17

Endoscopic Diagnosis and Treatment for Colorectal Cancer

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1. Introduction

Colonoscopy plays an important role in the medical care of patients with colorectal cancer. It is generally used for both the diagnosis of different stages of colorectal cancer and the treatment of early colorectal cancer and its precursors. The recent progress in colonoscopy has been remarkable. Endoscopes with variable rigidity and small diameters provide efficient insertion to the cecum and result in lower distress for patients. Trained colonoscopists can insert endoscopes into the cecum within a few minutes, and it is not necessary to anesthetize patients without severe peritoneal adhesion.

We can obtain good-quality pictures and special images to assist in diagnosis by using high-vision endoscopes, magnifying endoscopes, dye spray, and narrow-band imaging (NBI). Determining whether a colorectal carcinoma can be curatively resected by endoscopic treatment or whether the carcinoma has a risk of lymph node metastasis is a very delicate and important task. In particular, the depth of cancer invasion is related to lymph node metastasis; therefore, endoscopic ultrasonography and the classification of pit patterns, capillary patterns via NBI, and the lesion-lifted condition are used to diagnose the depth of cancer invasion (Kato, 2001, Sano, 2008).

Treatment for colorectal neoplastic lesions begins with hot biopsy and snare polypectomy, and recently, endoscopic submucosal resection (EMR), piecemeal EMR (EPMR), and endoscopic submucosal dissection (ESD) have become available for large and flat lesions of the colon and rectum. Early colorectal carcinoma is defined as a carcinoma within the submucosal layer that is not invading the muscularis propria. Carcinoma in situ (mucosal carcinoma) and carcinoma that slightly invades the submucosa and without risk factors for metastasis do not metastasize into lymph nodes or distant organs. Nonmetastatic carcinoma is cured by local resection with colonoscope. It is important to make an accurate diagnosis by endoscopy and to perform confident resection for pathological evaluation.

In this chapter, we describe endoscopic diagnosis for colorectal carcinoma and differential diagnosis, and treatment options for early colorectal cancer without metastasis and for adenoma which is regarded as a precancerous condition. In addition, we briefly discuss risk factors for lymph node metastasis in early colorectal carcinoma.

2. Endoscopic diagnosis of colorectal carcinoma

Colorectal carcinomas are the most common malignancies in industrialized countries, and are classified as early or advanced according to the depth of invasion. In advanced cancers, the invasion reaches the muscularis propria (MP) or the deeper layers. In endoscopic diagnosis, macroscopic classification is the most basic information. In this section, endoscopic diagnosis of colon carcinoma is discussed.

2.1 Macroscopic classification of colorectal carcinoma

Colonoscopy is a valuable tool in the diagnosis and management of colorectal neoplasms. Advanced colorectal carcinoma can be divided into 4 groups based on endoscopic appearances (Fig. 1).

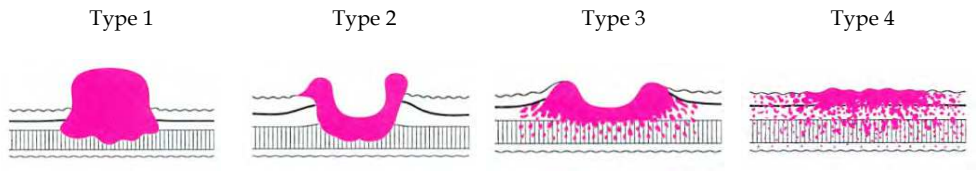
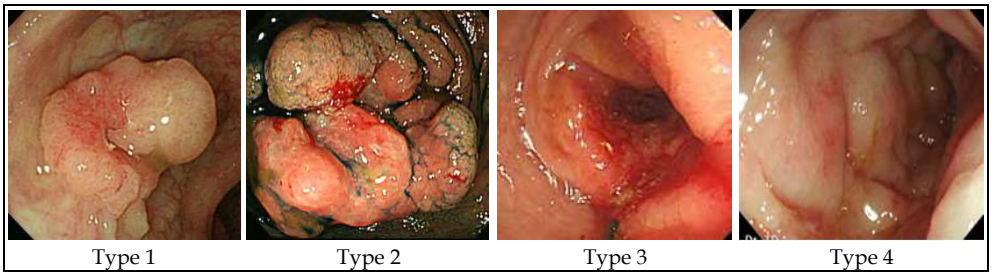


Fig. 1. Macroscopic types of advanced colorectal carcinoma



Type 1 lesion, protuberant tumor with fold convergence
Type 2 lesion, showing an irregular ulceration and clear marginal swelling
Type 3 lesion, showing an irregular ulceration and unclear marginal swelling
Type 4 lesion, showing an irregularly edematous mucosa with luminal stenosis due to diffuse infiltration, Ulceration is not pointed out on the lesion.

Fig. 2. Endoscopic view of each type of advanced colorectal carcinoma

Localized carcinoma is classified as a polypoid- (protuberant type) or ulcerative–type lesion. More than 90% of colorectal carcinomas are ulcerative-type lesions. To further distinguish early colorectal carcinoma and unclassified advanced colorectal carcinoma, the macroscopic type is subclassified from Type 0 to Type 5 (Sugihara, 2009). Early cancers are defined by the depth of cancer invasion into mucosal or submucosal layers. In this manual, early carcinoma is classified as Type 0, and advanced carcinoma is classified as Type 1 to 5.
The subclassification of Type 0 carcinoma is described in further detail in the next section. Type 1 lesions are protuberant. Type 2 lesions include ulcerative-type lesions with clear margins, and Type 3 lesions include ulcerative-type lesions with infiltration. Diffusely infiltrating lesions are classified as Type 4 lesions (Fig. 2). Type 5 lesions are an unclassified type. Type 2 is the most common type of advanced colorectal carcinoma. Circular carcinoma

of Type 2 is occasionally observed as a stenosis due to the tumor of the large intestine, and ulceration is not always detected by endoscopy. Pathological examination of biopsy specimen from the stenosis or edge of ulceration reveals adenocarcinoma. Type 4 lesion is observed like hard mucosal stenosis and neither obvious tumor nor ulceration is always recognized by endoscopy. And pathological diagnosis from biopsy is very difficult because the carcinoma is covered with normal mucosa.

2.2 Early colorectal carcinoma

Early colorectal carcinoma is defined as a carcinoma that is confined to the mucosa (M) and submucosa (SM). Early colon carcinoma may occur in an adenomatous polyp or may be difficult to distinguish from a nonmalignant adenomatous polyp by colonoscopy. For example, a 2-cm-wide villous adenoma has an approximately 40% chance of harboring cancer (Kim, 1997). Polyp risk factors for malignancy include villous rather than tubular histology, large size, sessile morphology, and high numbers of colonic polyps (Morson, 1972). Another route of carcinogenesis is "de novo" carcinogenesis, which produces small, aggressive carcinomas that do not appear to develop from adenomas (Kudo, 1997; Mueller, 2002). Macroscopic depressed type is the most common type of this carcinoma. This type is difficult to diagnose early using colonoscopy let alone barium enema; therefore, it is important to observe these lesions by endoscope extremely carefully. Early colorectal carcinoma is asymptomatic. It is usually revealed by screening colonoscopy or a positive stool occult blood test followed by colonoscopy. Colorectal screenings are important for detecting early colorectal carcinoma, which may be curatively treated by endoscopy.

2.2.1 Macroscopic type of early colorectal carcinoma

Regarding the classification of macroscopic-type lesions, the Japanese colorectal cancer handling protocol and Paris classification are representative classification systems. Both are used to judge endoscopic findings. Early colorectal carcinoma is classified as any Type 0 lesion judged to be a superficial carcinoma.

2.2.2 Japanese classification of colorectal carcinoma

Type 0 is subclassified into Type 0-I (tubercle type) and 0-II (surface type). Type 0-I is further subclassified as Ip (pedunculated), Isp (subpedunculated), and Is (sessile), whereas Type 0-II is further subclassified as IIa (surface tubercle), IIb (surface flatness), and IIc (surface depressed) (Fig. 3).

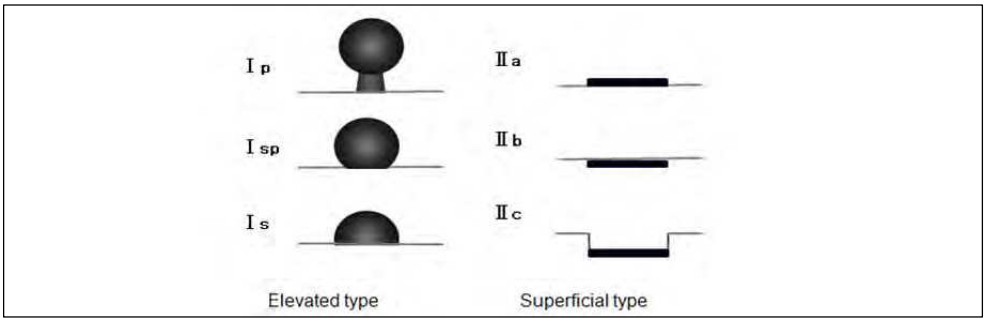


Fig. 3. Classification of superficial colorectal carcinoma (Japanese protocol)

Carcinomas can also be mixed-type lesions, which are lesions possessing elements of both Type 0-I and 0-II. Mixed-type lesions include types 0-IIc+IIa, 0-IIa+IIc, 0-IIc+Is, and 0-Is+IIc.

2.2.3 Paris classification

Terms used in the Paris classification of macroscopic-type lesions are unified by the terms used in a paper by Schlemper in 2002 (Fig. 4).

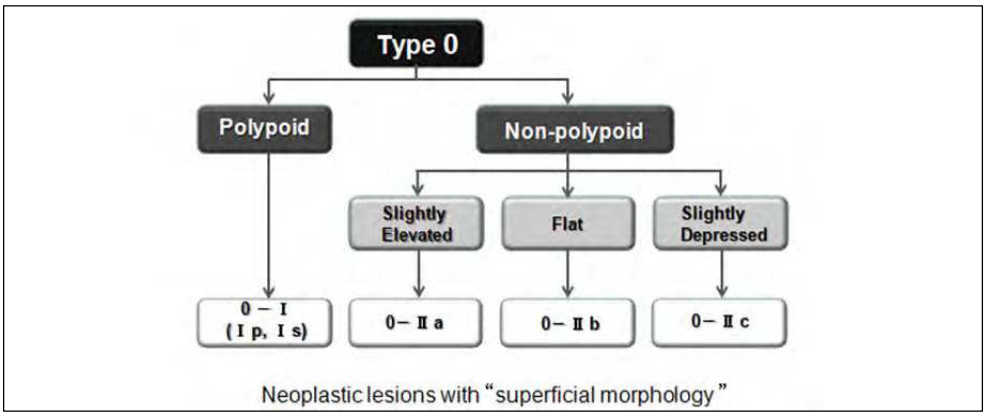


Fig. 4. Paris classification of superficial colorectal carcinoma

Firstly, lesions are divided into polypoid (Type 0-I) and non-polypoid (Type 0-IIa, IIb, IIc) lesions, and Type 0-I is subclassified as Type 0-Ip (pedunculated) and Type 0-Is (sessile). Type 0-III carcinomas comprise excavated-type lesions in the original classification, but these lesions are rare in the colon and rectum. Isp lesions are classified in the Japanese colorectal carcinoma handling protocol as Type 0-Is. Type 0-IIa lesions include those in which their height does not exceed that of closed biopsy forceps (about 2.5 mm), and lesions with heights exceeding this threshold are classified as type0-Is. Mixed-type lesions include Type 0-IIa+IIc, 0-IIc+IIa, 0-IIc+Is, and 0-Is+IIc (Fig. 5,6).

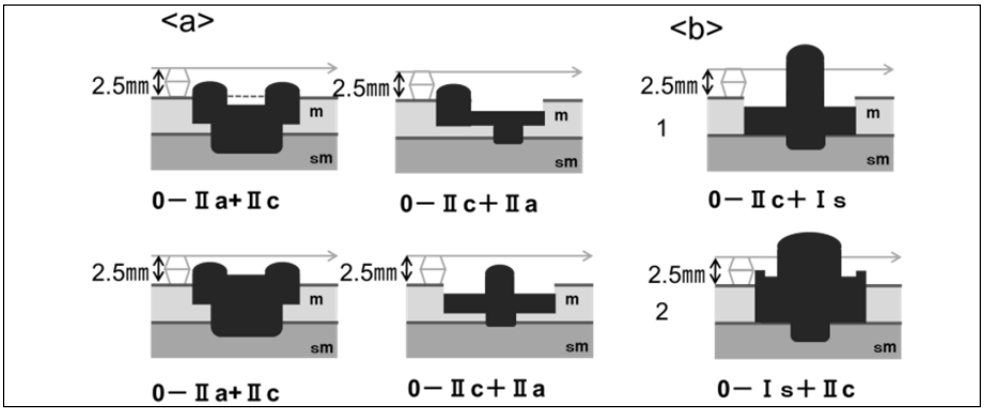


Fig. 5. Classification of mixed-type lesions (Paris classification)

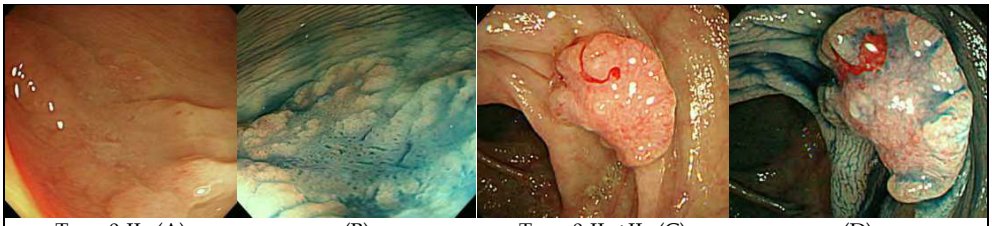


Fig. 6. (A) Type 0-IIc, Ordinary colonoscopic picture showing a depressed area with erosion (B) Type 0-IIc, Indigocarmine dye spraying view (C) Type 0-IIa+IIc, Ordinary colonoscopic picture showing a flat elevated lesion with irregular depressed area (D) Type 0-IIa+IIc, Indigocarmine dye spraying view

The importance of an endoscopic classification system for superficial lesions is that it permits endoscopic staging. In other words, we can predict the depth of invasion of a superficial carcinoma and predict the risk of lymph node metastasis, both of which assist in treatment selection (endoscopic treatment or surgical resection). Regarding Type 0-I lesions, if a lesion becomes large size, the risk of submucosal invasion is increased gradually. Conversely, Type 0-IIc lesions have deep invasion tendencies despite their small size. In addition, Type 0-IIa+IIc lesions frequently infiltrate the deep stratum submucosum, and their potential for progression is higher than that of other types.

2.3 Endoscopic ultrasonography (EUS) and diagnosis of depth invasion for colorectal carcinoma

EUS is an imaging technique for ultrasound scanning of the gastrointestinal tract lumen. It can depict lesions as vertical tomographic images. EUS can be used to evaluate the depth of invasion of epithelial tumors and carcinomas, as well as for qualitative diagnosis, such as the differential diagnosis of extramural lesions in patients with submucosal tumors. EUS is an important diagnostic procedure for deciding the treatment policy and assessing the status of diseases involving the lower gastrointestinal tract. This section focuses on the diagnosis of colorectal cancer.

The lower gastrointestinal tract has the highest incidence of colorectal cancer; EUS is indicated for the diagnosis of the depth of wall invasion and lymph node metastases. EUS is also indicated for the evaluation of submucosal tumors. Malignant lymphomas, gastrointestinal stromal tumors (GIST), lymphangiomas, and lipomas arise at a relatively high frequency in the lower gastrointestinal tract.

2.3.1 Instruments and ultrasonic probe (USP) of EUS

Ultrasonographic instruments specifically for the colorectum and ultrasonic probes are available for EUS of the colorectal region. Endoscopic three-dimensional ultrasonic probes are also commercially available.

An ultrasonic probe is attached to the tip of a direct-viewing electronic endoscope to perform mechanical radial ultrasonic scanning. One advantage of using a specialized device is the excellent ultrasonic resolution, allowing distinct tomographic images to be obtained throughout the entire intestine. Scanning can be performed at either of two frequencies (7.5 MHz, 20 MHz), and the frequency best suited for a given lesion can be selected. The higher

frequency is better suited for low and superficial lesions, whereas the lower frequency is recommended for the assessment of high and deep lesions and the examination of lymph node metastases and other lesions around the intestine. A disadvantage of specialized devices is the large outer diameter of the scope and the long hard tip, often precluding insertion into the proximal side of the sigmoid colon.
A USP can usually be inserted in the forceps channel of the endoscope. Either a 12-, 20-, or 30-MHz probe is selected, depending on the lesion. A USP is inferior to a specialized device in terms of lateral resolution and durability, but excels with respect to targeting because ultrasonic procedures can be done while directly viewing a lesion. Lesions associated with stenosis are also good indications for a USP.

2.3.2 Diagnostic technique of EUS for colorectal carcinoma

The colorectal wall is fundamentally depicted as a 5-layer structure on EUS. Starting from the lumen, the first, hyperechoic layer and the second, hypoechoic layer correspond to the mucosa, the third, hyperechoic layer to the submucosa, the fourth, hypoechoic layer to the muscularis propria, and the fifth, hyperechoic layer to the sabserosa and serosa (the tunica adventitia at sites with no serosa) (Fig. 7.).

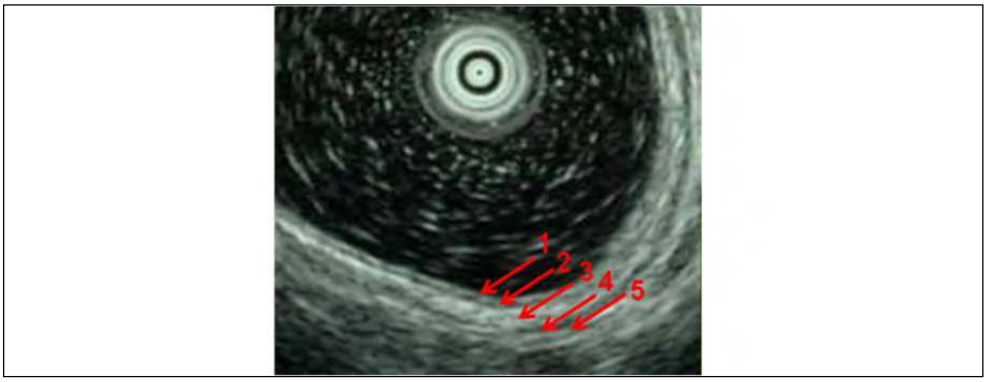


Fig. 7. Layer structure of the normal intestinal wall

With the use of high-frequency devices (20-30 MHz), the muscularis mucosae is depicted as a thin hypoechoic layer with a hyperechoic border at the upper margin of the third layer. In the fourth layer, the connective tissue of the muscularis is depicted as a thin hyperechoic layer, and the colorectal wall is sometimes depicted as a 9-layer structure. An understanding of these characteristics is essential for the diagnosis of lesions by comparison with the layer structure of the intestinal wall.

2.3.3 Diagnosis of colorectal carcinoma on EUS

On EUS, the depth of wall invasion is evaluated on the basis of what layers are preserved or destroyed by a hypoechoic mass. In M cancer (intramucosal cancer), the mass is confined to the first to second layers. In SM cancer (cancer invading the submucosa), the third layer is narrowed or ruptured by the mass, but the fourth layer remains intact. In MP cancer (cancer invading the muscularis propria), the fourth layer is narrowed or ruptured by the mass, but the fifth layer remains intact (Fig. 8.).

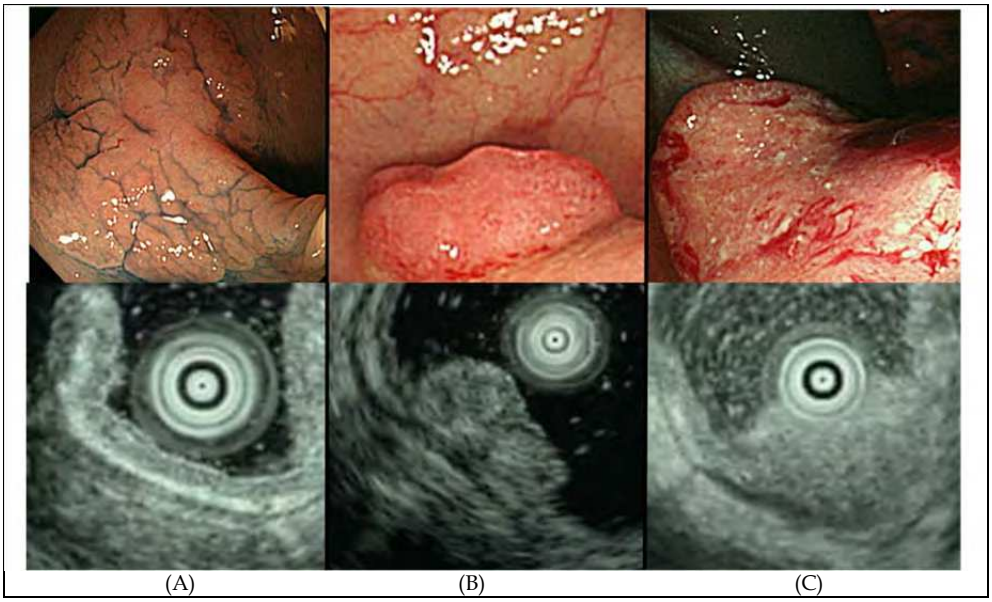


Fig. 8. Endoscopic view and EUS image, (A) Mucosal cancer, (B) SM cancer, (C)MP cancer

In SS to SE cancer (cancer invading the sabserosa or serosa) or A cancer (cancer invading the tunica adventitia), the fifth layer is narrowed or ruptured by the mass, but the border with the adjacent organ remains intact. In SI or AI cancer (cancer invading the adjacent organ), up to the fifth layer is destroyed by the mass, and the border with the adjacent organ is unclearly demarcated.

2.3.4 Diagnosis of invasion depth of SM cancer

Intramucosal cancer and SM cancer with mild invasion to a vertical depth of less than 1000 μm from the lower border of the muscularis mucosae have virtually no risk of metastasis, and cure can be expected after endoscopic treatment. Endoscopic therapy is thus indicated for such lesions (Sugihara, 2009). On EUS, SM cancers are classified into lesions with shallow invasion and those with deep invasion at the time of diagnosis based on Kudo's classification of SM cancer (Kudo, 2000). The third layer, corresponding to the normal submucosa adjacent to cancer, is subdivided into 3 equal layers, and the location of deepest region of the hypoechoic mass is determined. Masses that are confined to the shallowest third of the submucosa are classified as sm1, those that invade the second third are classified as sm2, and those that invade deeper than the second third, but do not extend beyond the region near the medial border of the fourth layer are classified as sm3. SM cancers with shallow invasion correspond to sm1, and those with deep invasion correspond to sm2 and sm3. EUS diagnosis thus plays an important role in the selection of treatment for early colorectal cancer.

2.3.5 Diagnosis of lymph node metastasis

Normal lymph nodes are not depicted on EUS. Lymph nodes visualized on EUS that have a shortest diameter of ≥5 mm, a hyperechoic and homogeneous internal echo, and are either

circular or irregularly shaped are considered positive for metastasis. However, differential diagnosis from enlarged lymph nodes associated with inflammation is challenging. The rate of correctly diagnosing lymph node metastases has been reported to be 70% to 80% (Tio, 1991, Cho E, et al. 1993). The diagnostic ability of EUS is thus not considered good.
EUS is useful for diagnosis of the invasion depth of colorectal cancer because it can depict lesions as vertical tomographic images. It is thus an important diagnostic procedure for deciding treatment policy and evaluating disease status.

2.4 Diagnosis of colorectal neoplastic lesions by chromoendoscopy and image-enhanced endoscopy

If a colorectal lesion is detected by conventional endoscopy, the location, size, macroscopic type, color, surface pattern, presence of fold conversion, and air-induced deformation can be observed. The indigo carmine dye-spraying method more clearly reveals the extent and surface pattern. In addition, magnifying endoscopy after staining with indigo carmine or crystal violet is useful for pit pattern classification (Kudo et al., 1994), as it enables the differentiation of neoplasms as well as histological grading and depth evaluation of early cancers. This leads to the selection of endoscopic therapy or surgery.
The combination of image-enhanced endoscopic techniques such as NBI with magnification is used to observe the capillary pattern of the tumor surface, and these techniques can also improve diagnosis (Sano et al., 2006).

2.4.1 Classification of pit pattern

Pit patterns in the large intestine were classified into 7 types by Kudo (Fig. 9). Type I includes round pits that are observed in normal mucosa. Type II includes stellar or papillary pits, and these pits always indicate hyperplasia. Type IIIs includes small tubular or round pit that are smaller than normal pits, and they indicate neoplastic lesions, occasionally including carcinoma that can be resected by endoscopy. Type IIIL includes

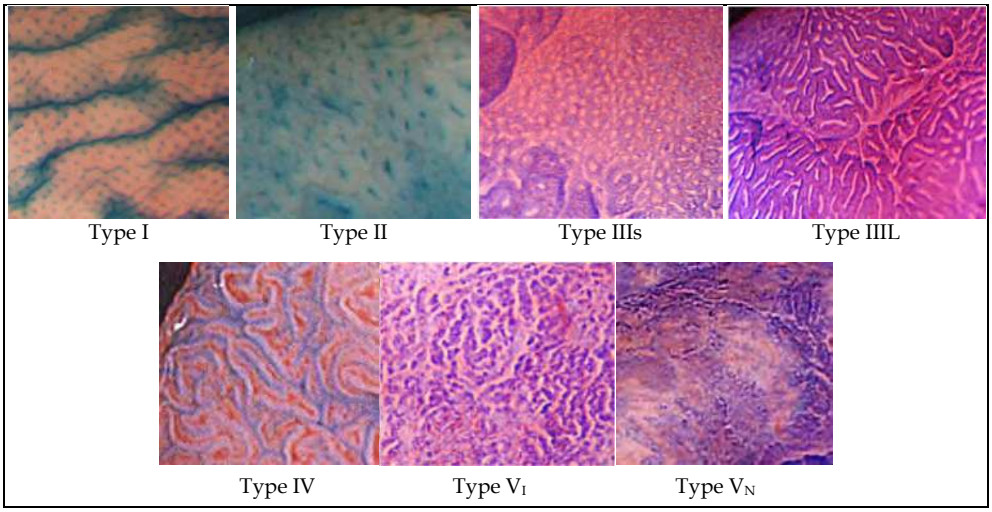


Fig. 9. Classification of pit pattern

tubular or roundish pits that are larger than normal pits. Almost all of Type IIIL lesions are tubular adenomas in pathology, which can be treated by polypectomy. Type IV includes branch-like or gyrus-like pits, most of which are tubulovillous adenoma. Mucosal carcinoma is present in 35% of these pits and can be treated by endoscopy. Type V_I includes irregularly arranged pits that may be submucosal invasive carcinoma, for which the proper treatment straddles the borderline between endoscopic and surgical therapy. Lastly, type V_N includes nonstructured pits, which indicate massive submucosal invasive carcinoma and require surgical resection with lymph node dissection.
Kudo reported that small round pit patterns (type IIIs) and non-pit patterns (type V) were common in depressed lesions and that these depressed lesions had invaded the deeper layers more rapidly than had protruding lesions.

2.4.2 Classification of capillary pattern by magnified NBI

The NBI system involves modifying spectral features by narrowing the bandwidth of spectral transmittance using various optical filters (Sano, 2001). This modification provides a unique image that emphasizes the capillary pattern, as well as the surface structure, by simple operation of a button on the control panel of the endoscope. Because of its similarity to chromoendoscopy, NBI can be referred to as optical or digital chromoendoscopy. Sano et al. (2006) classified 3 types and names (CP types I, II, and III) of microvascular architectures based on the magnified NBI pattern. CP type I has no meshed capillary vessels. CP type II has meshed capillary vessels surrounding the mucosal glands. CP type III lesions were further classified into 2 groups: types IIIA and IIIB. CP type IIIA has irregular meshed capillary vessels, whereas irregular meshed capillary vessels disappear or loosen in CP type IIIB (Fig.10). CP types I, II, IIIA, and IIIB are observed in nonneoplastic lesions, adenomas, mucosal or slightly invasive submucosal carcinoma, and massive invasive submucosal carcinoma, respectively. Capillary patterns, as assessed by magnifying NBI, are useful for differentiating small colorectal nonneoplastic polyps from neoplastic ones (accuracy, 95.3%; sensitivity, 96.4%; and specificity, 92.3%) (Sano, 2008), and they are highly accurate for distinguishing low-grade dysplasia from high-grade dysplasia/invasive cancer (accuracy, 95.5%; sensitivity, 90.3%; and specificity, 97.1%) (Katagiri, 2008). Therefore, capillary patterns can be used to predict the histopathology of colorectal neoplasia.

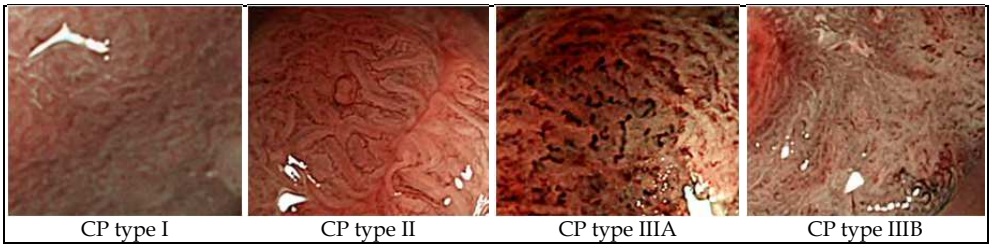


Fig. 10. Capillary pattern by magnified NBI

2.5 Risk factor for lymph node metastasis of submucosal invasive carcinoma

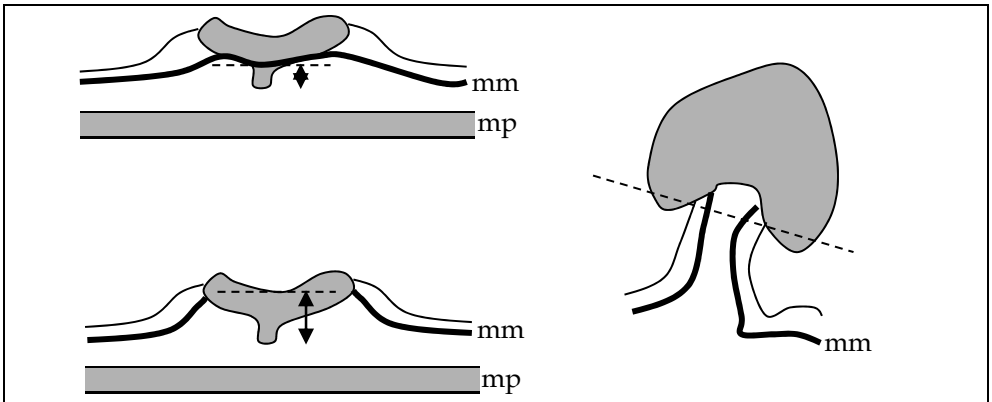
Lymph node metastasis is reported to occur in approximately 10% of SM cancers. SM cancer is a boundary lesion, and its treatment plan involves endoscopic treatment or surgical

resection with lymph node dissection. Therefore, investigation of the risk factors for lymph node metastasis is important. The risk factors for lymph node metastasis are described on the "Colorectal Cancer Treatment Guideline 2009," written by the Japanese Society for Cancer of the Colon and Rectum; these guidelines are listed below. When a risk factor for metastasis is revealed upon examination of an endoscopically resected SM cancer specimen, additional surgical resection with lymph node dissection is recommended.

1. Carcinoma that is histologically classified as poorly differentiated adenocarcinoma, signet ring cell adenocarcinoma, or mucinous carcinoma
2. Depth of submucosal invasion >1000 μm
3. Vascular invasion is positive
4. Grade 2/3 budding

In classifying the histological type of a carcinoma, the predominant pattern is adopted as its representative histological type in the Japanese classification of colorectal carcinoma (Sugihara, 2009). For example, for a tumor consisting mainly of well-differentiated carcinoma with a small portion of moderately differentiated carcinoma, a diagnosis of "well-differentiated carcinoma" should be made. High-grade carcinomas that are poorly differentiated adenocarcinomas, signet ring cell adenocarcinomas, or mucinous carcinomas have strong proliferative and metastatic capabilities.

When it is possible to identify the muscularis mucosae, the depth of submucosal invasion is the distance between the deepest edge of the muscularis mucosae and the deepest invasion. If the muscularis mucosae cannot be identified, the depth of submucosal invasion is the distance between the surface of the tumor and the deepest invasion. In Ip lesions with disrupted muscularis mucosae, the depth of submucosal invasion is the distance between the deepest invasion and the reference line, and it is defined as the boundary between the tumor head and the pedicle. When cancer does not invade beyond the reference line, it is defined as head invasion (Fig. 11). According to Kitamura, for pedunculated SM cancer, the rate of lymph node metastasis was 0% in cases of head and stalk invasion with depths <3000 μm if lymphatic invasion was not observed. For nonpedunculated SM cancer, the rate of lymph node metastasis was also 0% if SM depth was <1000μm (Kitajima, 2004).



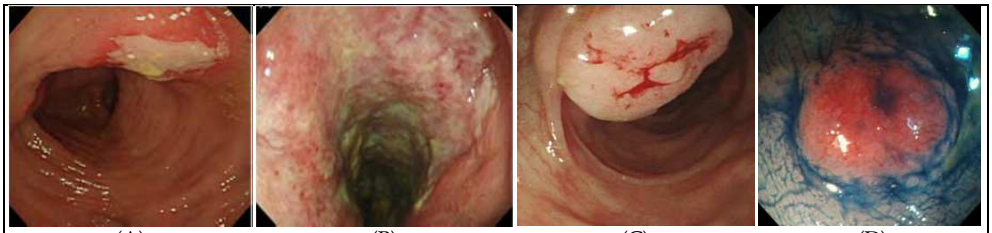
mm, muscularis mucosae; mp, muscularis propria

Fig. 11. Depth of submucosal invasion in SM cancers

Vessel invasions contain 2 types of lymphatic invasion and venous invasion. The distinction is not so easy. When cancer nests are located in lymphatic ducts lined by flat endothelial cells, it is considered positive lymphatic invasion. Cancer nests existing near an artery are very likely to represent venous invasion, which can be confirmed by determining the presence of an internal elastic membrane and plain muscle around the cancer nests. Occasionally, it is difficult to detect venous invasion by hematoxylin and eosin staining. Elastica van Gieson staining, however, is useful for detecting venous invasion.
Budding is defined as cancer nests comprising less than 5 cancer cells and invading the interstitial tissue of the cancer growth front. The area where budding appears most frequently is selected and the number of instances is counted in a ×200 field. Budding is classified into 3 groups (grade 1, 0–4 pieces; grade 2, 5–9 pieces; and grade 3, ≥10 pieces), and grades 2 and 3 are risk factors for lymph node metastasis.

2.6 Differential diagnosis

There are many diseases that must be differentiated from colorectal carcinoma. The characteristic appearance of colorectal carcinoma does not cause interpretive difficulties generally.
Metastatic lesions in the large intestine: Cancers that frequently metastasize to the large intestine include those of the stomach, pancreas, ovaries, lung, and breasts in descending order of frequency. The endoscopic appearance of metastatic lesions generally includes (1) extraluminal masses with or without hyperemia, (2) wall thickening, and (3) hyperemia. Extraluminal masses are often smooth, but the base is not distinct. Mucosal hyperemias are often multiple, and the border is obscure. Ulcerated tumors are also the findings of metastatic lesions, but the marginal elevation typical of primary cancers is rarely observed (Fig. 12A).
Peritonitis carcinomatosa: Peritonitis carcinomatosa does not affect the mucosal surface.
Malignant lymphoma and sarcoma: Polypoid-type lymphomas are often smooth-surfaced. Colon cancer ulcers are usually accompanied by irregular margins, but that of ulcerative-type malignant lymphoma often contains a smooth margin (Fig. 12B, C). Sarcomas are likely to be malignant lymphomas.



A, metastatic colon cancer from gastric cancer (poorly differentiated adenocarcinoma);
B, ulcerative type of malignant lymphoma; C, elevated type of malignant lymphoma;
D, carcinoid

Fig. 12. Colorectal neoplasmas

Carcinoids: Carcinoids are covered with the normal mucosa initially. In addition, carcinoids are usually elastic, hard, and yellowish. Endoscopic ultrasound staging (EUS) is useful for

diagnosing the internal state and present layer. If they invade mucosa, vessels and ulcer formation occur (Fig.12D)

Inflammatory disease: Inflammatory colonic diseases, such as Crohn disease (CD), ulcerative colitis (UC), and colonic tuberculosis (TBc), are sometimes likely to resemble colonic carcinoma regarding its endoscopic features. CD often includes longitudinal ulceration, but the ulcer is sharp and smooth. UC is rarely displayed as a self-limited ulcer, but ulcers of UC are soft and thin. Colonic TBc is rarely similar to Type 2 cancer, but the ulcers of TBc are not hard or irregular.

3. Endoscopic treatment for colorectal carcinoma and its precursors

There are many methods of treating colorectal tumors, such as hot biopsy and snare polypectomy, EMR, EPMR, and ESD. Advances in endoscopic instruments and techniques have led to a large increase in the number of endoscopically resected lesions. Safe and reliable endoscopic treatment for colorectal carcinoma requires diagnostic ability and skill in colonoscopy.

3.1 Hot biopsy and polypectomy

Colonic polyps less than 0.8 cm in diameter are usually removed by hot biopsy, particularly when they are sessile, whereas polyps more than 0.8 cm in diameter are usually removed by snare polypectomy, particularly when they are pedunculated (Mann, 1999). Hot biopsy involves grasping the top part of the polyp upward and moderately cauterizing the polyp. Hot biopsy is performed cautiously in the cecum using a low amplitude and brief duration of current because the colonic wall is the thinnest and most vulnerable to transmural necrosis in this region (Weston, 1995). One limitation of hot biopsy is that only a portion of the polyp can be examined pathologically because the polyp cannot be completed removed. Therefore, we also perform snare polypectomy for even polyps smaller than 0.8 cm in diameter.

Snare polypectomy is chiefly applied to pedunculated and sessile lesions of 0.5 to 2.0 cm in diameter. Sessile polyps between 2 and 3 cm in diameter may be removed by snare polypectomy after creating a pseudopedicle by injecting normal saline or other solution into the polyp base, as described in the following section (Waye, 1997; Kato, 2001, 2008). Sessile polyps more than 3 cm in diameter may be unamenable to conventional snare polypectomy but can be removed by sequential piecemeal polypectomy over several colonoscopies (Dell'Abate, 2001).

The complication rate of therapeutic colonoscopy is 1.4–2.0% (Jentschura, 1994; Nelson, 2002; Kato, 2008). The most common postpolypectomy complications are gastrointestinal bleeding, colonic perforation, and local peritonitis. In local peritonitis, a patient develops abdominal pain, leukocytosis, and localized peritoneal irritation from an almost transmural burn occurring during polypectomy. This occurs in up to 1% of polypectomies (Waye, 1996). This syndrome is usually managed medically by the cessation of oral intake, intravenous hydration, and antibiotic administration (Waye, 1993).

3.2 EMR and EPMR

EMR combines the classic principles of conventional snare polypectomy with submucosal injection to remove more deeply affected mucosa or submucosa by resecting the lesion

through the middle or deep submucosa. It is a less invasive treatment option for colorectal lesions even if the lesion is flat and difficult to remove by snare polypectomy. When we want to resect early colorectal carcinoma surrounded by the normal mucosa, EMR is a suitable procedure. After observation of the lesion, hypertonic saline solution with epinephrine is injected into the submucosal layer. At this time, the lesion-lifted condition is observed as follows (see section 3.3). When the lifted condition is complete, the bulging lesion is captured in a surgical snare and removed by cauterization with a high-frequency current.

A lesion less than 2.0 cm in diameter can generally be resected en bloc. The relationship between tumor size and the en bloc resection rate in our medical center between 2000 and 2010 is presented in Fig. 13. Lesions smaller than 20 mm in diameter were resected en bloc in more than 90% of colorectal carcinoma cases. Most lesions larger than 26 mm in diameter are treated by the piecemeal method.

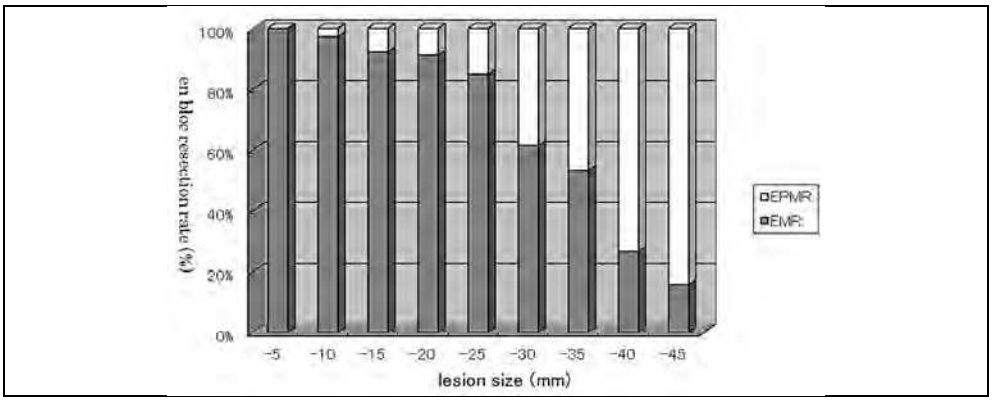


Fig. 13. Relationship between lesion size and en bloc resection (EMR) vs. EPMP

Among 281 cases of early colorectal carcinomas treated by EMR, only 2 cases recurred during the observation period of 5 years (recurrence rate, 0.8%). The recurrent cases could be retreated by endoscopic methods. Conversely, 8 cases among 148 cases treated by EPMR recurred (recurrence rate, 5.4%), and 2 of these cases were treated surgically. Therefore, the recurrence rate of EMR is significantly lower than that of EPMR ($p<0.01$). However, these methods are used to treat lesions of different sizes, and thus, simple comparisons of recurrence rates can be misleading. However, we believe that en bloc resection is better than piecemeal resection from the point of view of accurate pathological diagnosis. Large superficial carcinomas without lymph node metastasis requiring en bloc resection are currently resected using ESD at our medical center.

Bergmann (2003) reported that local recurrence after EMR was observed in 2 of 59 completely resected adenomas and in 0 of 6 early-stage carcinomas during a mean follow-up of 18 months. He concluded that advanced non-polypoid colorectal adenomas and early-stage carcinomas can be safely and effectively resected by EMR.

Jin et al. (2009) reported that recurrence was found to be related to piecemeal resection and diameters larger than 20 mm and that >20-mm-diameter is an independent risk factor for laterally spreading tumors (LSTs) treated by EMR. They stated that for the LSTs larger than 20 mm in diameter, another method, such as ESD or even a major operation, should be considered.

3.3 Classification of lesion-lifted condition

Special findings such as depression, ulceration, fold convergence, bleeding tendency, irregular shape, and a non-lifting sign indicate a deep invasion (Uno, 1994; Kobayashi, 2007). The "non-lifting sign" is a simple yes/no classification, and compared to EUS, it is a much easier method to determine whether EMR is indicated. However, because it is by no means rare for submucosal invasion to be found among lesions that exhibit a negative lifting sign, we have created a more detailed classification of the lesion-lifted condition. In a previous study, we focused on the tumor's lifted condition after submucosal injection and classified lesions into 4 types (Kato, 2001).

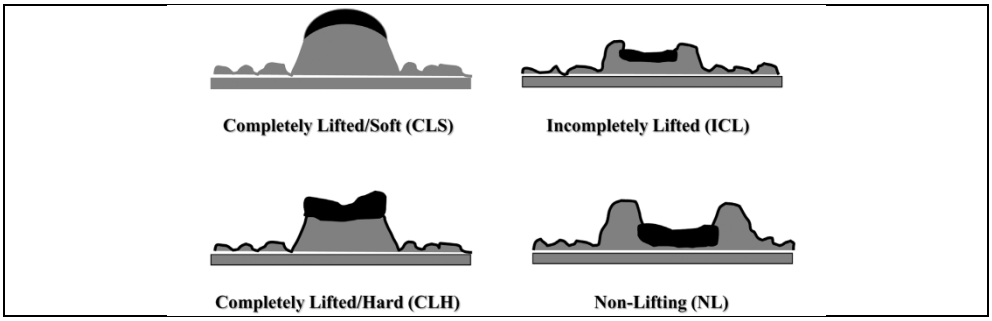


Fig. 14. Classification of the lesion-lifted condition (Kato, 2001)

This classification is closely related to the depth of invasion, and has proved to be particularly useful in the identification of early colorectal cancers that are good candidates for endoscopic treatment without requiring any special apparatus. We classified the lesion-lifted condition at the time of submucosal fluid injection into 4 categories (Fig. 14): (1) completely lifted/soft (CLS), (2) completely lifted/hard (CLH), (3) incompletely lifted (ICL), and (4) non-lifting (NL). A CLS lesion is completely lifted by submucosal injection, and it stretches softly like a dome. A CLH lesion is completely lifted, but it is rigid and maintains its original form. An ICL lesion is slightly lifted, but the surrounding mucosa lifts higher than the lesion. An NL lesion is not lifted, and only the surrounding mucosa is elevated (Fig. 15).

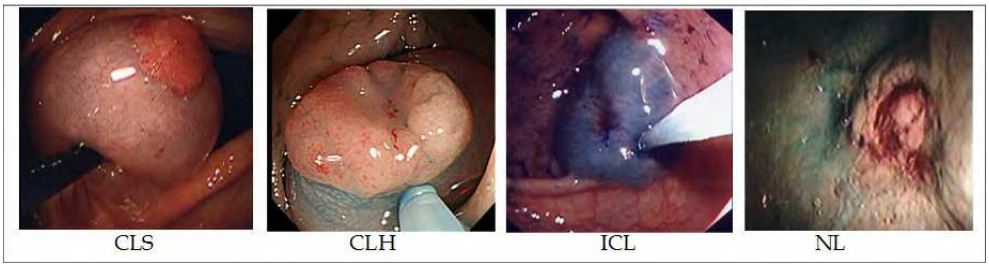


Fig. 15. Classification of the lesion-lifted condition (Kato, 2001)

Lesion-lifted conditions are related to tumor pathology and the extent of tumor invasion, and they often correspond to particular macroscopic types of tumors. The relationship between the lifted condition and macroscopic type is shown in Table 1. Type IIa predominates among CLS lesions, whereas elevated lesions such as types Ip, Isp, and Is tend

to fall into the CLH category. On the other hand, type IIa+IIc is relatively common type of morphology among ICL and NL lesions. The relationship between lifted conditions from CLS to ICL lesions and their corresponding macroscopic types are statistically significant ($p<0.001$).

	Ip	Isp	Is	IIa	IIc	IIa+IIc	LST
CLS	4	30	66	324	24	9	105
CLH	25	73	90	77	13	8	18
ICL	0	10	22	21	7	12	13
NL	0	0	8	2	1	5	2

Table 1. Relationship between lifted condition and macroscopic type ($p<0.001$)

Classification of submucosal invasion is based on the division of the submucosa into 3 layers from sm1 to sm3. sm1, sm2, and sm3 are lesions that are limited to the upper, middle, and lower thirds of the submucosal layer, respectively. sm1 lesions are further subdivided into 3 categories (a, b, and c) with regard to the degree of horizontal involvement of the upper submucosal layer (ratio of involved part and non-involved part). Whereas sm1a+sm1b lesions have a very low risk for metastasis, the malignant potential increases with increasing depth of submucosal invasion (Kudo, 1997; Kashida, 2006). The relationship between the lesion-lifted condition and the depth of invasion is shown in Table 2. We used Kudo's classification to subclassify the depth of SM cancer. All CLS lesions are found to be sm1 or shallower, whereas the CLH category included 20 sm2 and 14 sm3 lesions. The rate of SM massive cancer (sm2 or sm3) among CLH lesions was 11.0%. ICL lesions range from sm1 to sm3, and most of the NL lesions exhibit invasion to sm3 or deeper. Four noncancerous cases and 1 mucosal cancer case of NL lesions were recurred adenomas and cancers that had previously been treated by endoscopic therapy. The rates of SM massive cancer among ICL and NL lesions are 38.5% and 74.1%, respectively. The lesion-lifted condition well correlates with the depth of invasion.

	nc	cia	m	sm1	sm2	sm3-
CLS	451	65	34	3	0	0
CLH	123	75	58	18	20	14
ICL	20	14	7	7	10	20
NL	4	0	1	0	1	13

nc, noncancerous lesion; cia, cancer in adenoma; m, mucosal cancer; sm1, shallow SM cancer; sm2, moderate SM cancer; sm3, deep SM cancer
Chi-square test, $p < 0.0001$

Table 2. Relationship between the lesion-lifted condition and the depth of invasion (Number of the lesions)

When the lifted condition of a lesion is CLS or CLH, it is a good indication that endoscopic resection will be successful. When the lifted condition is ICL, however, endoscopic resection has a smaller chance of success. And almost all of NL lesion without previous endoscopic therapy had better receive surgical treatment.

3.4 ESD

ESD is a resection technique for superficial neoplastic lesions of the gastrointestinal tract without the use of snaring. It was developed for en bloc resection of large superficial mucosal tumors, and it was initially used in the stomach and later in the esophagus, colon, and rectum. ESD is superior to EMR for a more reliable en bloc resection of a targeted area of the mucosa. It also provides a higher complete resection rate with a lower recurrence rate compared with EPMR (Saito, 2010). The drawbacks of ESD include that it is a time-consuming procedure, has greater technical demands, and has a higher rate of perforation. For these reasons, ESD for colorectal tumor is performed as an advanced medical treatment because it is currently not recognized as treatment covered by the national health insurance system of Japan in 2011.

3.4.1 Method of ESD

Method of ESD is incising mucosa around a lesion lifted by injected fluid and dissecting the submucosal space under the lesion (Fig.16). ESD for colorectal tumors is considered more technically demanding than ESD in the stomach for a variety of reasons including the following: (1) the colonic wall is thinner and softer than the gastric wall; (2) endoscopic control is difficult in some parts of the colon because of its meandering form; and (3) there are limitations in the retroflex approach due to the narrow lumen of the colon, and tumors can be located on or behind a prominent fold of the colon.

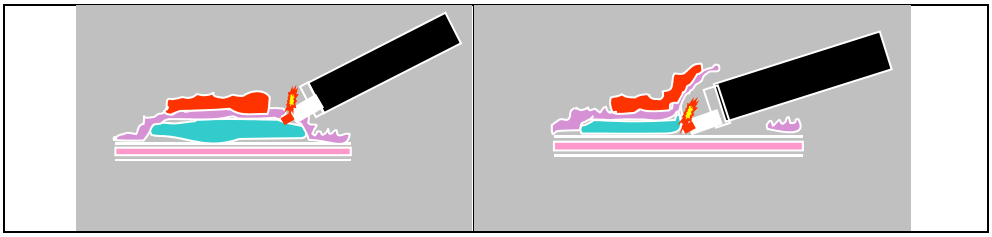


Fig. 16. Method of ESD

First, the borders of the tumors are determined by chromoendoscopy with indigo carmine spraying for enhanced or magnified observation using NBI. Marking around the tumor is not necessary in most cases because colorectal neoplasms typically have clear margins.

The use of 0.4% sodium hyaluronate solution for submucosal injection keeps the tumor lifted for long periods (Yamamoto, 1999). For successful ESD, the position of the patient should be selected such that the lesion is located at the top of the colonic lumen with regard to gravity. Because the lesion is naturally pulled down and blood flows down from the bleeding point by gravity, good visualization of submucosal space can be maintained.

Next, the mucosal incision in front of the tumor is made with a short needle knife such as FlushKnife BT™ (1.5 mm; Fujifilm Corp., Tokyo, Japan) (Fig.17). Only the needle part should be used for the incision, keeping the tip of the sheath touching the surface of the mucosa without pushing the sheath into the submucosal layer. We use the endcut mode of electric surgical unit for the mucosal incision. After repeated submucosal injection, submucosal dissection is performed parallel to the muscular layer by sliding the knife from the center to the side while hooking submucosal fibers with the knife. We use the swift coagulation mode of electric surgical unit at this time. When thick vessels can be observed in

the submucosal layer, grasping and soft coagulation are performed using coagulation forceps. Furthermore, a surrounding incision is made, and submucosal dissection is performed while lifting up the dissected part of the tumor with the edge of the transparent cap at the tip of the scope. Finally, hemostasis and the lack of a weak point of the muscularis propria are confirmed after resection.

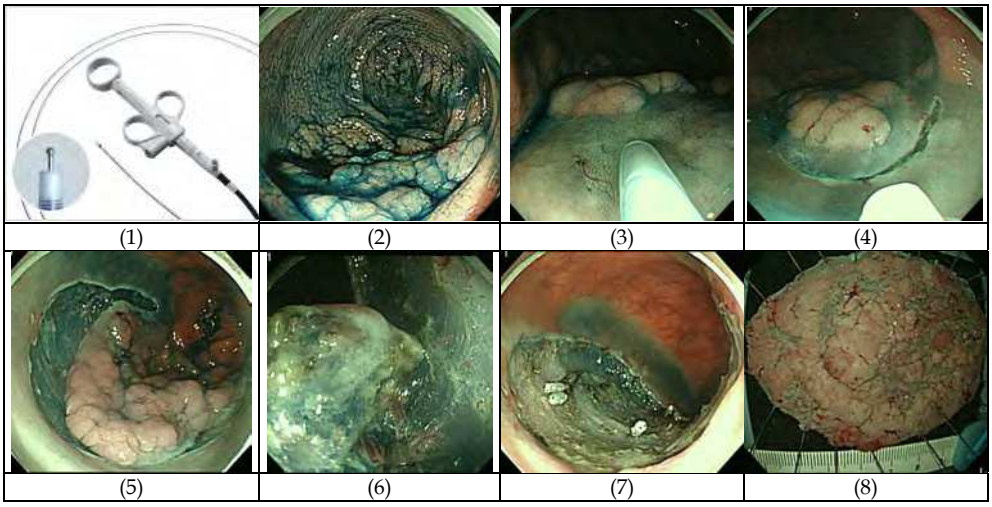


Fig. 17. ESD using FlushKnife BT™ for rectal mucosal carcinoma of 80mm in diameter

The usefulness of new grasping-type scissor forceps (GSF) such as ClutchCutter™ (Fujifilm Corp., Tokyo, Japan) was reported by Akahoshi et al. (2010). ESD using GSF is a safe (no intraoperative complication) and technically efficient (curative en bloc resection rate, 92%) method for the dissection of early gastrointestinal tumors. The use of GSF is a promising option for performing ESD in early-stage GI tract tumors both safely and effectively. We typically use GSF on the lesions that are difficult to approach or control by endoscopy. The ability to confirm that GSF is not grasping the muscle layer before coagulation or cutting is a point of safety (Fig.18).

Fig. 18. ESD using Clutchcutter™ (Fujifilm Corp., Tokyo, Japan)

3.4.2 Cases of ESD

We investigated 116 patients with colorectal lesions for whom ESD was performed between Jan 2005 and Mar 2011. The tumors were entirely located in the large intestine (27 in the

transverse colon and 25 in the rectum) (Table 3). Type IIa was the most common macroscopic type (Table 4). The average diameter was approximately 30 mm (range, 4–82 mm). The average operation time was 75 min. Regarding complications, an incision in the muscularis propria was found in 6% cases. Perforation was experienced in 7%. But all of the perforation hole could be closed by endoscopic clip without surgical procedure.
Approximately half the lesions were adenomas, and the rest were carcinomas. One patient with carcinoma in situ exhibited recurrence in the mucosa and received endoscopic treatment. Additional colectomy was performed in 8 patients with submucosal invasion. There are pathological residual cancer nests in 2 cases. One patient had persistent carcinoma in the colonic wall, and another had lymph node metastasis.

	C	A	T	D	S	R
No of Lesions (%)	12 (10)	19 (16)	27 (23)	8 (7)	18 (16)	25 (22)

C, cecum; A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum

Table 3. location of the ESD lesions

	Is	IIa	IIc	SMT
No of Lesions (%)	24 (21)	82 (71)	4 (3)	6 (5)

SMT, submucosal tumor

Table 4. Macroscopic types of ESD lesions

3.4.3 Comparisons among EMR, EPMR and ESD

Clinicopathological data were compared among EMR, EPMR, and ESD between 2000 and 2011. The size in diameter of the lesions that were treated by each technique was compared. Very large lesions can be treated by EPMR and ESD. The mean sizes of lesions treated by EMR, EPMR, and EMR were 13.1 (range, 2–45), 24.6 (4–69), and 29.7 mm (4–82), respectively (Fig. 19).

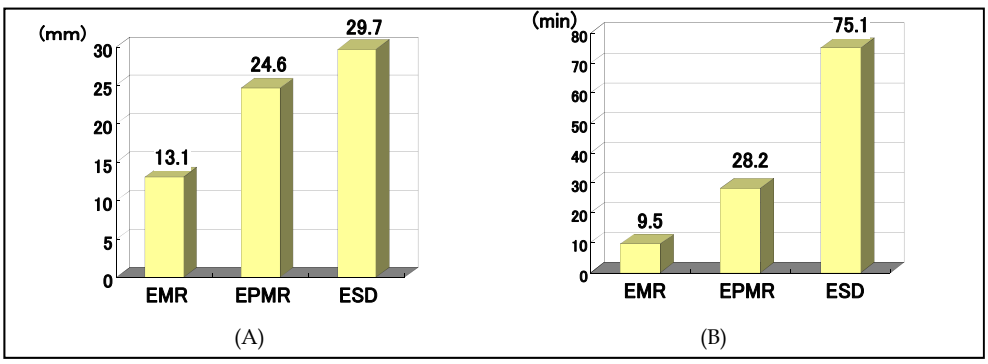


Fig. 19. (A)Mean diameter of the lesions treated by each method , (B) Mean operation time

The mean operation times of the 3 methods were also compared. ESD required about 75 minutes to perform and longer than the other techniques. Regarding ESD complications, postoperative hemorrhage is not frequent, but perforation and muscularis propria incision are more common with ESD than with EMR or EPMR. However, all perforations and muscle incisions could be closed by endoscopic clipping, and there was no negative effect in the clinical course (Table 5).

	EMR (n=1039)	EPMR (n=147)	ESD (n=116)
Postoperative hemorrhage: endoscopic hemostasis	16(1.5%)	6(4.1%)	3(2.6%)
Perforation: endoscopic closure	1(0.1)	0	8(6.9)
Perforation: surgical closure	1(0.1)	0	0
Incision of muscularis propria: endoscopic clipping	0	0	7(6.0)
Local peritonitis: conservative therapy	2(0.2)	2(1.4)	2(1.7)

Table 5. Complications of endoscopic treatments for colorectal tumor

Colorectal ESD can be performed in all sites of the large intestine, and even a large lesion could be resected en broc using ESD. However, the procedure was lengthy and involved more complications than did other treatments. Further technical proficiency and instrumental improvements are expected in the future.

4. Conclusions

New methods of endoscopic diagnosis and treatment have been recently developed. Patients with early-stage colorectal carcinoma can be diagnosed by colonoscopy. Endoscopic treatment facilitates healing, and the method is less invasive, more cost-effective, and less time-consuming for patients. Endoscopic apparatuses, devices, and techniques must be further improved in the near future. Endoscopy for colorectal carcinoma will remain important in medical education and practice.

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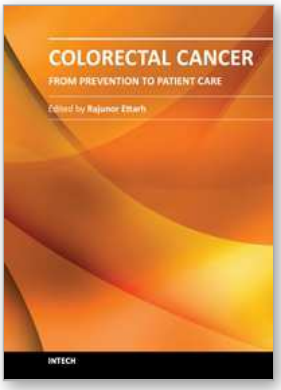

Colorectal Cancer - From Prevention to Patient Care
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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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