/LST) in the right side colon is the point of diagnosis in elderly person.

1.5.3.2 IBD Dysplasia/Carcinoma

Inflammatory Bowel Disease (IBD) associated with carcinoma/dysplasia (IBD dysplasia/carcinoma) is one of problems for pathological diagnosis. It is unlikely that characteristic histological findings of dysplasia (noninvasive tumor lesion associated with IBD) and cancer have become generalized.

These are sometimes called dysplasia/dysplasia-associated lesions and masses: DALMs, also taking into account macroscopic images.

IBD cancer includes standard differentiated adenocarcinoma, but has more poorly differentiated adenocarcinoma (por) or neuroendocrine cell carcinoma (NEC) than normal carcinoma. Even mucinous adenocarcinoma (muc) or Signet-ring cell carcinoma (sig) is sometimes seen [11]. The terms such as in situ anaplasia or pancellular type neoplasia has been proposed by Riddell et al. [12, 13]. There are several patterns for the form of dysplasia.

While nuclear atypia of adenomatous type neoplasia has similar form to standard adenoma (sporadic adenoma: SA), structural atypia has villious or club-shaped villi different from SA. Some patients show invasion in crypt. The invasion mode is also different from SA in terms of proliferation being different between cortical layer and deep part. Basal cell type neoplasia is not common and sometimes diagnosed as regenerating epithelium. As the features, stratified nuclei or nucleus rotundus called beluga caviar like nucleus rotundus associated with cascade nucleus without disorder of polarity should be focused on. Regarding clear cell type neoplasia, which can be regarded as serrated lesion, it is difficult to consider where the tumor lesion starts, similar to diagnosis of serrated lesions. It may be diagnosed as hyperplastic mucosa in some cases, possibly already associated with the invasion in the deep part. Additionally,

structural or cellular atypia associated with IBD cancer/dysplasia includes crawling glands and dystrophic goblet cells. There are problems with pathological diagnosis affecting the treatment option [14]. Clinicopathological efforts are required for uniform accessibility in the future. If increase in IBD cancer is expected, genetic diagnosis should be considered to narrow down subjects with complication of cancer (high-risk group) [15, 16].

On the other hand, malignant transformation of Crohn's disease (CD cancer) is still at the stage of case report in Japan. Recent statistics reported that the cumulative incidence rate of UC cancer is 2% in 10 years, 2.5–8% in 20 years, and 8–18% in 30 years of duration of illness as average data. In Japan, 5% in 10 year and 10% in 20 years according to the report. On the other hand, regarding CD cancer, there is report as 2–3% in 10 years, 5–6% in 20 years, and 8–9% in 30 years. The number of subjects is small in Japan with 1% or less. Historically, UC cancer has been reported in 1925 by Crohn and Rosenberg [17] for the first time and CD cancer has been reported in 1948 by Warren et al. [18] for the first time. In Japan, the number of subjects with long-term follow-up for IBD is increasing, indicating the possibility of increase in IBD cancer.

It has been demonstrated that the mode of carcinogenesis of UC cancer is different from that of sporadic colorectal cancer. A *p53* genetic mutation occurs at a relatively early stage, resulting in multiple premalignant lesions called dysplasia (tumor). The *p53* genetic mutation may occur in mucosa which cannot be morphologically diagnosed [19]. Subsequently, genetic abnormality involved in dysplasia-invasive carcinoma is added. The mechanism mediated reactive oxygen or nitrogen is considered as the cause of genetic mutation. Recently, a gene editing enzyme inducing mutation to DNA or RNA has been identified and it has been demonstrated that especially activation-induced cytidine deaminase (AID) develops *p53* genetic mutation at a high rate because of the persistent expression [20]. The results from the future research are required together with abnormal methylation of DNA and inflammatory carcinogenesis [21]. These early-stage lesions will be target for endoscopic therapy (for purpose of diagnosis and treatment).

1.5.3.3 Clinical Evaluation and Treatment of T1-Ip Type Carcinoma [3]

The subclassification of early carcinoma (0 type; superficial type) is as follows: I: Protruding type (Ip: pedunculated, Isp: subpedunculated, Is: sessile) and II: Superficial type (IIa: Slightly elevated type, IIb: Superficial and flat type, IIc: Slightly depressed type). The superficial type represents lesions possibly including Tis (intramucosal carcinoma), T1 carcinoma (submucosal invasive carcinoma). For macroscopic judgment of superficial type, endoscopic findings are taken priority for large intestine. There is even a term called LST (laterally spreading tumor) for laterally spreading tumor with a diameter of 10 mm or more [22].

Regarding Ip type carcinoma, disrupted muscularis mucosae in some cases cannot be measured the invasion depth. In reports on metastases to lymph nodes of Ip carcinomas [23], 384 cases were tabulated from multiple centers to investigate the rate of metastasis to lymph node/recurrence from observation period for 44 months in average. The rate of metastasis to lymph nodes in all cases was 3.5% and metastasis to lymph nodes and recurrence of head invasion cases were zero; however, the rate of metastasis to lymph nodes was 6.2% and the rate of recurrence was 0.8% in the pedicle invasion cases.

This is the reason why head invasion is clinically regarded as intramucosal invasive carcinoma. For T1 colorectal carcinomas only associated with head invasion, the rate of metastasis to lymph node/recurrence was extremely low, resulting in the conclusion that it is likely to be completely cured by endoscopic therapy.

This is clinically relevant for diagnosis of head invasion. Although T1 cancer (Ip) is a lesion which can be completely cured by endoscopic therapy, sufficient accuracy control of endoscopic excision and pathological diagnosis is necessary. In the future, in case of diagnosis made for Ip type carcinoma, a strategy to directly

measure from level 2 line as intramucosal carcinoma for head invasion, and SM (T1) carcinoma for pedicle invasion is important to consider additional surgery.

1.6 Conclusion

In this issue, we have discussed the early carcinomas of EGI tracts and several problems and Japanese topics related to the pathological diagnosis.

We hope that this English textbook will be widely accepted and used worldwide to bring about improvements in quality of diagnosis, treatment, and prognosis of patients with early carcinomas in EGI tracts.

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Morphological Description of Early GI Neoplasia

2

Shinji Tanaka

The Paris classification has been widely used as a macroscopic classification of superficial neoplastic lesion in colon (Fig. 2.1) [1]. In brief, it is divided into polypoid and non-polypoid (superficial) lesion. In this classification, the height of the 0-Is lesion is clearly defined in each organ. As for neoplasia in the columnar epithelium (Barrett's esophagus, stomach and colon), 0-Is lesion is determined to be higher than 2.5 mm (the height of the closed biopsy forceps). On the other hand, regarding neoplasia in the squamous cell epithelium, 0-Is lesion is determined to be higher than 1 mm. The reason for this is based on the fact that esophageal squamous carcinoma higher than 1 mm shows high frequency of submucosal invasion.

In Japan, in esophagus and stomach 0-Ip and 0-Is are got together into 0-I. Because of the difficulty in exact measuring of the height of the lesion in clinical practice, gastric 0-Is is determined to be higher than about 2–3 mm. However, regarding neoplasia in the squamous cell epithelium, 0-I lesion is determined to be higher than 1 mm as well as Paris classification. As for colorectal lesion in Japan, polypoid type is divided three subtypes: 0-Ip, 0-Isp (subpedunculated) and 0-Is (Fig. 2.2). Also, the absolute height is not defined and macroscopic type emphasize the real shape of the lesion based on the reason I mentioned above. As there are no acid and peptic ulcer, Japanese classification does not include 0-III in early colorectal neoplasia.

The term "laterally spreading tumor" (LST) was originally proposed by Kudo for colorectal tumors that tend to extend laterally and circumferentially, rather than vertically along the colonic wall [2]. Recently, the concept of LST has been accepted not only in Japan but also in Western countries (Fig. 2.3) [3]. LSTs are divided into two subtypes based on their detailed endoscopic appearance: granular type (LST-G), which has even or uneven nodules on the surface, and non-granular type (LST-NG), which has a smooth surface. Furthermore, each type has two subtypes: LST-G has a "homogeneous type" and a "nodular mixed type," while LST-NG has a "flat elevated type" and "pseudodepressed type."

Besides, the term "LST" is not the terminology for morphologic classification [3]. The term LST is a nickname for superficially spreading tumor [3]. Relationship between macroscopic classification and LST subclassification is described in Fig. 2.3. Generally, LST-G homogeneous type has a lower malignant potential than LST-G nodular mixed type, and that LST-G homogeneous type has a very low frequency of submucosal invasion [4, 5]. On the other hand, LST-NG, pseudodepressed type shows a higher

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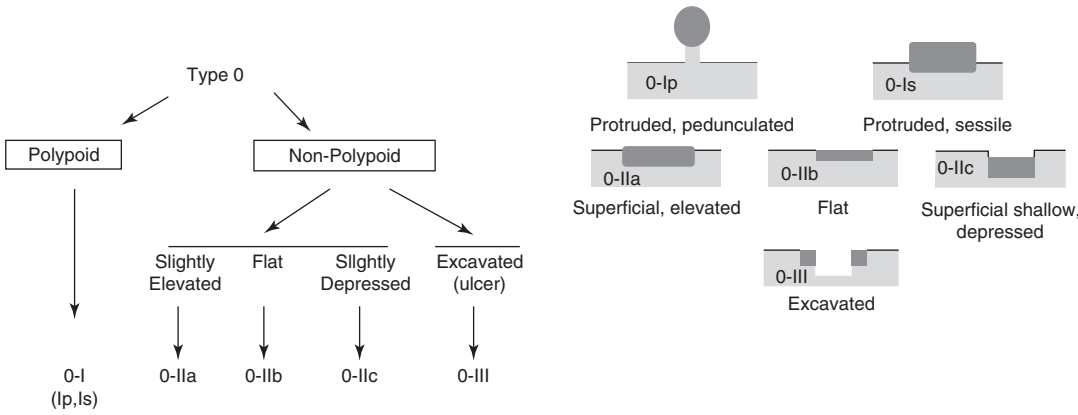

Fig. 2.1 The Paris endoscopic classification of superficial neoplastic lesions; esophagus, stomach, and colon. November 30–December 1, 2002, Participants in the Paris Workshop, Paris, France

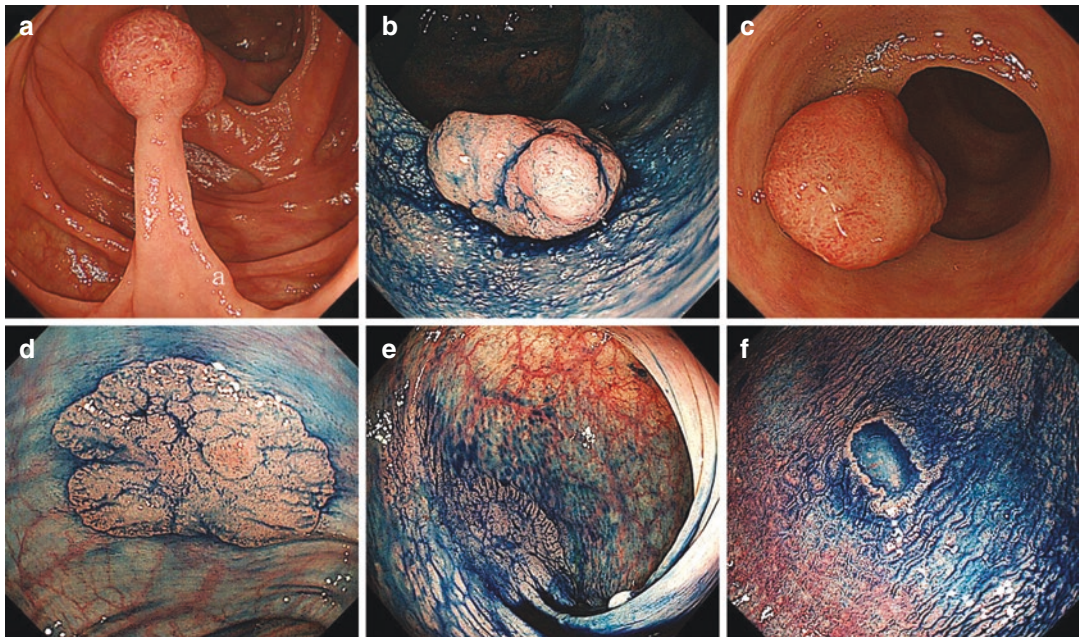

Fig. 2.2 Each lesion among macroscopic classification (colorectal tumor). (**a**) 0-Ip type, polyp with distinct stalk, (**b**) 0-Isp type, subpedunculated shape (globular shape), (**c**) 0-Is type, broad based polypoid lesion, (**d**) 0-IIa type, superficial flat elevated shape, (**e**) 0-IIb type, height of the lesion is almost equal to surrounding normal mucosa, (**f**) 0-IIc type, superficial depressed shape often accompanied by slight marginal elevation (reactive hyperplasia)

malignant potential and has a very high frequency of submucosal invasion, often multifocally [4, 5].

The recognition of detailed gross appearance and its classification is very important in daily endoscopic examination. Although there are few reports in this point of view [6], for recognition of the detailed gross appearance contrast chromoendoscopy such as indigo carmine dye spraying is useful. Staining chromoendoscopy such as crystal violet or methylene blue staining is useful in detailed observation of lesion surface pattern (pit pattern) using magnification; however, it is not suitable for diagnosis of gross appearance, especially for shallow depressed area and concavity and convexity.

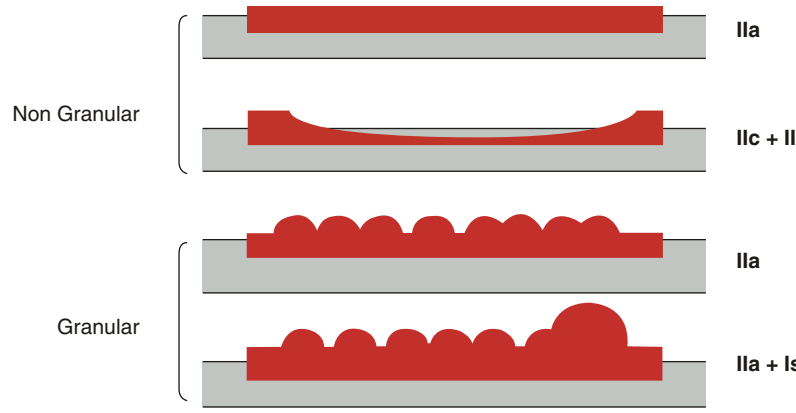

Fig. 2.3 Relationship between macroscopic classification and LST subclassification. Cited from Kudo S, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. *Gastrointest Endosc* 68, 2008 (Suppl)

TABLE 2. Subtypes of LST lesions: morphologic classification of LST lesion and their correspondance the Paris-Japanese classification*

Subtypes of LST	Classification in type 0
LST granular	
Homogenous type	0-IIa
Nodular mixed type	0-IIa, 0-Is + IIa, 0-IIa + Is
LST nongranular	
Elevated type	0-IIa
Pseudodepressed type	0-IIa + IIc, 0-IIc +IIa

* the term " laterally spreading type (LST)" refers to the lateral growth of lesions at least 10 mm in diameter; this is in opposition to traditional polypoid (upward growth) or flat and depressed lesions (downward growth).

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