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EDITORIAL

Definition and Staging of Early Esophageal, Gastric and Colorectal Cancer

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ABSTRACT

Accurate diagnosis of gastrointestinal (GI) cancer in early stages, endoscopically showed as *superficial* noninvasive lesions, is the current optimal strategy for optional outcome. "*Superficial*" GI cancer is defined as both mucosal and submucosal cancer with or without lymph node metastases. Curability however, is related to the risk of lymph node metastases, which is the major factor related to long-term outcome. A concept of "early GI cancer" therefore is "local lesion which has no risk of lymph node metastasis", while "invasive" cancer is a "*superficial*" cancer with lymph node metastases. According to retrospective studies from surgically rejected specimens of early stage GI cancer with extensive lymph dissection, the rate of lymph node metastases was very low in mucosal carcinomas, which are considered curable by endoscopic rejection alone, but much higher in cases of submucosal invasion. For deep mucosal and slightly submucosal carcinomas there are subtle but important organ specific differences with m3-sm1 esophageal carcinomas to have high risk of lymph node metastases (>20%) despite the *superficial* appearance, while for m3-sm1 gastric and colorectal lesions have low risk of lymph node metastases and should be also considered for endoscopic treatment. Accurately preoperative staging of GI cancer is the present difficulty in clinics, which is vitally important for choosing appropriate treatment method. Chromoendoscopy in combination with high-resolution, magnification endoscopy and narrow band imaging (NBI) system has been introduced in clinical setting in order to identify subtle GI lesions. The combination of all these techniques permitted real time accurate endoscopic diagnosis of early GI cancer. Moreover, in Japan they have already established standardized endoscopic classifications for staging early GI cancer, using combined macroscopic classification, chromoendoscopy and NBI magnification endoscopy Pit pattern classification is described for colorectal lesions for years. Using NBI magnification it has been established the IPCL pattern classification for early stage easophageal cancer, while for gastric and colorectal cancers there have been described specific NBI magnifying classifications. Based on these classifications a real-time, reliable endoscopic diagnosis of early GI cancer can be made.

Key words: Early gastrointestinal cancer; Definition; Lymph node metastases; Staging

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INTRODUCTION

According to Paris[1] classification of *superficial* gastrointestinal (GI) lesions: *in the esophagus, stomach and colon, neoplastic lesions of the digestive tract are called "superficial" at endoscopy, when the endoscopic appearance suggests either a small cancer or a noninvasive neoplastic lesion (dysplasia/adenoma)*, while WHO[2] defined "*superficial*" GI cancer as both mucosal and submucosal cancer with or without metastases[3-5]. "*Superficial*" tumors correspond to the T1 stage of the TNM[3-5] classification, in which invasion is limited to the mucosa and submucosa (Tables 1, 2 and 3)[3-5]. "*Superficial*" tumors are non-obstructive, usually are asymptomatic and often are detected as an incidental finding or by screening.

Table 1 Depth of tumor invasion for esophageal cancer[3].

TX	Depth of tumor invasion cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor invades mucosa
T1a-EP	Carcinoma in situ (Tis)
T1a-LPM	Tumor invades lamina propria mucosa (LPM)
T1a-MM	Tumor invades muscularis mucosa (MM)
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)

Table 2 Depth of tumor invasion (T) for Gastric cancer[4].

TX	Depth of tumor unknown
T0	No evidence of primary tumor
T1	Tumor confined to the mucosa (M) or submucosa (SM)
T1a	Tumor confined to the mucosa (M)
T1b	Tumor confined to the submucosa (SM) *(For gastric cancer SM may be subclassified as SM1 or T1b1 (tumor invasion within 0.5mm of muscularis mucosae) or SM2 or T1b2 (tumor invasion is 0.5mm or more deep into the muscularis mucosae).*
T2	Tumor invades the mscularis propria (MP)
T3	Tumor invades the sudserosa (SS)
T4	Tumor invasion is contiguous to or exposed beyond the serosa (SE) or tumor invades adjacent structures (SI)
T4a	Tumor invasion is contiguous to the serosa or penetrated the serosa and is exposed to the peritoneal cavity (SE)
T4b	Tumor invades adjacent structures (SI)

The depth of tumor invasion is recorded as the T-category. Conventional characters denoting depth of tumor invasion are also recorded: M, SM, MP, SS, SE, SI (see table). The prefixes "c" and "p" are used in conjunction with the T-category and not with the characters M, SM etc (e.g. a pathologically diagnosed mucosal tumor should be recorded as pT1 and not pM). Tumor invasion into the muscularis mucosa is included in the M category. Early gastric cancer comprises of T1a and T1b1 tumors.

Table 3 Depth of tumor invasion (T) for colorectal cancer (TNM classification)[5].

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of the lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4	Tumor directly invades other organs or structures, and/or perforates visceral peritoneum

The term "*superficial*", however, is in some way confusing, because it is not directly related to histology or invasiveness of a GI cancer, but simply describes the endoscopic appearance of a lesion, which looks to be restricted to *superficial* layers of GI tract.

Instead of the term "*superficial*", more accurate and clinically useful should be the term "early GI cancer", which suggests a "curable" disease and has been already used and defined in Japan for decades[3-5].

Curability of early stage GI cancer is related to the risk of lymph node metastases, which is the major factor related to long-term outcome of the GI cancer[6,7]. A concept of early cancer therefore is "local lesion which has no risk of lymph node metastasis."

One of the major factors that found to be related to the risk of lymph node metastases is the depth of invasion (mucosal versus submucosal)[8]. Infiltration pattern B, C and vessel permeation (ly, v) are another independent risk factors for lymph node involvement.

DEPTH OF INVASION AND RISK OF LYMPH NODE METASTASES

According to review studies from surgically rejected specimens of early stage GI cancer with extensive lymph dissection, the rate of lymph node metastases was very low in mucosal carcinomas, 2%-4% for gastric[8-11], 2% -3% for esophageal[12,13], and 0% for colorectal carcinomas[14-16], but much higher in cases of submucosal invasion; namely 14-20% for gastric[10,17], 37-53% for esophageal[12] and 3% -18% for colorectal carcinomas[14-16] (Tables 4, 5).

Table 4 Relationship between depth of invasion and lymph node metastasis in superficial GI cancer (for surgically rejected cases).

Depth	Lymph node metastasis (%)		
	Gastric	Esophageal	Colorectal
Mucosal cancer	2-4%	2-3%	0%
Submucosal cancer	14-20%	37-53%	3-18%

Table 5 Relationship between depth of invasion (sub classifications) and lymph node metastasis in superficial GI carcinoma (surgically resected cases)[6,8,15,17].

Depth	Lymph node metastasis (%)		
Depth	*Gastric*	*Esophageal*	*Colorectal*
m1	0%	0%	0%
m2	0%	0%	0%
m3	0%	8%	0%
sm1 Stomach[17]: < 300μm Esophagus[6]: < 200μm Colon[16]: upper1/3)	0%	17%	0% ([1]sm1a, sm1b)
sm2	14-20%	28%	10% (sm1c)
sm3	19-24.3%	49%	10%

[1] Submucosal colorectal cancers are divided into sm1, 2 and 3 according to the depth of invasion and further sm1 lesions are divided into sm1a, 1b and 1c, according to width of invasion (Figure 8).

Further subclassification of mucosal (m1-3) and submucosal (sm1-3) GI cancers, according to the depth of invasion (Figure 1), has been proposed in Japan, in order to select those patients with minimal risk of lymph node metastases, who would benefited from endoscopic treatment[2-4,18].

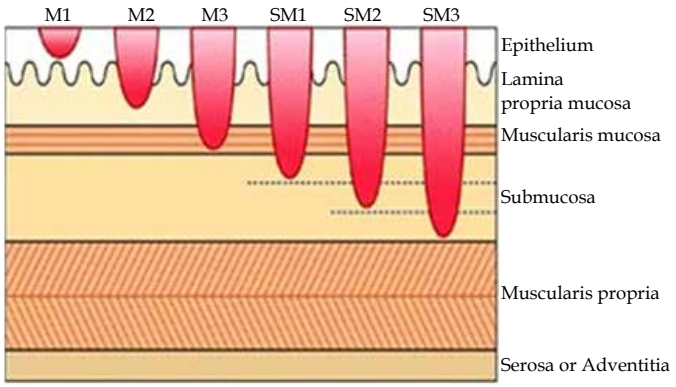

Figure 1 Subclassification of invasion depth by superficial carcinoma. m1 Intraepithelial non-invasive carcinoma, namely carcinoma in situ; m2, carcinoma invading the lamina propria; m3, carcinoma extending to or invading the muscularis mucosa; sm1, sm2, and sm3 carcinoma invading the upper, middle and lower one-third of the submucosa, respectively.

This subclassification was possible, after review studies of mucosal and submucosal thickness in surgically rejected specimens from early stage esophageal, gastric and colonic cancer and subsequent division of the submucosal space into three equal parts[3,5,6,18].

This precise subdivision into six layers has been proposed because the risk of nodal metastases increases from nil to high with the depth of invasion in the successive layers of the mucosa and submucosa and because they have already established endoscopic classification system for predicting the depth of invasion using combined macroscopic classification, chromoendoscopy and NBI magnification endoscopy and lately endocytoscopy[19-25]. The combination of all these techniques permitted the real time accurate endoscopic prediction of the depth of invasion for otherwise *superficial* lesions. This is important for precise definite treatment decision (endoscopic versus surgery). In Japan it has been already established treatment guidelines based on these classifications for GI *superficial* cancers[26,27]. The correspondence between depth of invasion and the most appropriate treatment is shown in table 6.

Table 6 Absolute (+relative) indications for endoscopic resection of neoplastic lesions.

Factor	Esophagus	Stomach, Barrett's esophagus, colorectum
Histology	High-grade (+low-grade) dysplasia, squamous cell carcinoma	High-grade (+ low-grade) adenoma/dysplasia well- or moderately (+ poorly) differentiated adenocarcinoma
Depth	m1, m2 (+m3, sm1) [1]	m (+sm1) [1]
Type	IIa, IIb, IIc, but not I or III	IIa, IIb, IIc without scar, I, but not III
Size	<3 cm (+larger lesions), <three-quarters of circumference (+whole circumference)	IIa, I: <2 cm (+larger lesions), IIc: <1 cm (+1 ~ 3cm) (+poorly differentiated carcinoma ,< 1 cm)

[1] m: Mucosa; m1, intraepithelial extension; m2: invasion into the lamina propria but not reaching the muscularis mucosae; m3: intramucosal invasion reaching the muscularis mucosae; sm1: invasion into the superficial portion of the submucosal.

Submucosal 1 (Sm1) GI carcinoma, was then defined, as carcinoma invading the upper one third of the submucosa and was estimated for esophageal cancer less than 200 μm, (sm1 esophageal cancer)[6,18], for sm1 gastric cancer less than 300 μm and less than 500 μm for sm1 colon cancer, respectively[26,28,29].

According to these sub classifications, in all types of GI cancer-esophageal, gastric and colorectal cancer- m1 and m2 GI carcinomas have no risk of lymph node metastasis and are considered curable by endoscopic rejection alone, while sm2-sm3 have high risk of lymph node metastasis (up to 49%)[3-6,32] and should be treated by surgery. (Table 5, Figures 2 A-C)[10,12,16,17]. Regarding m3 and sm1 subtypes and risk of lymph node metastases, there are subtle but important differences between the different GI organs, which are presented below. It is obvious therefore that the term "*superficial*" used in Paris classification[1] is not equal to the term "early" GI cancer used here, while detailed histological classification (mucosal versus submucosal) of early stage GI cancer is of great importance.

Esophageal cancer: Depth of Tumor Invasion (T)

Particularly, for esophageal squamous cell (SCC) carcinoma (figure 2A), up to 10% of m3 carcinomas and about 20% of sm1 esophageal SCC have lymph node metastasis and are not absolutely indicated for endoscopic treatment[5,35] (Table 7).

In conclusion, in esophageal SCC, m1 and m2 lesions have no risk of lymph node metastases and are absolutely indicated for endoscopic treatment, while sm2-sm3 and the majority of m3 and sm1 have high risk of lymph node metastases and should be treated by surgery.

Lately, some subtypes of m3-sm1 esophageal SCCs, which present specific narrow band imaging (NBI) pattern (IPCL-V3A pattern classification, Inoue's classification[36]) (Figure 14), had no risk of lymph node metastases despite the *superficial* submucosal invasion and are also relative candidates for endoscopic rejection (endoscopic submucosal dissection). According to this data, "early" esophageal carcinoma is defined the *superficial* mucosal carcinoma with m1-m2 invasion and m3-sm1 subtype with IPCL-V3A NBI pattern

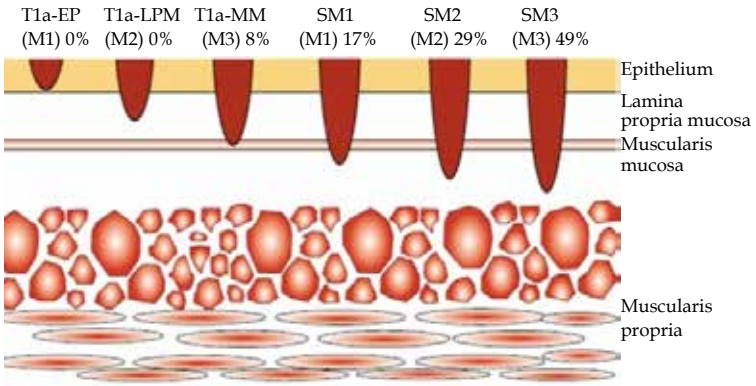

Figure 2 A Subclassification for superficial **esophageal** cancer and rate of lymph node metastases according to depth of invasion. (modified from the Guidelines for Esophageal Cancer Treatment).

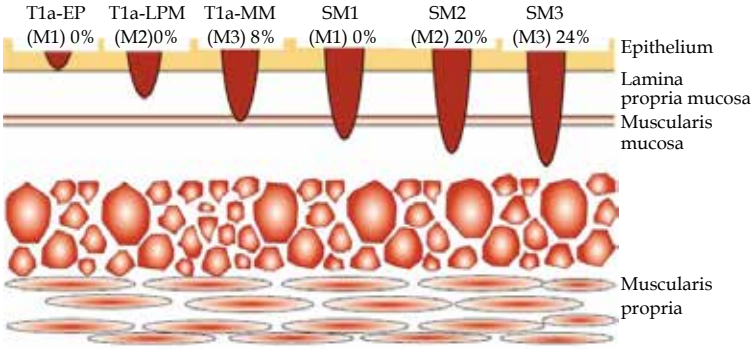

Figure 2 B Subclassification for superficial **gastric** cancer and rate of lymph node metastases according to depth of invasion (modified from the Guidelines for Gastric Cancer Treatment).

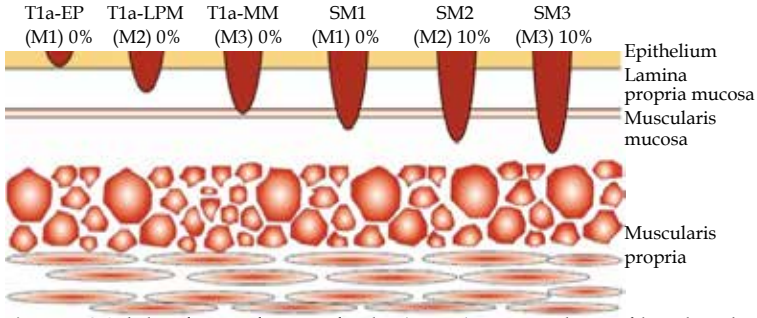

Figure 2 C Subclassification for superficial **colorectal** cancer and rate of lymph node metastases according to depth of invasion (modified from the Guidelines for Colorectal Cancer Treatment).

Table 7 Squamous epithelium of the esophagus –nodal invasion [1].

m1+m2 [*n*/N (%)]	m3+sm1 [*n*/N (%)]	Sm2+sm3 [*n*/N (%)]
0/71 (0)	4/47 (8)	37/86(43)

Note: The depth of invasion is divided into 3 groups: superficial (2/3 of the mucosa of (m1 + m2); intermediate (last layer of the mucosa + first layer of the submucosa or m3 + sm1); deep (2/3 of the submucosa or sm2 + sm3). [1] Proportion of nodal metastases with reference to the depth of invasion in the mucosa (m) of submucosa (sm). An endoscopic series with pathology confirmation from Tokyo Medical and Dental University, 1985-1995 (204 lesions type 0). (From H. Inoue, unpublished data from the Paris workshop.)

classification[36].

The type T1 of esophageal cancer [tumor confined to mucosa (M) or submucosa (SM), according to TNM classification[2]], was further divided into two groups: T1a (mucosal cancer) and T1b (submucosal cancer) (Table 1). The T1a was further subdivided into three groups: T1a-EP (carcinoma in situ, Tis), T1a-LPM (tumor invasion through the lamina propria mucosa) and T1a-MM (tumor invasion to the muscularis mucusae). The depth of invasion in the submucosa (T1b) is divided into 3 sections of equivalent thickness: *superficial* (SM1), middle (SM2) and deep (SM3) (Table 1).

The relation between macroscopic classification of type 0 esophageal SCC and depth of invasion is shown in table 8[27]. According to this multicenter analysis conducted in Japan, protruding type "0-Ip+Is" and excavated type "0-III" esophageal lesions had higher risk of deep submucosal invasion (79% and 84% respectively)[27].

Table 8 Squamous epithelium of the esophagus – depth of invasion[1].

	m1 + m2 [*n* (%)]	m3 + sm1 [*n* (%)]	sm2 + sm3 [*n* (%)]
0-I			
Ip+Is	11(4)	44(16)	207(79)
0-IIa,b			
IIa	62(20)	94(31)	147(48)
IIb	152(69)	36(16)	33(15)
0-IIc			
IIc	256(39)	245(34)	206(27)
0-III			
III	2(3)	9(13)	58(84)
Total	483(31)	428(27)	651(41)

Note: The depth of invasion is divided into three groups: superficial (2/3 of the mucosa of (m1 + m2); intermediate (last layer of the mucosa + first layer of the submucosa or m3 + sm1); deep (2/3 of the submucosa or sm2 + sm3). [1] Depth of invasion into the mucosa (m) or submucosa (sm) with reference to major macroscopic categories within type 0. A multicenter analysis conducted in Japan in 143 institutions: 1562 lesions with pathology confirmation in the operative specimen[27].

Gastric cancer: Depth of Tumor Invasion (T)

In stomach, no risk of lymph node metastases was found for gastric m3, sm1 cancers, while sm2-sm3 lesions have high risk of lymph node metastases (>20%)[8-11,17]. (Table 5, figure 2B)[37].

Especially for gastric cancer, a simplest two-grade classification (sm1 and sm2) in regard to the invasion depth has been proposed. Sm1 gastric cancer is defined as submucosal penetration less than 500μm from muscularis mucosa and Sm2 as invasion of 500 μm or more (Figure 3).

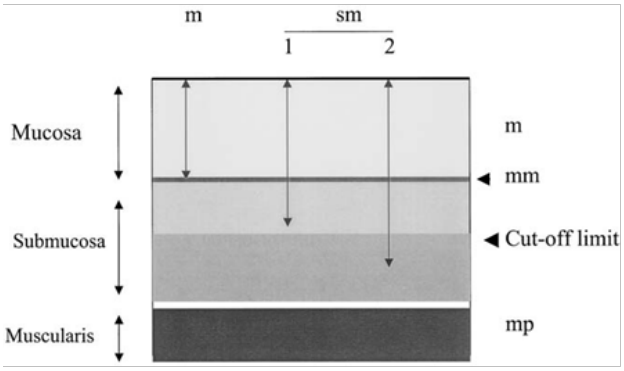

Figure 3 Depth of invasion of the submucosa in the columnar epithelium (Barrett's esophagus and stomach) assessed in the specimen obtained after surgery. Depth of submucosal invasion is divided into two groups: superficial (sm1) and deep (sm2) with respect to a cutoff limit determined on a micrometric scale (500 μm in the stomach).

Gotoda *et al*[29] in a large number of patients with early stage gastric cancer found that sm1 (<500 μm) gastric lesions had lower risk of lymph node metastases and when they were combined with other independent risk factors such as (a) differentiated type; (b) size smaller than 30 mm and (c) absence of lymphatic-vascular involvement, no lymph node metastases were found in patients with sm1 (<500 μm) submucosal gastric cancer[29].

The two grade classification of the submucosal gastric cancer (sm1, sm2) is more practical and useful and it was adapted in TNM classification (JCGC[38]) (Table 9). The type T1 of gastric cancer (tumor confined to mucosa (M) or submucosa (SM), according to TNM classification[2]), was further subclassified into T1a (mucosal cancer) and T1b (submucosal cancer) and the T1b was further subclassified to SM1 or T1b1 (tumor invasion within 0.5 mm of muscularis mucusae) and SM2 or T2b2 (tumor invasion is 0.5 mm or more deep into the muscularis mucosae) (Table 2 and 9).

Table 9 Stomach-nodal invasion[1].

Size in mm	<500 [n/N (%)]	>500m [n/N (%)]
<10	1/31 (3)	5/39 (13)
10-20	4/71 (6)	28/195 (14)
21-30	4/71 (6)	52/273 (19)
>30	6/92 (7)	86/319 (27)
Total	15/265 (6)	171/826 (21)

Note: The depth of invasion into the submucosa is divided into two groups with respect to the cutoff limit: 500 1 from the lowest layer of the muscularis mucosae. [1] Proportion of nodal metastases with reference to the depth of invasion into the submucosa. Results (numbers and percentages) presented in two groups of depth and 4 groups for size of the lesion. Cases with pathology confirmation (1091 lesions type 0), treated by surgery or endoscopic mucosectomy in National Cancer Center Hospital in Tokyo[31].

This subclassification was imposed from the necessity to accurate distinguish endoscopically curable early gastric cancer. This subclassification was absolutely necessary in the era of endoscopic submucosal dissection (ESD) en block rejection of early GI cancer.

Further clinical studies by Gotoda[31] and colleagues from large number of surgically treated patients with early stage gastric cancer, were able to identify additional groups of patients with no or lower risk of lymph node metastases than the risks of mortality from surgery[31].

Except for the submucosal invasion depth, other risk factors such as tumor size, histological type and lymphatic-vascular involvement, were also found to be independently related to the risk of lymph node metastases in submucosal gastric cancer[29].

Histologically well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma were classified as differentiated histological type; poorly differentiated adenocarcinoma and signet-ring cell carcinoma were classified as undifferentiated histological type[39,29]. Regarding early gastric cancer tubular and papillary variants represent 50% and 30% respectively of cases. Signet ring cell carcinoma and "poorly differentiated" carcinoma represent 25% and 15% respectively and are usually depressed or ulcerated[2].

Initial studies demonstrated, that undifferentiated mucosal gastric adenocarcinomas, even in absence of submucosal invasion, had higher probability of lymph node metastases (4.2%) compared with differentiated mucosal gastric carcinomas (0.4%) and are not absolutely considered for endoscopic treatment (EMR/ESD)[31,40,41].

Subsequent studies, however, showed that other factors as well, such as tumor size, lymphatic invasion, depth of invasion and ulceration had predictive value on the risk of lymph node metastasis in undifferentiated gastric adenocarcinomas. Particularly, gastric

tumor less than 20 mm in size, confined to the mucosa, without lymphatic invasion or ulceration had very low risk for lymph node metastases and could be considered for curative ESD resection[31,42,43]. Under these conditions endoscopic treatment is currently recommended for undifferentiated gastric adenocarcinomas (relative indication)[31,42-44] (Table 6, figure 4 and 5D).

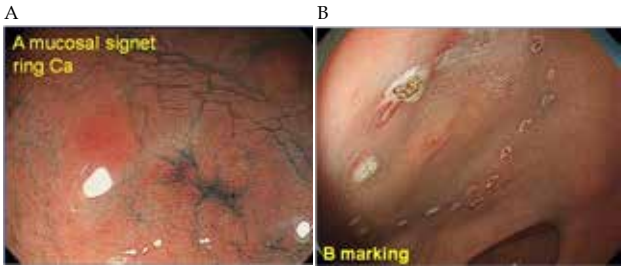

Figure 4 A: A very small slightly depressed 0-IIc gastric lesion, proved to be early signet ring mucosal carcinoma; B: Marking before ESD rejection.

There are also cases of early signet cell gastric carcinoma that have been complete rejected by ESD, such as a case from the Showa University, Northern Yokohama Hospital, Japan shown in figure 4.

Further clinical studies by Gotoda[31] and colleagues from large number of surgically treated patients with early stage gastric cancer, were able to identify additional groups of patients with no or lower risk of lymph node metastases than the risks of mortality from surgery[31].

These results allowed the development of an expanded list of candidates with no risk of lymph node metastases, suitable for endoscopic resection for early gastric cancer, as shown in table 10. The rationale of this recommendations is based upon the knowledge that larger-size lesions or lesions with undifferentiated histology type are more likely to extend into the deep submucosal layer and thus have a higher risk of lymph node metastases[29-31,45].

Table 10 Proposed extended criteria for endoscopic submucosal dissection (ESD) for early gastric cancer.

Depth / Histology	Mucosal cancer UL(-) ≤20	Mucosal cancer UL(-) 20≤	Mucosal cancer UL(+) ≤30	Mucosal cancer UL(+) 30≤	Submucosal cancer SM1 ≤30	Submucosal cancer SM2 any size
Differentiated						
Undifferentiated						

Guideline criteria for EMR; Surgery; Extended criteria for ESD; Consider Surgery[1]

[1] Although the possibility of metastasis is very low in this category, surgery is considered because endoscopic en bloc removal is sometimes difficult in undifferentiated type tumors.

Moreover, according to study by Tsujitanui *et al*[45] early stage gastric cancer depressed type (0-IIc) of less than 1 cm in diameter and the elevated type (0-IIa) of less than 2 cm in diameter are suitable for endoscopic treatment (EMR/ESD) (Table 11 and figure 5).

According to the results of this study, in *superficial* gastric cancer, elevated type of more than 3 cm (0-I) and depressed type of 1 to 3 cm in diameter (0-III) were related to high risk of lymph node metastases and should be treated surgically, while depressed type of less than 1cm in diameter (0-IIc) and the elevated type (0-IIa) of less than 2 cm in diameter are suitable for endoscopic treatment (EMR/ESD) (Tables 10 and 11).

The presence of lymph node metastasis is the most important prognostic factor for *superficial* gastric cancer. Because radical surgery with lymph node dissection has provided an excellent therapeutic outcome in early stage gastric cancer, with 5-year survival rate after curative resection more than 90% including recent European studies[29], precise diagnosis (pick up) of early gastric cancer and accurate indications for local EMR/ESD rejection, are fundamental for optional curative outcome.

As a result of this policy, in cases with *superficial* gastric cancer with one or more risk factors for lymph node metastases (Table 12), such as undifferentiated type, size larger than 2 cm, the presence of lymphatic/venous involvement, submucosal invasion and ulcerative change, gastrectomy with lymph node dissection is recommended and usually performed, although the gastric lesion can be complete removed by endoscopy[31,46].

However, in similar cases with contraindications for major surgery due to comorbidities or advanced age combined ESD rejection

Table 11 Early gastric cancer with no risk of lymph node metastasis.

Criteria	Incidence	95% CI
Intramucosal cancer Differentiated adenocarcinoma No lymphovascular invasion Irrespective of ulcer findings Tumor less than 3 cm in size	0/1230; 0%	0–0.3%
Intramucosal cancer Differentiated adenocarcinoma No lymphovascular invasion Without ulcer findings Irrespective of tumor size	0/929; 0%	0–0.4%
Undifferentiated intramucosal cancer No lymphovascular invasion Without ulcer findings Tumor less than 2 cm in size	0/141; 0%	0–2.6%
Minute submucosal penetration (SM 1) Differentiated adenocarcinoma No lymphovascular invasion Tumor less than 3 cm in size	0/145; 0%	0–2.5%

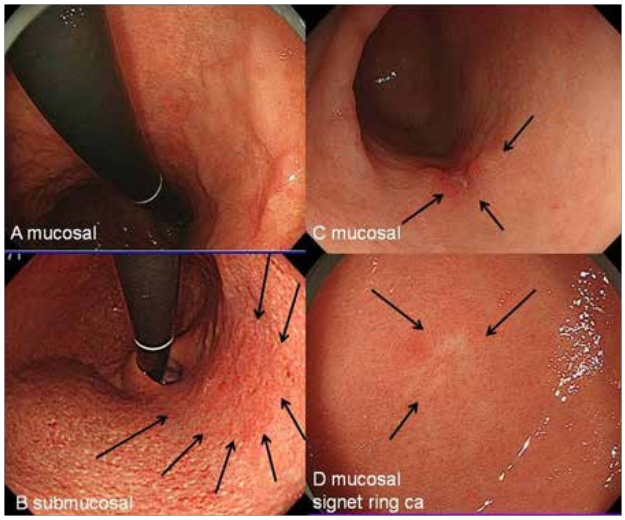

Figure 5 Endoscopic image of superficial gastric cancer type A: 0-IIa, B: 0-IIb, C: &, D: 0-IIc. Finally the A, C, D 0-IIa, 0-IIc, 0-IIb proved to be mucosal cancer (m) = early gastric cancer and rejected en block by ESD. The 0-IIb (B) lesion was submucosal cancer.

Table 12 Main risk factors for lymph node metastases in superficial gastric cancer.

Undifferentiated type
Tumor size larger than 2 cm
Presence of lymphatic/venous involvement
Submucosal invasion
Ulcerative change

for the gastric tumor with laparoscopic lymph node rejection has been reported to be efficacious, in small group of patients with early stage gastric cancer, with one or more factors for lymph node metastases[46]. Furthermore, ESD rejection does not preclude future surgery, if needed. In contrast precise assessment of the en block rejected specimen provide a complete "biopsy", crucial for further treatment planning (Figures 6 and 7). In view of these evolutions, a strict schedule was adapted and proposed, according to the JCGC[38], for handling the endoscopical rejected ESD specimen.

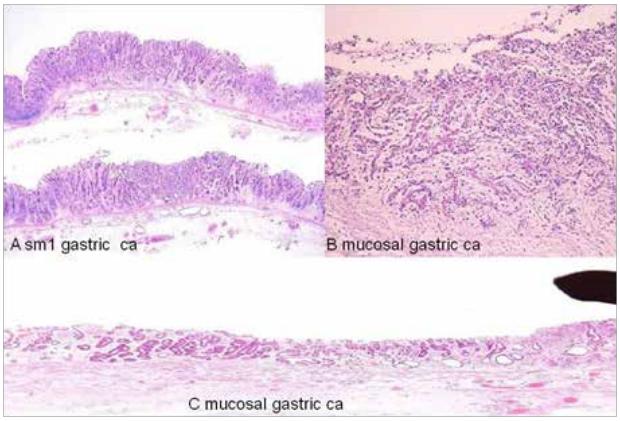

Figure 6 A: Submucosal (sm1) well-moderate differentiated gastric cancer with submucosal penetration less than 500 μm from the muscularis mucosa. B and C: Mucosal gastric cancer. (HE stain, original magnification ×4).

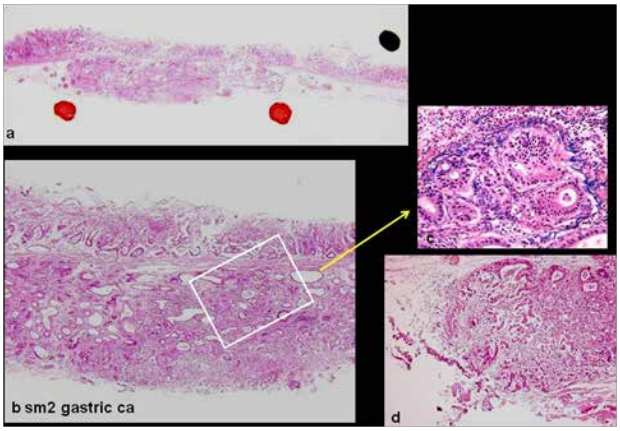

Figure 7 a-d: Submucosal gastric cancer (sm2) estimated with submucosal penetration more than 500μm from the muscularis mucosa. (HE stain, original magnification ×4). c: Sm1 with lymphatic vascular involvement (white arrow) (HE stain, original magnification ×10).

Colorectal cancer: Depth of Tumor Invasion (T)

According to Japanese Classifications of Colorectal Cancers (JCCC)[5] the depth of tumor invasion for colorectal cancer is as follow (Table 3):

M: Invasion confined to mucosa

M: Invasion to submucosal

MP: Invasion to muscularis propria

For parts of intestine that have serosa/visceral peritoneum

SS: Invasion to subserosa

SE: Invasion penetrating serosa

SI: Direct invasion to adjacent organs or structures

For parts of intestine that do not have serosa/visceral peritoneum

A: Invasion through muscularis propria into pericolic or perirectal tissues

AI: Direct invasion to adjacent organs or structures

In colorectal cancer except for the depth of invasion important factor for lymph node metastases is also the width of invasion (Figure 8).

Submucosal colorectal cancers are divided into sm1, 2 and 3 according to depth of invasion, while sm1 lesions are further divided into sm1a, 1b and 1c, according to width of invasion as shown in figure 8[26]. When the width of the submucosal invasion is less than the half of the total width, as in sm1a sm1b lesions, there is no risk of lymph node metastases and they defined as slightly invasive submucosal cancers (SMs). Sm1c (submucosal invasion more than the half of the total width), sm2 and sm3 lesions show substantial proportion of lymph node metastases (approximately 10%) and are defined massively invasive submucosal cancers (SMm)[26]. According to this data "early" colorectal cancer is defined the m1-m3 mucosal and sm1a, sm1b submucosal carcinoma, while sm1c, sm2-sm3 are invasive cancer.

In conclusion for colorectal cancer m3, sm1a and sm1b lesions had no risk of lymph node metastases and are indicated for endoscopic treatment only, while sm1c, sm2 and sm3 colorectal cancer has more than 10% risk of lymph node metastases and should be treated by surgery[26] (Tables 4, 5 and figure 2C).

The relation between macroscopic classification and size of type 0 colorectal cancer and depth of invasion is shown in table 13. According to this Japanese data presented in Paris classification[1], protruded type "0-Ip+Is", *superficial* elevated and flat type "0-IIa+IIb" colorectal lesions less than 15 mm have low risk of submucosal invasion (<8%), while size more than >20 mm the risk of submucosal invasion increased to more than 17%. Depressed type "0-IIc" lesions are related with the higher risk of submucosal invasion even in small size (<5 mm)[47-49]. Type "0-IIc" colorectal lesions with diameter of more than 5 mm have >40% risk of submucosal invasion[48]. Based on the results of these studies specific treatment guidelines have been recommended.

DEFINITION OF SUPERFICIAL, MUCOSAL, SUBMUCOSAL, EARLY GI CANCER

According to the results of the above-mentioned studies, *Superficial*, Mucosal, Submucosal, Early GI cancer were defined as follow:

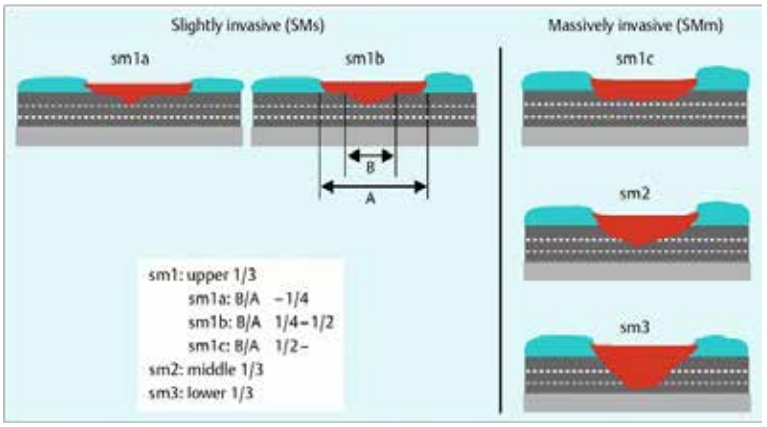

Figure 8 Classification of the degree of submucosal invasion of colorectal cancer. SMs: Submucosal colorectal cancers are divided into sm1, 2 and 3 according to depth of invasion and sm1 lesions are further divided into sm1a, 1b and 1c, according to width of invasion[1]. Sm1a sm1b does not metastasize and defined as slightly invasive submucosal cancers (SMs) and sm1c, sm2 and sm3 show substantial proportion of lymph node metastases (approximately 10%) and are defined massively invasive submucosal cancers (SMm)[1].

Table 13 Colon size and macroscopic appearance in relation to invasion depth [1].

	5 mm or less	6-10 mm	11-15 mm	16-20 mm	21 mm or more
0-I					
Ip+Is	0/5400(0%)	49/4045 (1.2%)	80/1002(8%)	58/330 (17%)	56/187 (30%)
0-IIa,b	2/6214 (<0.1%)	2/1015 (0.2%)	9/493 (1.8%)	17/165 (10%)	53/235 (23%)
IIa+IIb					
0-IIc					
All IIc	17/236(7%)	58/132(44%)	42/63(67%)	18/20(90%)	13/15 (87%)
0-III		0	0	0	0
III	0				
Total	19/11850 (<0.2%)	109/5192 (2%)	131/1558(8%)	93/1523 (18%)	122/437 (28%)

[1] Proportion (numbers and percentages) of invasion into the submucosa, with reference to the major macroscopic categories within type 0 and to the diameter of the lesion (in 5 groups). Endoscopy series with pathology confirmation (19.560 lesions in the period April 1985- April 2003) in Red Cross Hospital in Akita and Showa Northern Hospital in Yokohama. (From S. Kudo, unpublished data from Paris workshop.)

Superficial GI cancer is defined both mucosal and submucosal cancer with or without metastases[3-5] and generally corresponds to T1sm of TNM classification[3-5] (Figures 2 A, B and C).

Mucosal cancer is defined as cancer confined to mucosal layer and corresponds to intramucosal cancer, T1m, T1a. (Figure 2 A, B, C, tables 1, 2, 3).

Submucosal cancer is defined as invasive cancer to submucosal layer and corresponds to T1sm, T1b (TNM classification[37], WHO[49]). (Figures 2 A, B, C and tables 1, 2, 3).

As a consequence of the above-mentioned results, taking into account the organ specific differences of lymph node metastases organ specific definitions of early GI cancer are proposed:

Early gastric cancer is defined as mucosal (m1-m3) or upper submucosal (sm1 <500 μm) carcinoma without lymph node metastases and is corresponding to T1a and T1b1 of the TNM classification (Figure 6 A-C).

Early esophageal cancer is defined as upper mucosal (m1, m2) carcinoma without lymph node metastases and is corresponding to T1a of the TNM classification.

Early colorectal cancer is defined as mucosal (m1-m3) or slightly invasive submucosal (SMs=sm1a sm1b) carcinoma without lymph node metastases and is corresponding to T1a and T1b1 of the TNM classification.

All these early GI cancers can curably be treated by endoscopic means (EMR or ESD).

In contrast to early GI cancer, we would like to distinguish "invasive" *superficial* GI cancer from "advanced" GI cancer.

"Advanced" GI cancer is a GI cancer invading the muscularis propria or deeper (corresponding to T2-T4 of Borrmann's macroscopic classification), in contrast:

"Invasive" cancer is a "*superficial*" cancer with lymph node metastases, and organ specific definitions is as follow:

"Invasive" gastric cancer is defined as deep submucosal (sm2 >500 μm) carcinoma with lymph node metastases and is corresponding to T1b2 of the TNM classification (Figure 7 a-d).

"Invasive" esophageal cancer is defined as deep mucosal (m3) carcinoma and submucosal cancer (Sm2-Sm3), with lymph node metastases, (no correspondence to TNM classification)

"Invasive" colorectal cancer is defined as deep invasive submucosal (SMm=sm1c) carcinoma with lymph node metastases, (correspond to T1b2 of TNM classification)

GENERAL PRINCIPLES OF PREOPERATIVE STAGING OF *SUPERFICIAL* GI NEOPLASMS

Accurate preoperative staging of *superficial* GI neoplasms is the present difficulty in clinics, which is vitally important for choosing appropriate treatment method (endoscopic versus surgery). In the West, endoscopists tend to base treatment decisions largely on tumor size and location and on the histology of biopsy specimens. However, in Japan, endoscopists have found that endoscopic classification of a GI lesion can be an important determinant of treatment decision especially, when endoscopic therapy should be applied. The high burden of GI cancer in Japan, forced Japanese investigators to develop advanced imaging techniques for endoscopic detection of very early GI cancer.

Based on the knowledge of Japanese Society of Endoscopy, especially (JCGC, JSED, JSCCR)[3-5] an international group of endoscopists, surgeons and pathologists proposed the Paris endoscopic classification of *superficial* lesions of the esophagus, stomach, and colon (Paris 2002)[1].

During the past two decades however, Japanese endoscopists had learnt unlike the western endoscopists, how to diagnose and endoscopically treat early stages GI neoplasia. This goal was achieved by the earlier use of technical progress, including high resolution magnifying endoscopes and enhanced imaging capabilities, such as narrow-band imaging (NBI) system and mainly by precise classification and treatment guidelines, including development guidelines for minimal invasive endoscopic treatments[53].

Chromoendoscopy in combination with high-resolution, magnification endoscopy and enhanced imaging technology such as NBI system has been introduced in clinical setting in order to identify subtle lesions. These endoscopic advancements were initially studied at leading Japanese medical centers and resulted in precise endoscopic description, with accurate prediction of invasion depth and optional treatment decisions.

In view of these evolutions, revision of Paris classification is urgent, in order to incorporate classifications based on the new imaging technologies.

Endoscopic detection and chromoendoscopy

Recent models of videoendoscopes meet the requirements for the acquisition of a high-quality digital image in terms of resolution, color reproduction, contrast, and structure enhancement. The primary step in diagnosis is to identify the presence of a mucosal area slightly discolored (more pale or more red), an irregular microvascular network, or a slight elevation or depression.

The second step in diagnosis is based on chromoendoscopy, to help in the meticulous description of the lesion. Chromoendoscopy should be readily available and should be performed when a target lesion has been detected. The routine use of endoscopic dyes to improve the imaging of a focal lesion does not mean that a systematic application covering the entire mucosal surface must be performed in every case. Diffuse staining to increase the yield of detection has, however, been proposed in those at high risk of neoplasia (e.g., familial colorectal cancer or ulcerative colitis).

A variety of agents have been proposed for chromoendoscopy. Iodine solution (1.5%-2%), a vital stain, is the basic agent used for the stratified squamous epithelium of the esophagus[54,55]. Neoplastic areas remain unstained (negative stain), in contrast to the dark brown positive stain of the normal epithelium.

The dye most commonly used on abnormal areas of the stomach and the colon is indigo carmine solution (0.5%-1%), a contrast stain. Chromoendoscopy with indigo carmine helps in the distinction between non-neoplastic (hyperplastic) or neoplastic lesions in the large bowel. Indigo carmine dye spraying, which is practiced routinely in Japan[56,57], has been also used in the West[58-62] but is still uncommon[63].

Methylene blue chromoendoscopy has been used for the detection of intestinal metaplasia in the esophagus and the stomach and has been used in the large bowel by spraying a 0.1% solution in successive segments[64-69]. In a recent randomized study, this procedure was applied to the surveillance of patients with ulcerative colitis[70].

An increased yield of non-polypoid neoplastic lesions was obtained in the group of patients evaluated with chromoendoscopy with magnification endoscopy[70]. Magnification optics were believed to be a major factor of improved efficacy[71]. The endoscopic application of dilute acetic acid has been proposed as a useful agent in studying the architecture of the metaplastic mucosa in Barrett's esophagus[72,73] and lately in evaluation of early gastric cancer in combination with NBI magnifying endoscopy[74].

ORGAN SPECIFIC ENDOSCOPIC CLASSIFICATIONS OF EARLY GI CANCER

NBI magnifying esophagoscopy and IPCL pattern classification of early esophageal cancer

Magnification endoscopy combined with NBI constitutes a novel advanced imaging technology, which enhances microvascular architecture of the *superficial* esophageal mucosa and permits real-time, accurate diagnosis of *superficial* malignant and premalignant esophageal lesions[75].

Stratified squamous esophageal epithelium has no pit pattern, which is routinely observed in glandular epithelium of stomach and colon, instead a specific *superficial* capillary pattern, the Intra-epithelial Papillary Capillary Loop (IPCL), is identified[36,76,77] (Figure 9). The IPCL, which rises perpendicularly from the branching vessel, is barely recognizable under conventional endoscopy. By using the magnifying scope, which has magnification capability up to 80 times, the IPCL of the normal mucosa is identified as red dots.

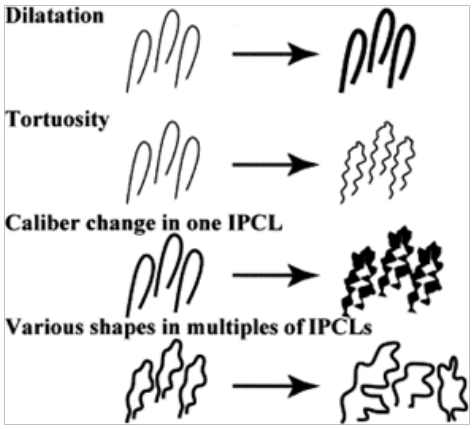

Figure 9 Schematic diagram illustrating 4 factors used to assess change in IPCL. The capillary pattern as demonstrated by magnifying endoscopy is classified according to the degree of change in these 4 factors, i.e., dilatation, tortuosity, or caliber change in a single IPCL, or variation in the shape of multiple IPCLs.

NBI enables more vivid observation of the IPCL. Branching vessels which are located at the relatively deeper layer are observed as green, and IPCL which is located at more *superficial* layer, is observed as brown loops (brown dots)[76,78,79]. In esophagus due to relatively narrow lumen, there is sufficient light to perform a complete visual survey of the mucosa under NBI imaging system.

In Japan, as NBI imaging highlights better *superficial* malignant and premalignant esophageal lesions than white light endoscopy, it is routine to begin the diagnostic examination in esophagus with NBI with low optical magnification[77]. In the esophagus and pharynx, due to relatively narrow lumen, there is sufficient light to perform a complete visual survey of the mucosa under NBI. Any suspicious area is initially visualized as "brownish" area under NBI with low magnification and is further evaluated with NBI high magnification in combination with iodine (Lugol) chromoendoscopy.

All suspicious "brownish" areas in esophagus are assessed with NBI high magnification endoscopy (×80), in order to detect characteristic changes of IPCL pattern, which are directly related to tissue atypism and cancer invasion depth[36,76,77]. Switch from NBI to white light technique is easy accomplished just by pushing a button on the top of the handle of the endoscope.

In *superficial* squamous cell esophageal carcinoma (SCC), four main characteristic changes of IPCL pattern have been detailed described (Figure 9)[80]: (a) Dilation; (b) Tortuosity; (c) Caliber change in a single IPCL and (d) Variation in the shape (uneven form) in multiple IPCLs.

Based on these changes, IPCL pattern classification[36,75] systems of NBI magnifying findings have been described in order to demonstrate the tissue characterization for flat lesions (cancer versus non-cancer) and to predict the depth of invasion[36,81-83,75,77,84] (Figure 10). According to IPCL pattern classification, accurate selection of patients with early esophageal cancer for endoscopic (EMR/ESD) versus surgical treatment can be accomplished[36,76,77,80].

The IPCL pattern classification includes two sets of diagnostic criteria. IPCL pattern classification from IPCL type I to Type V-1 (Figure 10) demonstrates the tissue characterization for flat lesion (normal to mucosal cancer), while IPCL pattern classification from type V-1 to type VN reflects cancer infiltration depth (m1, m2, m3 Sm1 to Sm2) (Figures 10-14).

The IPCL pattern is categorized from type I (normal mucosa) to type V (carcinoma) (Figures 10,12 and 13):

IPCL Type I: corresponds to normal mucosa.

IPCL Type II: is often equivalent to regenerative tissue or inflammation.

IPCL type III: is a borderline lesion which potentially includes esophagitis, but is often related to low-grade intraepithelial neoplasia (category 3 in revised Vienna classification[85]) (table 14). IPCL type III should be considered for further follow-up.

IPCL Type IV: is equivalent to high-grade intraepithelial neoplasia or carcinoma in situ (category 4.1 and 4.2 revised Vienna classification85).

IPCL Type V1: represent mucosal cancer (m1).

IPCL Type V2: represent mucosal cancer (m2) (category 4.4 revised Vienna classification[85]).

Local endoscopic treatment with EMR/ESD should be considered for IPCL type IV, type V-1 and type V-2, which definitely represent Tis and mucosal cancer m1 or m2, with no risk of lymph node metastases.

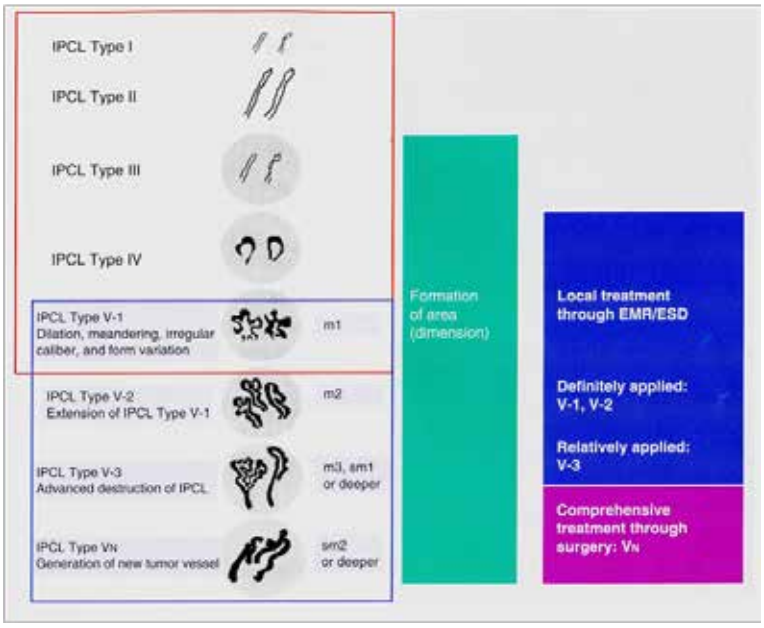

Figure 10 IPCL pattern classification includes two sets of diagnostic criteria. IPCL pattern classification from IPCL Type 1 to Type V-1 demonstrates the tissue characterization for flat lesion (square with red line). IPCL pattern classification from IPCL Type V-1 to Type V-N reflects cancer infiltration depth (square with blue line). IPCL type III corresponds to borderline lesion, which potentially includes esophagitis, low-grade intraepithelial neoplasia. IPCL type III should be considered for a further follow-up study. In IPCL Type IV, high-grade intraepithelial neoplasia or carcinoma in situ appears, and then further treatment with EMR/ESD should be considered. EMR/ESD should be also considered for IPCL types V-1 and V-2 as they are definite m1 and m2 lesion with no risk of lymph node metastases. The IPCL pattern V-3 lesion, which corresponds to m3 lesion, diagnostic EMR/ESD should be applied as a complete biopsy to decide treatment strategy. Furthermore, IPCL Type VN corresponds to a new tumor vessel, which is often associated with sm2 invasion with significantly increased risk of lymph node metastases and surgical treatment should be recommended.

Table 14 The revised Vienna classification of gastrointestinal epithelial neoplasia.

Category	Diagnosis	Clinical management
Group 1	Negative for neoplasia	Optional follow up
Group 2	Indefinite for neoplasia	Follow up
Group 3	Mucosal low grade neoplasia	Endoscopic resection or follow up[1]
	Low grade adenoma Low grade dysplasia	
Group 4	Mucosal high grade neoplasia	Endoscopic or surgical local resection[1]
Subgroup 4.1	High grade Adenoma/dysplasia	
Subgroup 4.2	Non-invasive carcinoma (carcinoma in situ)	
Subgroup 4.3	Suspicious for invasive carcinoma	
Subgroup 4.4	Intramucosal carcinoma	
Group 5	Submucosal invasion by carcinoma	Surgical resection[1]

[1] Choice of treatment will depend on the overall size of the lesion; the depth of invasion as assessed endoscopically, radiologically, or ultrasonographically; and on general factors such as the patient's age and comorbid conditions. For gastric, oesophageal, and non-polypoid colorectal well and moderately differentiated carcinomas showing only minimal submucosal invasion (sm1) without lymphatic involvement, local resection is sufficient. Likewise, for polypoid colorectal carcinomas with deeper submucosal invasion in the stalk/base but without lymphatic or blood vessel invasion, complete local resection is considered adequate treatment.

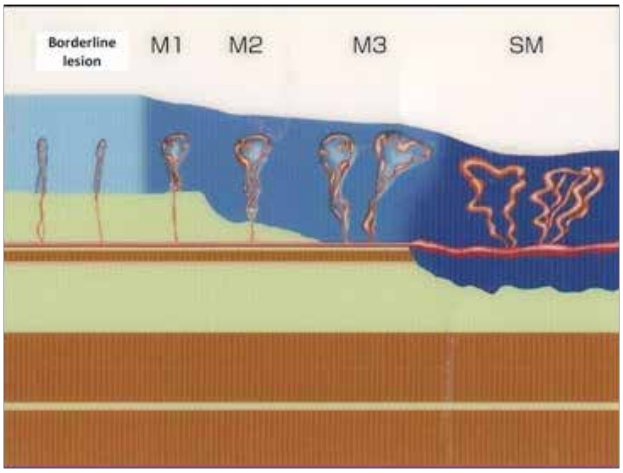

Figure 11 IPCL pattern and depth of invasion.

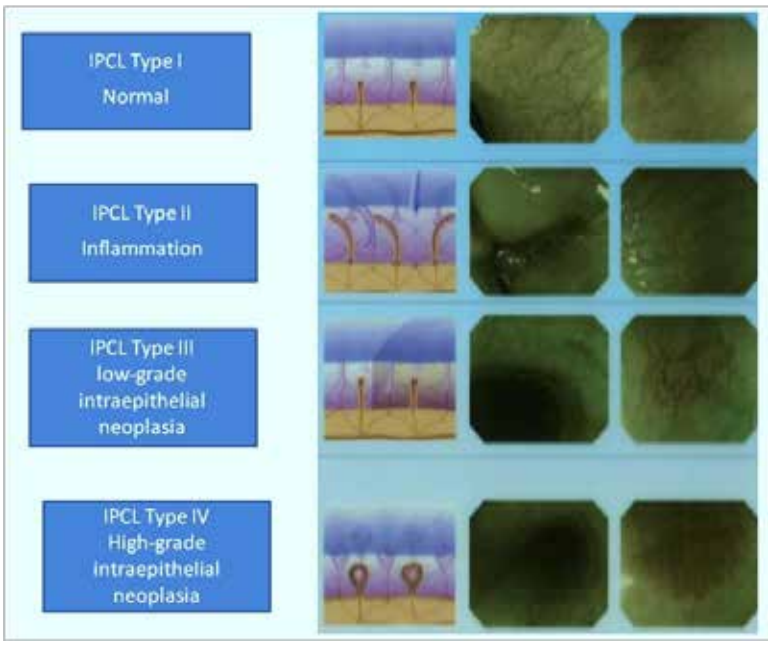

Figure 12 IPCL pattern type I to IV.

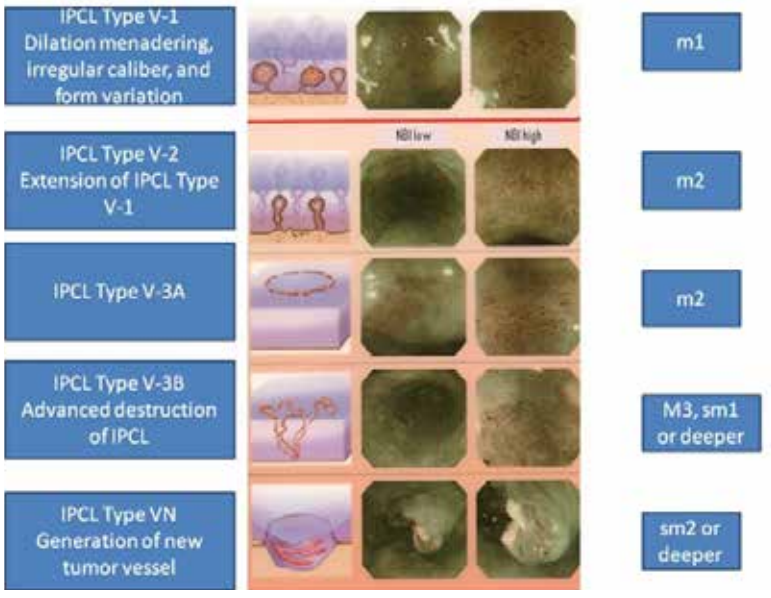

Figure 13 IPCL pattern type V-1-VN.

IPCL Type V3 is subdivided into (Figure 14):

IPCL Type V3A: corresponds to non invasive mucosal cancer, m2 (category 4.4 revised Vienna classification[85]) which is considered for endoscopic treatment (ESD).

IPCL Type V3B: is referred to deep mucosal cancer m3 with submucosal invasion (Sm1) (category 5 revised Vienna classification[85]), which should be considered for surgery as there is increase risk of lymph node metastases[36,76,77].

IPCL Type VN corresponds to new tumor vessel, which is cancer often associated with deeper invasion (sm2 or more) with significant risk of lymph node metastases and the surgical treatment should be recommended[76].

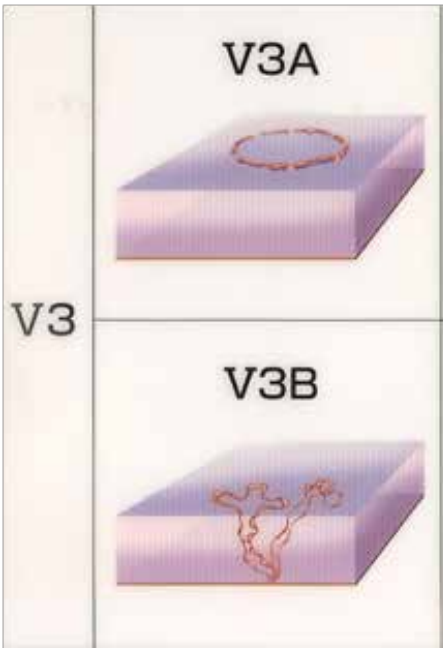

Figure 14 Sub classification of IPCL type V3. V3A is corresponds to non invasive mucosal cancer, m2 and is considered for endoscopic treatment (ESD). V3B: corresponds to deep mucosal cancer m3 and submucosal cancer (Sm1), which should be considered for surgery.

The above-mentioned IPCL pattern classification has been also used for detecting and evaluating suspected *superficial* pharyngeal lesions and has been found reliable and accurate method in guiding endoscopic rejection for pharyngeal cancer as well[77,81,86]. In the oropharyngeal area chromo-endoscopy is not possible and NBI imaging provides a virtual "chromoendoscopy" with real time optical diagnosis.

NBI magnification endoscopy in esophagus can be combined with chromo-endoscopy using iodine (Lugol) stain upon indication, which remains the best sensitive simple method for identification and precise delineation of squamous cell intraepithelial neoplasia or early cancer in esophagus[87]. Lugol chromoendoscopy in squamous cell epithelium reveals the "pink color sign" in the non-iodine-stained lesions, which confirms the existence of carcinoma or high-grade dysplasia. The "pink color" sign is recognized with NBI system as "shiny silver sign". Combination of both phenomena is called "pink-silver sign"[88] (Figure 15). Shiny silver sing starts appearing around seven minutes after iodine staining. This process will be shortened by spraying of sodium thiosulfate solution, immediately after iodine staining[76]. However, NBI magnification imaging is superior to iodine crhomoendoscopy in detecting the depth of invasion and defining the endoscopic respectability of *superficial* early esophageal cancer.

NBI magnification imaging technique has been extensively studied with promising results in evaluating esophageal early SCCs, while the IPCL pattern classification has been proved reliable and accurate method for exact diagnosis and treatment decision of esophageal *superficial* SCCs[36,75-77]. NBI magnification imaging system has been proved superior to conventional white light endoscopy in detection of early, even minute <2 mm, esophageal SCC[76,78,79].

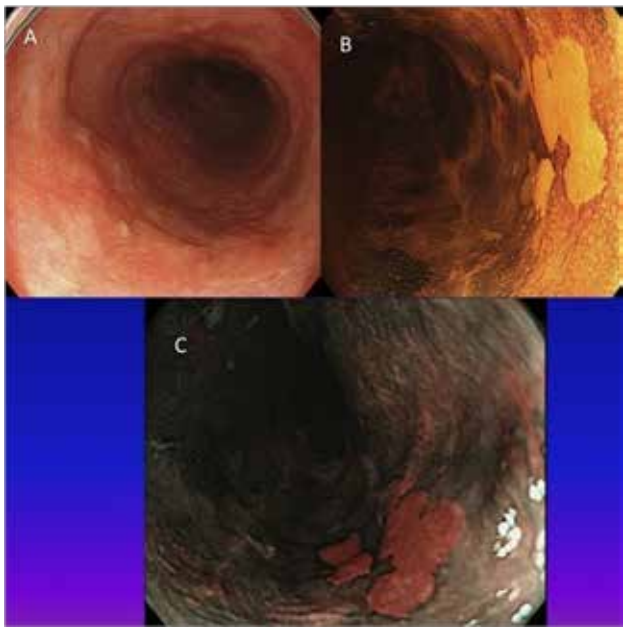

Figure 15 Early esophageal cancer in (A) standard endoscopy, (B) Pink sign after iodine staining and (C) silver pink sign after combined of NBI and Iodine chromoendoscopy.

NBI MAGNIFYING ENDOSCOPIC CLASSIFICATION OF EARLY GASTRIC CANCER

NBI magnification endoscopy in stomach enhances both the microvascular architecture and microsurface structure of the *superficial* gastric mucosa, revealing specific NBI patterns and based on these findings a real-time, reliable endoscopic diagnosis of early gastric cancer can be made, according to several reports[82,89-91].

Although there are no consistent guidelines for NBI magnification endoscopy for early gastric cancer, there are specific NBI classifications for gastric lesions, described in the literature[90,91]. Yao *et al*[90] first reported the "VS classification" (V=vascular pattern, S=surface pattern) and concluded that based on NBI magnification the major characteristic of early gastric cancer is the presence of a demarcation line with either irregular microvascular or irregular microsurface pattern[90].

Furthermore, specific NBI magnifying findings of early gastric cancer are useful in predicting the histological type. Particularly, differentiated type adenocarcinomas are characterized by disappearance of regular subepithelial capillary network (SECN), a demarcation line and irregular-microvascular pattern (IMVP), while undifferentiated-type adenocarcinoma is characterized by a reduced microvascular pattern[90].

Yokoyama *et al*[91] recently described a four pattern standardized classification- fine network (FNP), intralobular loop 1 (ILL1), intralobular loop 2 (ILL-2) and corkscrew (CSP) system patterns - (Figure 16) of NBI magnifying examination of early gastric cancer, which will be able to predict the histological subtype of most gastric carcinomas.

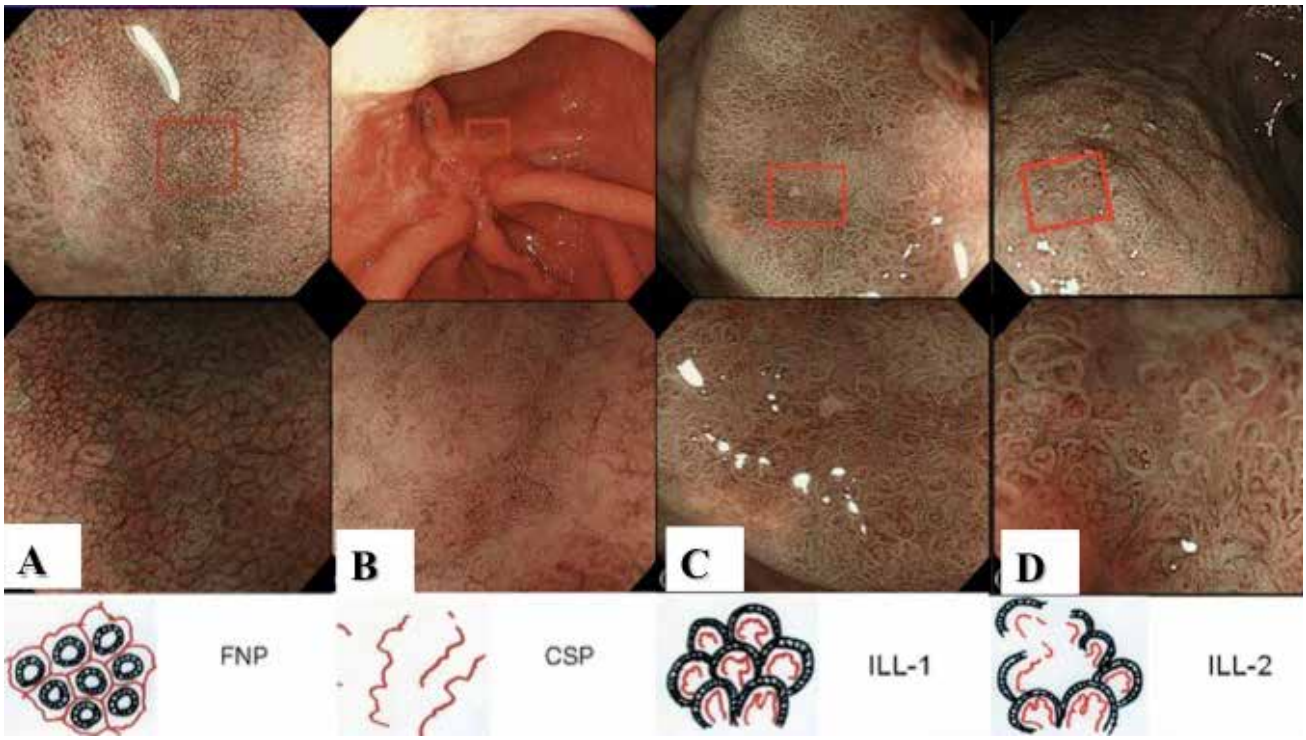

Figure 16 Narrow band imaging magnifying classification. (A) Fine network pattern (FNP) (B) Corkscrew pattern (CSP), (C) Intralobular loop pattern 1 (ILL-1) and (D) Intralobular Loop pattern 2 (ILL-2).

According to Yokoyama *et al*[91] differentiated-type adenocarcinomas mainly showed FNP or ILL pattern, with more than 80% of differentiated type adenocarcinomas were classified as ILL-1 or less ILL-2. Undifferentiated-type adenocarcinomas were all classified as ILL-2 or CSP. These findings are of great significance for treatment decision as differentiated early gastric cancer is good candidate for endoscopic removal, while undifferentiated gastric cancer may be invasive cancer.

Recently, acetic acid spray further emphasized the *superficial* gastric mucosal glandular structures and enhances the NBI magnifying endoscopic findings of early gastric cancer, revealing specific abnormal endoscopic patterns, such as small pit pattern, irregular villous pattern, or distorted pit pattern with absence of glandular structures (Figure 17)[74].

Acetic acid spray enhanced the accuracy of NBI magnification endoscopy in differentiating malignant from benign *superficial* gastric lesions, especially in controversial cases. A novel four-type NBI magnifying endoscopic classification after acetic acid spray for early gastric cancer is also published[74].

Up to now NBI imaging in combination with high resolution magnifying endoscopy is the acceptable accurate method of choice for the preoperative evaluation of *superficial* gastric lesions.

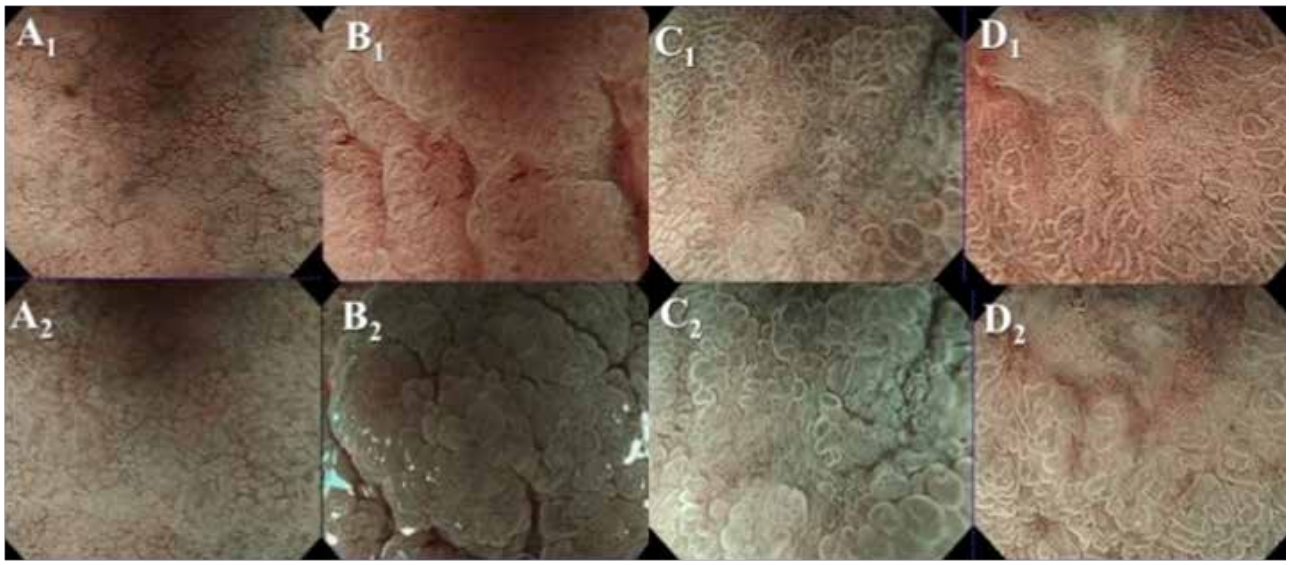

Figure 17 Novel NBI magnifying endoscopic classification for early gastric cancer after acetic acid spray: A: After acetic acid spray the fine network pattern (A1) is classified as small pit pattern (A2). B: The intralobular loop pattern 1 (ILL-1) (B1) is classified as irregular increased intensity of villous pattern (B2). C: The intralobular loop pattern 2 (ILL-2) (C1) is classified as irregular villous pattern combined with distorted pattern (C2) D: The corkscrew pattern is classified as distorted pattern combined with absence of glandular pattern (D2).

PIT PATTERN AND NBI MAGNIFYING ENDOSCOPIC CLASSIFICATION OF EARLY COLORECTAL CANCER

Colorectal lesions are classified according to modified Japanese classification of colorectal neoplasia[92] and Paris endoscopic classification of early GI cancer[1] by configuration, as depressed type (0-IIc), protruded type (0-Ip, 0-Isp, 0-Is) and flat type (0-IIa)[92,93] (Figure 18).

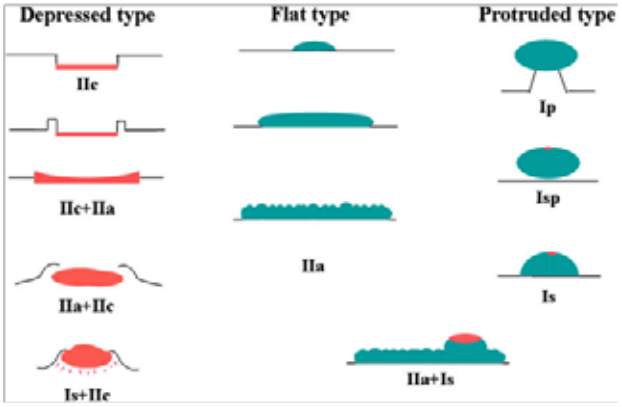

Figure 18 Gross configuration of colorectal neoplasm. The classification is a slight modification of the Japanese rule. The red colored area indicate the carcinomatous portion.

Some elevated colorectal lesions may reach a large (>10mm) lateral diameter without increasing in their height or protrusion above the mucosa. These are called "Lateral Spreading Tumors" (LST) and they tend to have a rather benign nature despite their large size. Laterally spreading colorectal tumors were divided into subgroups and are expressed as 0-IIa, 0-IIc+IIa, or 0-IIa+Is, according to the categories of the Paris classification[1].

Magnification colonoscopy enabled *in vivo* visualization of the fine surface microstructure of various colorectal lesions, while the combination of chromoendoscopy with magnifying colonoscopy is useful for detecting small localized lesions, for differential diagnosis and for determining not only the lateral extent but also the depth of a lesion.

'Pit pattern' is the specific arrangement of the openings of the glands in various kinds of colonic lesions under magnifying endoscopy[94,95]. Pit patterns basically divided into normal, non-neoplastic (hyperplastic), and neoplastic (adenomatous or cancerous) pattern. Although there are a variety of different classifications the most frequently used is the one described by S. Kudo and colleagues at the Akita Red Cross Hospital, which divides the pit patterns into six groups: types I, II, IIIL, IIIs, IV, and V (Figure 19 and 20). Pit patterns are useful in predicting the histological structure of a lesion. Particularly:

(1) The pits of the normal mucosa (type I) are round and regular in size and arrangement.

(2) The pits of non-neoplastic, hyperplastic polyps (type II) are larger than the normal pits, and star-shaped or onion like, but are regularly arranged.

(3) In polypoid adenomas, the pits often look elongated (type IIIL) The 'L' stands for 'Long' or Large') and sometimes branched (type IV).

(4) Lesions with compactly arranged pits smaller than the normal ones (type IIIS; the 'S' stands for 'small' or 'short') are characterized depressed and tend to be early cancers[96,97]. Such lesions are not frequent, but are highlighted nowadays as candidate precursors of advanced cancers of 'de novo' origin. The small pits reflect straight and compactly arranged glands of the lesion. Type IIIL and IIIS pits can be collectively called tubular pits.

(5) In intramucosal cancer (which might be regarded as high-grade dysplasia in Western countries) the pit pattern is fairly irregular (type V). In invasive cancer reaching the submucosa and in advanced cancer the surface of the lesion is rough and often ulcerated; therefore it is almost devoid of pits. This 'non-structural' pattern devoid of pits is also included in type V.

The correspondence between type of pit pattern and histological findings is quite well. Particularly, type II pit pattern is corresponding to non-neoplastic lesions in more than 70%, type IIIL, IIIS and IV are corresponding to adenomas in 79.6%, 86% and 75% respectively, type V_I is corresponding to carcinoma or high-grade dysplasia in 86% (61% carcinoma and 24% high-grade dysplasia), and VN is corresponding to carcinoma in 93% (65% is corresponding to submucosal invasive cancer).

The magnifying colonoscope has opened the door to the new field of diagnosing colorectal lesions. It is well established that histopathologic assessment of small lesions by observation with standard endoscopic instruments is imprecise. By magnifying endoscopy, however, it is possible to accurately differentiate true neoplastic tumors from non-tumorous lesions. The routine usage of magnification colonoscopy is assumed to reduce the requirement for biopsies and/or endoscopic resections for the small and numerous surface abnormalities without overt malignant pattern.

Furthermore, NBI imaging system in colon as in other parts of GI tract reveals specific vascular and mucosal patterns of *superficial* colonic lesions, which were found effective in distinguishing neoplastic from non-neoplastic lesions, as well as cancers from adenomas, with high accuracy (96.1%) in real time. NBI imaging combined with magnifying endoscopy allows an estimate of the likely histology of a polyp *in vivo*[26,98]. Wada *et al*[99], described a standardized NBI magnifying endoscopic classification for colorectal lesions and categorized vascular patterns of colonic neoplastic lesions into six groups (Figure 21).

Particularly, the normal colonic mucosa had a honey-comb-like vasculature (Figure 21A), hyperplastic polyp has a "faint" pattern (Figure 21B) and tubular adenomas showed a regular vessel-network pattern (Figure 21C) on NBI magnification. In villous and tubulovillous adenomas, the vessels were well developed and rather thick, which was the "dense" pattern (Figure 21D).

The NBI magnifying vascular structure in high-grade colorectal adenomas and early colorectal cancer varied depending on the different gross appearance of lesions. Protruded high-grade adenomas showed either a vessel-network pattern or a dense pattern (Figures 21 C and D). In protruded submucosally invasive cancers, the vessels were thick and irregular. Definition for "irregular" vascular pattern according to Wada *et al*[26] are (a) interruption of the network; (b) a tortuous course of vessels and (c) unusually large caliber of vessels (twice as large as that of surrounding vessels) (Figure 21E). In contrast the depressed-type lesions, especially depressed invasive cancers were characterized with decreased vessels, and this vascular pattern is called a "sparse" pattern (Figure 21F).

Based on the six patterns: normal, faint, network, dense, irregular and sparse of the above-mentioned NBI magnifying classification, it is able to differentiate neoplastic from non neoplastic colonic lesions with high sensitivity (83.5%), specificity (98.7%) and accuracy (98.2%), according to Wada *et al*[9926,98].

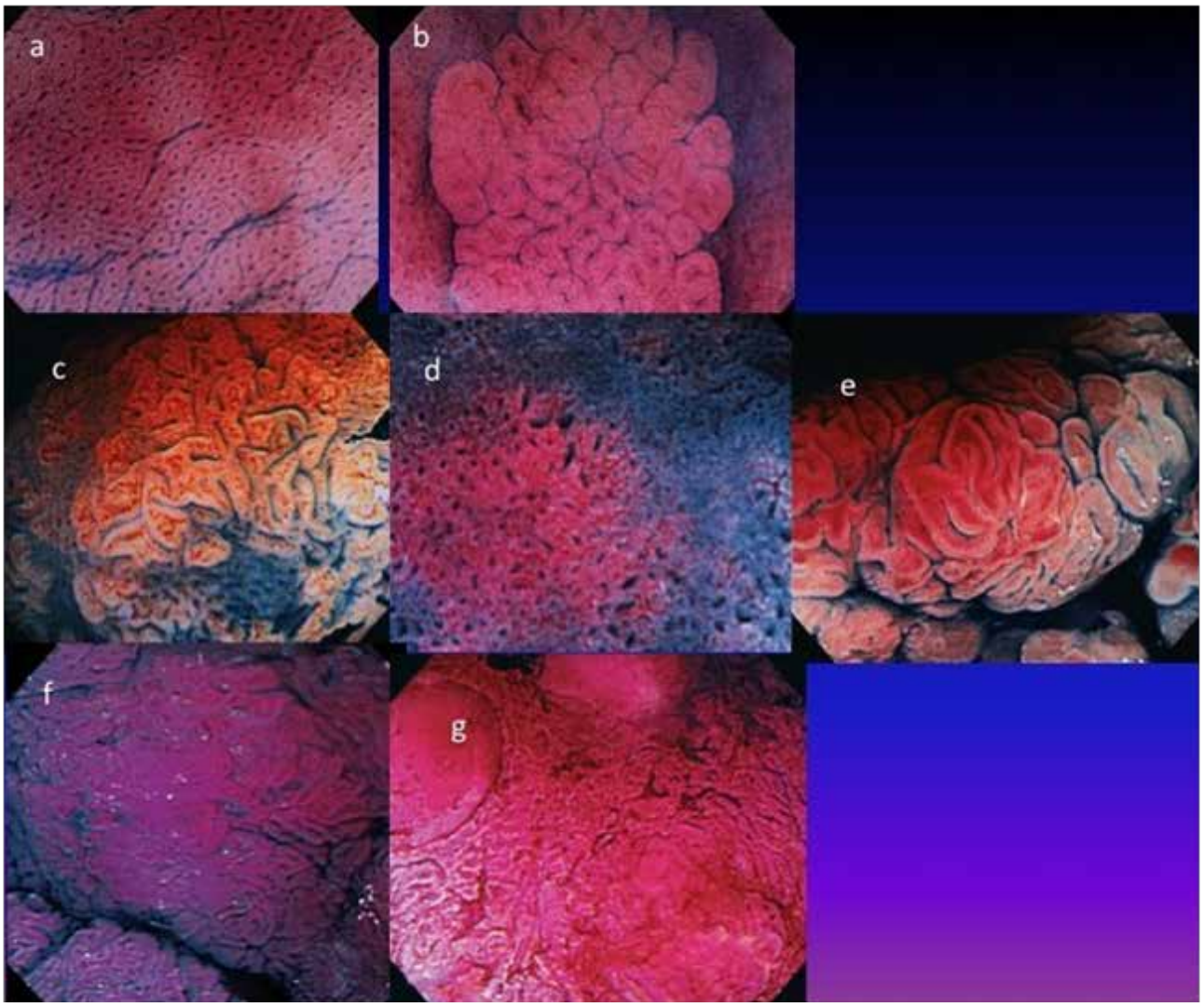

Figure 19 Pit pattern classification of colorectal neoplasia using magnifying endoscopy. a: Type I pit pattern consists of roundish pits with a regular distribution corresponding to normal mucosa; b: Type II pit pattern consists of relatively large star-like or onion-like pits corresponding to hyperplastic polyp or serrated adenoma; c: Type III$_L$ pit pattern is composed of tubular or roundish pits larger than normal ones corresponding to low grade adenoma; d: Type III$_S$ pit pattern is composed of tubular or roundish pits smaller than normal ones; e: Type I$_V$ pit pattern is a branched or gyrus-like pattern corresponding to adenoma with high-grade dysplasia; f: Type V pit pattern is divided into VI and V$_N$ corresponding to cancer. Pit pattern V$_I$ ('I' for 'irregular') has pits, which are irregular in shape, size and arrangement; g: Type V$_N$ ('N' for 'nonstructural') shows an absence of pit pattern corresponding to advanced cancer.

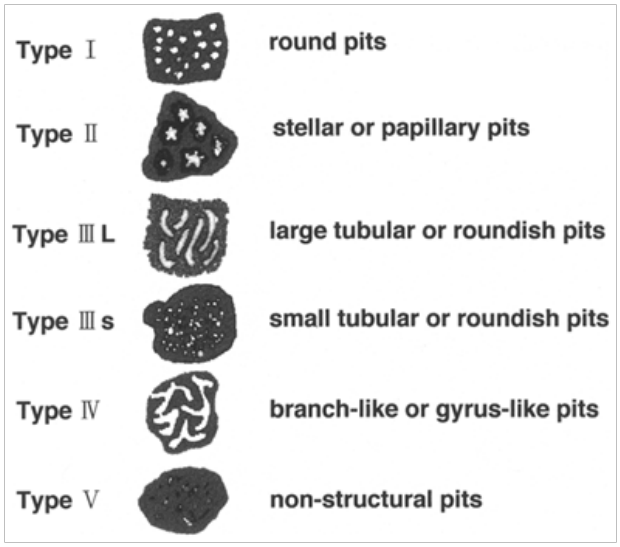

Figure 20 Pit pattern classification of colorectal neoplasia using magnifying endoscopy.

FOLLOW-UP AFTER ENDOSCOPIC TREATMENT OF EARLY GI CANCER

Accurate preoperative diagnosis and staging of early GI cancer, based on the technique and classifications described in this article, followed by precise patient selection for endoscopic (EMR or ESD) treatment according to established guidelines, resulted in favorable long-term outcome after curative endoscopic resections also for expanded indications in specialized centers[100-111].

Particularly, according to recent meta-analysis the local recurrence after ESD for early esophageal cancer was very low (0%-0.3% in mean observation period 19 months) and significantly lower than EMR (9%-11% in mean observation period 30 months)[102,112-115].

Regarding, early gastric cancer, the annual incidence (2.4%) of metachronous gastric cancer after endoscopic (ESD) resection was constant, with low cumulative 3-year incidence (3.3%-5.9%), while incidence of synchronous gastric cancer was also low (4%)[101,103,105-107]. Metachronous gastric cancers can be also treated curatively with repeat endoscopic resection[116]. ESD for undifferentiated early gastric cancer, is related to higher incidence of synchronous (14.5%) and

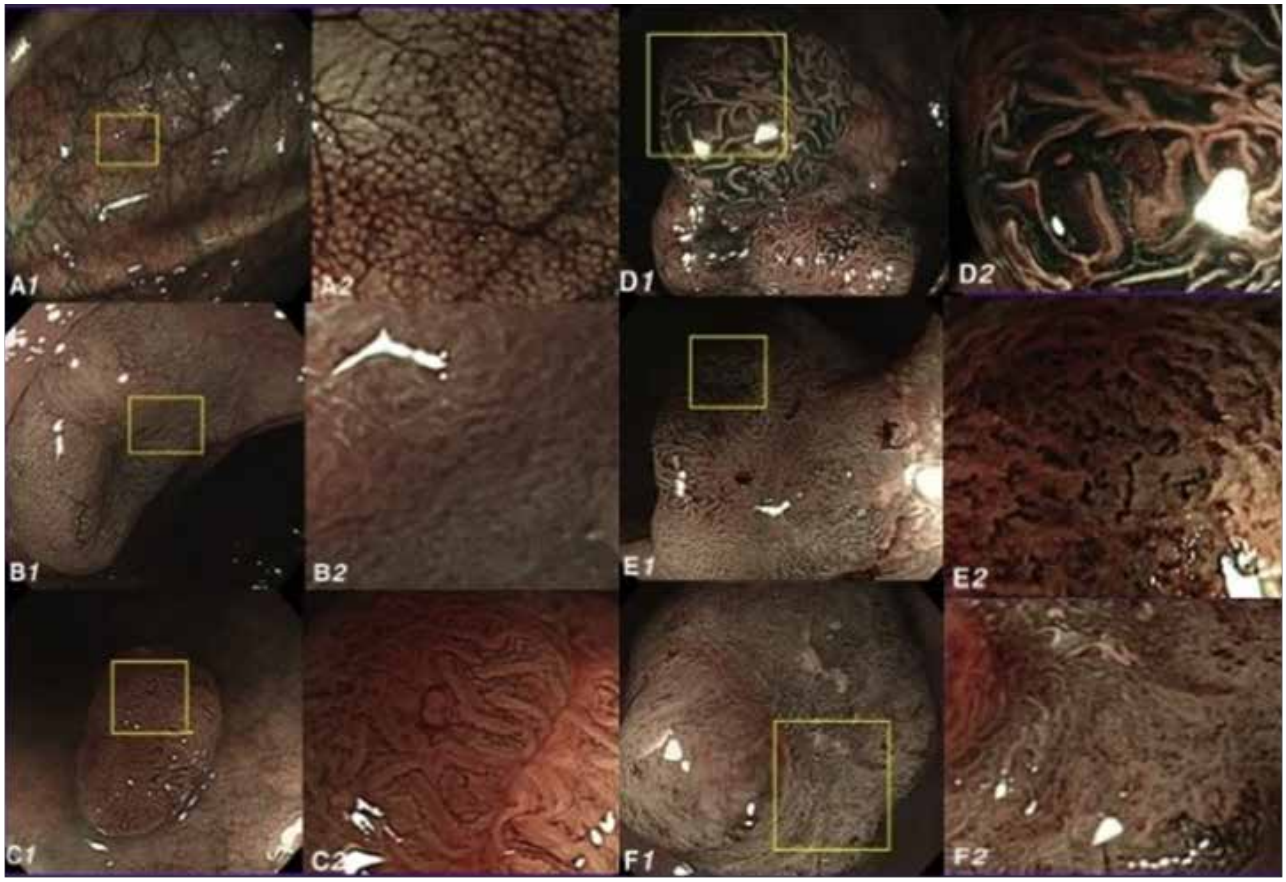

Figure 21 NBI magnifying endoscopic classification of the vascular pattern of colorectal lesions. A: Normal pattern (1, unmagnified; 2, magnified); B: Faint pattern (1, unmagnified; 2, magnified); C: Network pattern (1, unmagnified; 2, magnified); D: Dense pattern (1,unmagnified; 2, magnified); E: Irregular pattern (1, unmagnified; 2, magnified); F: Sparse pattern (1, unmagnified; 2, magnified).

metachronous (8.5%) gastric cancer, although generally low[108,117].

In order to detect synchronous or metachronous gastric cancer at an early stage, enough for a curative repeat ESD, an annual endoscopic surveillance program is recommended[101].

Finally, local endoscopic resection appears to be also effective for colorectal epithelial neoplasms, (adenomatous polyps and early-stage carcinoma) with overall favorable outcome[100,110,118,119.120]. Furthermore, en bloc colorectal ESD resection resulted in better outcome than piecemeal EMR[100,110,118,119,121]. Colorectal ESD can be also successfully applied as first line 'salvage' therapy in treating residual or locally recurrent neoplastic disease with favorable outcome alternatively to direct surgical resection[122].

CONCLUSIONS

The evolution in imaging technology (high resolution magnifying endoscopes, combined with chromoendoscopy and enhanced imaging capabilities, such as NBI technology) permitted the incorporation of endoscopic classifications of GI lesions in clinical setting, making precise endoscopic differential diagnosis (mucosal versus submucosal invasion) and staging of "*superficial*" GI lesions possible. Subsequently reliable accurate real-time treatment decisions (minimal invasive endoscopic versus surgical treatment) can be made.

In Japan there are currently in use standardized endoscopic classifications for early GI neoplasia. Pit pattern classification is used for colorectal lesions for years. NBI magnification endoscopy in esophagus, stomach and colorectum enhances both the mucosal microvascular architecture and microsurface structure, revealing specific NBI patterns. The IPCL pattern classification for early esophageal cancer and the NBI magnifying classifications for gastric and colorectal lesions, currently used in Japanese centers, permitted *in vivo* prediction of histology and are useful tools for reliable, real-time preoperative staging of early GI cancer.

Local treatment for mucosal GI cancer by endoscopic resection, either endoscopic mucosal rejection (EMR) or endoscopic submucosal dissection (ESD) has been generally accepted as an adequate therapeutic method in Japan, and is growing in the West. In submucosal invasive cancer, however, surgery with complete removal of lymph nodes has been recommended as the standard treatment, because the high incidence of lymph node metastases (approximately 10-40%)[5,26,29,123].

Finally, in stomach and colorectum, mucosal and slightly invasive submucosal cancer with no lymph node metastasis are good targets for endoscopic local resection (EMR/ESD), while in esophagus upper mucosal cancer only, without lymph node metastases, is indication for endoscopic therapy (EMR/ESD).

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

1 The Paris endoscopic classification of *superficial* neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endos*c 2003; **58**: S3-43

2 GY Lauwer. Gastric carcinoma In: FT Bosman, F Carneiro, RH Hruban, ND Theise, editors. WHO Classification of Tumours of the Digestive System, 4th edition, Volume 3. Lyon: International Agency for Research on Cancer (IARC) 2010

3 Japanese Esophageal Society: Japanese Classification of Esophageal Cancer: 10th edition. Tokyo: Kanehara; 2008. p 1-123

4 Japanese Research Society for Gastric Cancer. Japanese classification of gastric carcinoma. 1st English edition. Tokyo: Kanehara Co. Ltd 1995 p.73-88

5 Japanese Society for Cancer of the Colon and Rectum. Japanese classification of colorectal carcinoma. 2nd English edition, Kanehara & Co., Ltd., Tokyo, 2009. p.1-90

6 K Takubo, J Aida, M Sawabe, M Kurosumi, M Arima, M Fujishiro, T Arai. Early squamous cell carcinoma of the oesophagus: the Japanese viewpoint. *Histopathology* 2007; **51(6)**: 733-742

7 GK Schwartz, H Wang, N Lampen, N Altorki, D Kelsen, EP Albino. Defining the invasive phenotype of proximal gastric cancer cells. *Cancer* 1994; **73(1)**: 22-27

8 RJ Schlemper, Y Kato, M Stolte. Review of histological classifications of gastrointestinal epithelial neoplasia: differences in diagnosis of early carcinomas between Japanese and Western pathologists. *J Gastroenterol* 2001; **36(7)**: 445-456

9 T Yamao, K Shirao, H Ono, H Kondo, D Saito, H Yamaguchi, M Sasako, T Sano, A Ochial, S Yoshida. Risk factors for lymph node metastasis from intramucosal gastric carcinoma. *Cancer* 1996; **77(4)**: 602-606

10 T Sano, O Kobori, T Muto. Lymph node metastasis from early gastric cancer: endoscopic resection of tumour. *Br J Surg* 1992; **79(3)**: 241-244

11 Y Sano, M Kobayashi, Y Hamamoto. New diagnostic method based on color imaging using narrow-band imaging (NBI) system for gastrointestinal tract. *Gastrointest Endosc* 2001; **53(5)**: AB125

12 Y Tajima, Y Nakanishi, A Ochiai, Y Tachimori, H Kato, H Watanabe, H Yamaguchi, K Yoshimura, M Kusano, T Shimoda. Histopathologic findings predicting lymph node metastasis and prognosis of patients with *superficial* esophageal carcinoma: analysis of 240 surgically resected tumors. *Cancer* 2000; **88(6)**: 1285-1293

13 H Makuuchi. Endoscopic mucosal resection for early esophageal cancer: indications and techniques. *Dig Endosc* 1996; **8**: 175-179

14 SE Kudo. Early colorectal cancer: detection of depressed types of colorectal carcinoma. 1st ed. Tokyo: Igaku-Shoin. 1996: 81-93

15 H Yamano, S Kudo, Y Tamegai, Y Imai. The adoption of endoscopic therapy from the viewpoint of the degree of submucosal invasion in early colorectal carcinoma (in Japanese with English abstract). *Stomach Intestine (Tokyo)* 1999; **34(6)**: 769-774

16 RC Haggitt, RE Glotzbach, EE Soffer, LD Wruble. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985; **89(2)**: 328-336

17 K Omote, M Mai, M Mizoguchi, Y Takahashi, A Kawashima. Degree of submucosal invasion of early gastric carcinomas and risk for lymph node metastasis: consideration limiting of applicability for endoscopic resection (in Japanese with English abstract). *Stomach Intestin*e 1997; **32**: 49-55

18 Japan Esophageal Society. Guidelines of clinical and pathological studies on carcinoma of the esophagus, 10th edition Tokyo: Kanehara Co. Ltd 2007 (in Japanese)

19 H Inoue, SE Kudo, A Shiokawa. Novel endoscopic imaging techniques toward *in vivo* observation of living cancer cells in the gastrointestinal tract. *Clin Gastroenterol Hepatol* 2005; **3**: S61-63

20 Inoue H, Kudo SE, Shiokawa A. Technology insight: Laser-scanning confocal microscopy and endocytoscopy for cellular observation of the gastrointestinal tract. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 31-37

21 H Inoue, K Sasajima, M Kaga, S Sugaya, Y Sato, Y Wada, M Inui, H Satodate, SE Kudo, S Kimura, S Hamatani, A Shiokawa. Endoscopic *in vivo* evaluation of tissue atypia in the esophagus using a newly designed integrated endocytoscope: a pilot trial. *Endoscopy* 2006; **38(9)**: 891-895

22 H Inoue, A Yokoyama, SE Kudo. Ultrahigh magnifying endoscopy: development of CM double staining for endocytoscopy and its safety. *Nihon Rinsho* 2010; **68(7)**: 1247-1252

23 S Kudo, K Sasajima, H Inoue, F Ishida, K Otsuka, N Ikehara, Y Kudo, H Kashida, J Ukegawa, F Yamamura, S Hamatani, H Watanabe. Recent progress in endocytoscopy system: Classification of endocytoscopy. *Nihon Naika Gakkai Zasshi* 2007; **96(2)**: 252-265

24 SE Kudo, K Wakamura, N Ikehara, Y Mori, H Inoue, S Hamatani. Diagnosis of colorectal lesions with a novel endocytoscopic classification - a pilot study. Endoscopy 2011;43(10):869-875.

25. Y Kumagai, K Kawada, S Yamazaki, M Lida, K Momma, H Odajima, H Kawachi, T Nemoto, T Kawano, K Takubo. Endocytoscopic observation for esophageal squamous cell carcinoma: can biopsy histology be omitted? *Dis Esophagus* 2009; **22(6)**: 505-512

26 Y Wada, SE Kudo, H Kashida, N Ikehara, H Inoue, F Yamamura, K Otsuka, S Hamatani. Diagnosis of colorectal lesions with the magnifying narrow-band imaging system. *Gastrointest Endosc* 2009; **70(3)**: 522-531

27 M Kodama, T Kakegawa. Treatment of *superficial* cancer of the esophagus: a summary of responses to a questionnaire on *superficial* cancer of the esophagus in Japan. *Surgery* 1998; **123(4)**: 432-439

28 K Yasuda, N Shiraishi, T Suematsu, K Yamaguchi, Y Adachi, S Kitano. Rate of detection of lymph node metastasis is correlated with the depth of submucosal invasion in early stage gastric carcinoma. *Cancer* 1999; **85(10)**: 2119-2123

29 T Gotoda, M Sasako, H Ono, H Katai, T Sano, T Shimoda. Evaluation of the necessity for gastrectomy with lymph node dissection for patients with submucosal invasive gastric cancer. *Br J Surg* 2001; **88(3)**: 444-449

30 T Gotoda. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1-11

31 T Gotoda, A Yanagisawa, M Sasako, H Ono, Y Nakanishi, T Shimoda Y Kato. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000;3(4):219-225.

32 M Endo, K Takeshita, T Kawano, H Inoue. Indication: endoscopic treatment for early carcinoma of the esophagus. In Okubo A, Kimura K, Imawari M, Nakamura T eds. Shokaki-Shinryo practice. *Tokyo: Bunkodo* 1998: 139-142

33 H Makuuchi, H Shimada, O Chino. Survival of patients with *superficial* squamous cell carcinoma of the esophagus treated by esophagectomy. Rinsho-Shokakinaika (Clin. Gastroenterol.) (in Japanese). 1997:1749-1756

34 Japan Esophageal Society. Comprehensive registry of esophageal cancer in Japan. Available at http://esophagus.jp Last accessed 18 April 2007

35 M Oyama. T, Miyata Y, Shimatani S, Tomori A, Hotta K, Yoshida M. Lymph node metastasis of m3 and sm1 esophageal cancer. (in Japanese). *I Cho (Stomach Intestine)* 2002; **37**: 71-74

36 H Inoue. Endoscopic diagnosis of tissue atypism (EA) in the pharyngeal and esophageal squamous epithelium; IPCL pattern classification and ECA classification. *Kyobu Geka* 2007; **60**: 768-775

37 Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113-123

38 Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112

39 KS Nakamura, H Sugano, K Takagi. Carcinoma of the stomach in incipient phase; its histogenesis and histological appearances. *Gann* 1968; **59(3)**: 251-258

40 YD Park, YJ Chung, HY Chung, W Yu, HI Bae, SW Jeon, CM Cho, WY Tak, YO Kweon. Factors related to lymph node metastasis and the feasibility of endoscopic mucosal resection for treating

poorly differentiated adenocarcinoma of the stomach. *Endoscopy* 2008; **40(1)**: 7-10
41 H Ono, H Kondo, T Gotoda, K Shirao, H Yamaguchi, D Saito, K Hosokawa, T Shimoda, S Yoshida. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48(2)**: 225-229
42 N Abe, T Watanabe, M Sugiyama, O Yanagida, T Masaki, T Mori, Y Atomi. Endoscopic treatment or surgery for undifferentiated early gastric cancer? *Am J Surg* 2004; **188(2)**: 181-184
43 N Abe, T Watanabe, K Suzuki, H Machida, H Toda, Y Nakaya, T Masaki, T Mori, M Sugiyama, Y Atomi. Risk factors predictive of lymph node metastasis in depressed early gastric cancer. *Am J Surg* 2002; **183(2)**: 168-172
44 S Kitano. Can an intramucosal undifferentiated-type gastric cancer become a candidate for endoscopic submucosal resection? *Gastric Cancer* 2009; **12**: 125-126
45 S Tsujitani, S Oka, H Saito, A Kondo, M Ikeguchi, M Maeta, N Kalbara. Less invasive surgery for early gastric cancer based on the low probability of lymph node metastasis. *Surgery* 1999; **125(2)**: 148-154
46 N Abe, H Takeuchi, A Ohki, O Yanagida, T Masaki, T Mori, M Sugiyama. Long-term outcomes of combination of endoscopic submucosal dissection and laparoscopic lymph node dissection without gastrectomy for early gastric cancer patients who have a potential risk of lymph node metastasis. *Gastrointest Endosc* 2011; **74(4)**: 792-797
47 SE Kudo, Y Sugihara, H Kida H, F Ishida, H Miyachi, Y Mori, M Misawa, T Hisayuki, K Kodama, K Wakamura, T Hayashi, Y Wada, S Hamatani. Depressed-Type Colonic Lesions and "De Novo" Cancer in Familial Adenomatous Polyposis: A Colonoscopist's Viewpoint. *ISRN Gastroenterol* 2013; **2013**: 838134
48 S Kudo, S Tamure, T Nakajima, S Hirota, M Asano, O Ito, H Kusaka. Depressed type of colorectal cancer. *Endoscopy* 1995; **27(1)**: 54-57; discussion 61
49 SE Kudo, H Kashida. Flat and depressed lesions of the colorectum. *Clin Gastroenterol Hepatol* 2005; **3(7 supl 1)**: S33-36
50 SR Hamilton, LA Aaltonen, editors. World Health Organization classification of tumors: pathology and genetics of tumors of the digestive system (IARC). *Lyon (France): International Agency for Research on Cancer* 2000:103-119
5 RS Kwon, LM Wong Kee Song, DG Adler, JD Conway, DL Diehl, FA Farraye, SV Kantsevoy, V Kaul, SR Kethu, P Mamula, MC Pedrosa, SA Rodriquez, WM Tierney. Endocytoscopy. *Gastrointest Endosc* 2009; **70(4)**: 610-613
52 M Fujishiro, S Kodashima, K Takubo, N Kakushima, M Omata. Detailed comparison between endocytoscopy and horizontal histology of an esophageal intraepithelial squamous cell carcinoma. *Dis Esophagus* 2008; **21(2)**: 181-185
53 S Yoshida, T Kozu, T Gotoda, D Saito. Detection and treatment of early cancer in high-risk populations. *Best Pract Res Clin Gastroenterol* 2006; **20(4)**: 745-765
54 H Inoue, JF Rey, C Lightdale. Lugol chromoendoscopy for esophageal squamous cell cancer. *Endoscopy* 2001; **33(1)**: 75-79
55 Y Shimizu, H Tukagoshi, M Fujita, M Hosokawa, M Kato, M Asaka. Endoscopic screening for early esophageal cancer by iodine staining in patients with other current or prior primary cancers. *Gastrointest Endosc* 2001; **53(1)**: 1-5
56 H Mitooka, T Fujimori, S Maeda, K Nagasako. Minute flat depressed neoplastic lesions of the colon detected by contrast chromoscopy using an indigo carmine capsule. *Gastrointest Endosc* 1995; **41(5)**: 453-459
57 T Fujii, RT Hasegawa, Y Saitoh, D Fleischer, Y Saito, Y Sano, S Kato. Chromoscopy during colonoscopy. *Endoscopy* 2001; **33(12)**: 1036-1041
58 E Jaramillo, M Watanabe, P Slezak, C Rubio. Flat neoplastic lesions of the colon and rectum detected by high-resolution video endoscopy and chromoscopy. *Gastrointest Endosc* 1995; **42(2)**: 114-122
59 R Kiesslich, M von Bergh, M Hahn, G Hermann, M Jung. Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. *Endoscopy* 2001; **33(12)**: 1001-1006
60 CY Kim, DE Fleischer. Colonic chromoscopy. A new perspective on polyps and flat adenomas. *Gastrointest Endosc Clin N Am* 1997; **7(3)**: 423-437
61 GM Eisen, CY Kim, DE Fleischer, RA Kozarek, DL Carr-Locke, TC Li, CJ Gostout, SJ Heller, EA Montgomery, FH AI-Kawas, JH Lewis, SB Benjamin. High-resolution chromoendoscopy for classifying colonic polyps: a multicenter study. *Gastrointest Endosc* 2002; **55(6)**: 687-694
62 JC Brooker, BP Saunders, SG Shah, CJ Thapar, HJ Thomas, WS Atkin, CR Cardwell, CB Williams. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. *Gastrointest Endosc* 2002; **56(3)**: 333-338
63 JD Waye, AJ Ganc, HB Khelifa, J Kotrilik, A Kumar, K Ogoshi, GV Roig. Chromoscopy and zoom colonoscopy. *Gastrointest Endosc* 2002; **55(6)**: 765-766
64 MI Canto. Methylene blue chromoendoscopy for Barrett's esophagus: coming soon to your GI unit? *Gastrointest Endosc* 2001; **54(3)**: 403-409
65 MI Canto, S Setrakian, JE Willis, A Chak, RE Petras, MV Sivak. Methylene blue staining of dysplastic and nondysplastic Barrett's esophagus: an *in vivo* and ex vivo study. *Endoscopy* 2001; **33(5)**: 391-400
66 R Kiesslich, M Hahn, G Herrmann, M Jung. Screening for specialized columnar epithelium with methylene blue: chromoendoscopy in patients with Barrett's esophagus and a normal control group. *Gastrointest Endosc* 2001; **53(1)**: 47-52
67 P Sharma, M Topalovski, MS Mayo, AP Weston. Methylene blue chromoendoscopy for detection of short-segment Barrett's esophagus. *Gastrointest Endosc* 2001; **54(3)**: 289-293
68 E Rajan, LJ Burgart, CJ Gostout. Endoscopic and histologic diagnosis of Barrett esophagus. *Mayo Clin Proc* 2001; **76(2)**: 217-225
69 T Endo, T Awakawa, H Takahashi, Y Arimura, F Itoh, K Yamashita, S Sasaki, H Yamamoto, X Tang, K Imai. Classification of Barrett's epithelium by magnifying endoscopy. *Gastrointest Endosc* 2002; **55(6)**: 641-647
70 R Kiesslich, J Fritsch, M Holtmann, . Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003; **124(4)**: 880-888
71 CN Bernstein. The color of dysplasia in ulcerative colitis. *Gastroenterology* 2003; **124(4)**: 1135-1138
72 R Lambert, JF Rey, R Sankaranarayanan. Magnification and chromoscopy with the acetic acid test. *Endoscopy* 2003; **35(5)**: 437-445
73 M Guelrud, I Herrera, H Essenfeld, J Castro. Enhanced magnification endoscopy: a new technique to identify specialized intestinal metaplasia in Barrett's esophagus. *Gastrointest Endosc* 2001; **53(6)**: 559-565
74 N Eleftheriadis, H Inoue, H Ikeda, M Onimaru, A Yoshida, R Maselli, G Santi, SE Kudo. Acetic acid spray enhances accuracy of narrow-band imaging magnifying endoscopy for endoscopic tissue characterization of early gastric cancer. *Gastrointest Endosc* 2014; **79(5)**: 712
75 T Yoshida, H Inoue, S Usui, H Satodate, N Fukami, SE Kudo. Narrow-band imaging system with magnifying endoscopy for *superficial* esophageal lesions. *Gastrointest Endosc* 2004; **59(2)**: 288-295
76 I Inoue, M Kaga, Y Sato, S Sugaya, SE Kudo. Magnifying endoscopic diagnosis of tissue atypia and cancer invasion depth in the area pharyngo-esophageal squamous epithelium by NBI enhanced

magnification image: IPCL pattern classification. In: J Cohen, ed. Advanced Digestive Endoscopy: Comprehensive Atlas of High Resolution Endoscopy and Narrowband Imaging: Blackwell Publishing, 2009: 49-66
77 H Inoue, M Kaga, H Minami, S Sugaya, Y Sato, H Kida, H Satodate, SE Kudo. Endoscopic diagnosis of tissue atypia and cancer invasive depth in the pharynx and esophagus using NBI enhanced imaging technology. *Nihon Shokakibyo Gakkai Zasshi* 2007; **104(6)**: 774-781
78 S Nonaka, Y Saito, I Oda, T Kozu, D Saito. Narrow-band imaging endoscopy with S magnification is useful for detecting metachronous *superficial* pharyngeal cancer in patients with esophageal squamous cell carcinoma. *J Gastroenterol Hepatol* 2010; **25(2)**: 264-269
79 A Watanabe, M Taniguchi, H Tsujie, M Hosokawa, M Fujita, S Sasaki. The value of narrow band imaging endoscope for early head and neck cancers. *Otolaryngol Head Neck Surg* 2008; **138(4)**: 446-451
80 S Yoshida. Narrowband imaging: Historical background and basis for its development. In: J Cohen, ed. Advanced Digestive Endoscopy: Comprehensive Atlas of High Resolution Endoscopy and Narrowband Imaging: Blackwell Publishing, 2009: 3-5
81 M Muto, C Katada, Y Sano, S Yoshida. Narrow band imaging: a new diagnostic approach to visualize angiogenesis in *superficial* neoplasia. *Clin Gastroenterol Hepatol* 2005; **3(7) Suppl 1**: S16-20
82 Y Ezoe, M Muto, N Uedo, H Doyama, K Yao, I Oda, K Kaneko, Y Kawahara, C Yokoi, Y Sugiura, H Ishikawa, Y Takeuchi, Y Kaneko, Y Saito. Magnifying Narrowband Imaging Is More Accurate than Conventional White-Light Imaging in Diagnosis of Gastric Mucosal Cancer. *Gastroenterology* 2011; **141(6)**: 2017-2025 e3
83 K Gono, T Obi, M Yamaguchi, N Ohyama, H Machida, Y Sano, S Yoshida, Y Hamamoto, T Endo. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004; **9(3)**: 568-577
84 LY Huang, J Cui, CR Wu, YX Liu, N Xu. Narrow-band imaging in the diagnosis of early esophageal cancer and precancerous lesions. *Chin Med J (Engl)* 2009; **122(7)**: 776-780
85 M Stolte. The new Vienna classification of epithelial neoplasia of the gastrointestinal tract: advantages and disadvantages. *Virchows Arch* 2003; **442(2)**: 99-106
86 M Muto, M Nakane, C Katada, Y Sano, A Ohtsu, H Esumi, S Ebihara, S Yoshida. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. *Cancer* 2004; **101(6)**: 1375-1381
87 MJ Connor, P Sharma. Chromoendoscopy and magnification endoscopy for diagnosing esophageal cancer and dysplasia. *Thorac Surg Clin* 2004; **14**: 87-94
88 R Maselli, H Inoue, H Ikeda, M Onimaru, A Yoshida, EG Santi, H Sato, N Eleftheriadis, B Hayee, SE Kudo. The metallic silver sign with narrow-band imaging: a new endoscopic predictor for pharyngeal and esophageal neoplasia. *Gastrointest Endosc* 2013; **78(3)**: 551-553
89 K Yao, Y Takaki, T Matsui, A Iwashita, GK Anagnostopoulos, P Kaye, K Ragunath. Clinical application of magnification endoscopy and narrow-band imaging in the upper gastrointestinal tract: new imaging techniques for detecting and characterizing gastrointestinal neoplasia. *Gastrointest Endosc Clin N Am* 2008; **18(3)**: 415-433, vii-viii
90 K Yao, GK Anagnostopoulos, K Ragunath. Magnifying endoscopy for diagnosing and delineating early gastric cancer. *Endoscopy* 2009; **41(5)**: 462-467
91 A Yokoyama, H Inoue, H Minami, Y Wada, Y Saito, H Satodate, S Hamatani, SE Kudo. Novel narrow-band imaging magnifying endoscopic classification for early gastric cancer. *Dig Liver Dis* 2010; **42(10)**: 704-708
92 Japanese Society for Cancer of the Colon and Rectum. General rules for clinical and pathological studies on cancer of the colon, rectum and anus [in Japanese]. Kanehara and Co. 7th ed. Tokyo. 2006: 40
93 H Kashida, SE Kudo. Early colorectal cancer: concept, diagnosis, and management. *Int J Clin Oncol* 2006; **11**: 1-8
94 S Kudo, S Hirota, T Nakajima, S Hosobe, H Kusaka, T Kobayashi, M Himori, A Yagyuu. Colorectal tumours and pit pattern. *J Clin Pathol* 1994; **47(10)**: 880-885
95 S Kudo, H Kashida, T Nakajima, S Tamura, K Nakajo. Endoscopic diagnosis and treatment of early colorectal cancer. *World J Surg* 1997; **21(7)**: 694-701
96 S Kudo, H Kashida, T Tamura. Early colorectal cancer: flat or depressed type. *J Gastroenterol Hepatol* 2000; **15 Suppl**: D66-70
97 S Kudo, H Kashida, S Tamura, T Nakajima. The problem of "flat" colonic adenoma. *Gastrointest Endosc Clin N Am* 1997; **7(1)**: 87-98
98 Y Wada, SE Kudo, M Misawa, N Ikehara, S Hamatani. Vascular pattern classification of colorectal lesions with narrow band imaging magnifying endoscopy. *Dig Endosc* 2011; **23 Suppl 1**: 106-111
99 Y Wada, H Kashida, N Ikehara, K Wakamura, KI Mizuno, S Hamatani, SE Kudo. The diagnosis of colorectal lesions with magnifying narrow band imaging system [abstract]. *Gastrointest Endosc* 2008; **67(5)**: AB311-312
100 N Kobayashi, N Yoshitake, Y Hirahara, J Konishi, Y Saito, T Matzuda, T Ishikawa, R Sekiguchi, T Fujimori. Matched case-control study comparing endoscopic submucosal dissection and endoscopic mucosal resection for colorectal tumors. *J Gastroenterol Hepatol* 2012; **27(4)**: 728-733
101 T Nakajima, I Oda, T Gotoda, H Hamanaka, T Eguchi, C Yokoi, D Saito. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance? *Gastric Cancer* 2006; **9(2)**: 93-98
102 H Takahashi, Y Arimura, H Masao, S Okahara, T Tanuma, J Kodaira, H Kagaya, Y Shimizu, K Hokari, H Tsukagoshi, Y Shinomura, M Fujita. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). *Gastrointest Endosc* 2010; **72(2)**: 255-264, 264 e1-2
103 JS Han, JS Jang, SR Choi, HC Kwon, MC Kim, JS Jeong, SJ Kim, YJ Sohn, EJ Lee. A study of metachronous cancer after endoscopic resection of early gastric cancer. *Scand J Gastroenterol* 2011; **46(9)**: 1099-1104
104 I Oda, T Oyama, S Abe, K Ohnita, T Kosaka, K Hirasawa, K Ishido, M Nakagawa, S Takahashi. Preliminary results of multicenter questionnaire study on long-term outcomes of curative endoscopic submucosal dissection for early gastric cancer. *Dig Endosc* 2014; **26(2)**: 214-219
105 H Lee, WK Yun, BH Min, JH Lee, PL Rhee, KM Kim, JC Rhee, JJ Kim. A feasibility study on the expanded indication for endoscopic submucosal dissection of early gastric cancer. *Surg Endosc* 2011; **25 (6)**: 1985-1993
106 T Boda, M Ito, S Oka, Y Kitamura, N Numata, Y Sanomura, T Matsuo, S Tanaka, M Yoshihara, K Arihiro, K Chayama. Characteristics of metachronous gastric tumors after endoscopic submucosal dissection for gastric intraepithelial neoplasms. *Gastroenterol Res Pract* 2014; **2014**: 863595
107 MY Jang, JW Cho, WG Oh, SJ Ko, SH Han, HK Baek, YJ Lee, JW Kim, GM Jung, YK Cho. Clinicopathological characteristics of synchronous and metachronous gastric neoplasms after endoscopic submucosal dissection. *Korean J Intern Med* 2013; **28(6)**: 687-693
108 MK Choi, GH Kim, Y Park do, GA Song, DU Kim, DY Ryu, BE Lee, JH Cheong, M Cho. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a single-center experience. *Surg Endosc* 2013; **27(11)**: 4250-4258

109 M Kato, T Nishida, K Yamamoto, S Hayashi, S Kitamura, T Yabuta, T Yoshio, T Nakamura, M Komori, N Kawai, A Nishihara, F Nakanishi, M Nakahara, H Ogiyama, K Kinoshita, T Yamada, H Lijima, M Tsujii, T Takehara. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. *Gut* 2013; **62(10)**: 1425-1432

110 PH Zhou, LQ Yao, WF Chen. Endoscopic therapy of adenomatous polyps and early-stage carcinomas of the colon and rectum. *Zhonghua Wai Ke Za Zhi* 2008; **46(18)**: 1386-1389

111 M Fujishiro, N Yahagi, M Nakamura, N Kakushima, S Kodashima, S Ono, K Kobayashi, T Hashimoto, N Yamamichi, A Tateichi, Y Shimizu, M Oka, K Ogura, T Kawabe, M Ichinose, M Omata. Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. *Gastrointest Endosc* 2006; **63(2)**: 243-249

112 HM Guo, XQ Zhang, M Chen, SL Huang, XP Zou. Endoscopic submucosal dissection vs endoscopic mucosal resection for *superficial* esophageal cancer. *World J Gastroenterol* 2014; **20(18)**: 5540-5547

113 AY Teoh, PW Chiu, DK Yu Ngo, SK Wong, JY Lau, EK Ng. Outcomes of endoscopic submucosal dissection versus endoscopic mucosal resection in management of *superficial* squamous esophageal neoplasms outside Japan. *J Clin Gastroenterol* 2010; **44**: e190-194

114 Y Urabe, T Hiyama, S Tanaka, M Yoshihara, K Arihiro, K Chayama. Advantages of endoscopic submucosal dissection versus endoscopic oblique aspiration mucosectomy for *superficial* esophageal tumors. *J Gastroenterol Hepatol* 2011; **26 (2)**: 275-280

115 C Katada, M Muto, S Tanabe, K Higuchi, T Sasaki, M Azuma, K Ishido, T Masaki, M Nakayama, M Okamoto, W Koizumi. Surveillance after endoscopic mucosal resection or endoscopic submucosal dissection for esophageal squamous cell carcinoma. *Dig Endosc* 2013; **25 Suppl 1**: 39-43

116 JY Lee, IJ Choi, SJ Cho, CG Kim, MC Kook, JH Lee, KW Ryu, YW Kim. Endoscopic submucosal dissection for metachronous tumor in the remnant stomach after distal gastrectomy. *Surg Endosc* 2010; **24(6)**: 1360-1366

117 JH Seo, JC Park, YJ Kim, SK Shin, YC Lee, SK Lee. Undifferentiated histology after endoscopic resection may predict synchronous and metachronous occurrence of early gastric cancer. *Digestion* 2010; **81**: 35-42

118 PH Zhou, LQ Yao, XY Qin. Endoscopic submucosal dissection for colorectal epithelial neoplasm. *Surg Endosc* 2009; **23**: 1546-1551

119 A Repici, C Hassan, D De Paula Pessoa, N Pegano, A Arezzo, A Zullo, R Lorenzetti, R Marmo. Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review. *Endoscopy* 2012; **44**: 137-150

120 S Tanaka, S Oka, I Kaneko,M Hirata, R Mouri, H Kanao, S Yoshida, K Chayama. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. *Gastrointest Endosc* 2007; **66**: 100-107

121 Y Saito, T Uraoka, T Matsuda, F Emura, H Ikehara, Y Mashimo, T Kikuchi, KI Fu, Y Sano, D, Saito. Endoscopic treatment of large *superficial* colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; **66**: 966-973

122 DP Hurlstone, AJ Shorthouse, SR Brown, N Tiffin, SS Cross. Salvage endoscopic submucosal dissection for residual or local recurrent intraepithelial neoplasia in the colorectum: a prospective analysis. *Colorectal Dis* 2008; **10**: 891-897

123 T Okamura, S Tsujitani, D Korenaga, M Haraguchi, H Baba, Y Hiramoto, K Sugimachi. Lymphadenectomy for cure in patients with early gastric cancer and lymph node metastasis. *Am J Surg* 1988; **155(3)**: 476-480

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