Colonoscopy in Intestinal Diseases

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Colonoscopy is an examination of the colorectum and terminal ileum undertaken by inserting a scope with a camera device and flexible light source through the anus. In cases of infectious diseases, colonoscopy is helpful in making the differential diagnosis, revealing endoscopic gross findings, and obtaining the specimens for pathology. Additionally, colonoscopy provides clues for distinguishing between infectious disease and inflammatory bowel disease (IBD), and aids in the post-treatment monitoring of IBD.

colonoscopy intestinal diseases IBD

1. Introduction

Colonoscopy is an examination of the colorectum and terminal ileum undertaken by inserting a scope with a camera device and flexible light source through the anus. Since colonoscopy was first performed in the 1960s [1], it has been used as a key diagnostic and therapeutic tool for various intestinal diseases. There are many types of intestinal diseases, and they can be classified into infectious disease, inflammatory bowel disease (IBD), neoplasm, functional bowel disorder, bleeding, and others. Colonoscopy can visualize lesions associated with these diseases and find inflammation, ulcers, neoplasms, and hemorrhages. In addition, it provides information on macroscopic findings and enables tissue sampling by inserting instruments through various channels [2]. Moreover, because of the development of endoscopic resection techniques such as endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), endoscopic resection is used as the main treatment for early colorectal cancer [3]. Colonoscopy also plays an important role in large bowel obstruction (LBO). Colonoscopy not only enables the diagnosis of various diseases of LBO, but it is also useful as a treatment for balloon dilatation in benign stricture and metal stent insertion in malignant obstruction [4]. Additionally, when gastrointestinal bleeding occurs, endoscopic hemostasis is performed through endoclipping or an electronic surgical unit, and endoscopic perforation treatment can also be used for bowel perforation. However, in functional bowel disorders, colonoscopy is used to exclude other organic causes rather than to diagnose the disease itself [5]. As such, colonoscopy is widely used in various diseases and clinical situations.

2. Colonoscopy in Intestinal Diseases

2.1. Infectious Diseases

An intestinal tract infection can cause abdominal pain, fever, diarrhea, loose stool, and bloody or mucoid stool, and is caused by bacteria, viruses, or parasites. Common causes of infectious enterocolitis include *Yersinia*

enterocolitica, *Salmonella*, *Shigella*, *Escherichia coli*, *Campylobacter, Clostridium difficile*, *Mycobacterium tuberculosis,* cytomegalovirus (CMV), and *Entamoeba histolytica* [6]. In such infectious intestinal diseases, colonoscopy is more useful for diagnostics than therapeutics. In most cases of infectious colitis, endoscopic findings are accompanied by edema, redness, ulceration, exudation, and mucosal friability [7]. Therefore, it is difficult to discriminate between the causative microorganisms that cause infection using only endoscopic findings. Yet, the location of the lesion can be an important clue when making a differential diagnosis. **Table 1** summarizes the types of infectious enterocolitis that predominate according to the location of the lesion. Especially in immunocompromised people or men who have sex with men, infectious diseases such as *Neisseria gonorrhea, Chlamydia trachomatis*, herpes simplex virus, human papilloma virus, syphilis, and *Treponema pallidum* can occur in the rectum. In these conditions, symptoms such as anorectal pain, tenesmus, and mucopurulent discharge may be present [8].

Table 1. Prevalent sites of infectious enterocolitis according to the causative microorganism.

Prevalent Site of Infection	Causative Microorganism
Distal small bowel	*Yersinia* *Salmonella* *Shigella* *Campylobacter*
Distal ileum and cecum	Tuberculosis Amoebiasis
Right colon	*Salmonella* Amoebiasis *Yersinia*
Left colon	*Shigella* *Gonorrhea* *Chlamydia*
Pancolitis	*Escherichia coli* *Clostridium difficile* Cytomegalovirus

Although most cases of infectious enterocolitis yield similar endoscopic macroscopic findings, some cases of infectious enterocolitis have characteristic endoscopic findings. *Yersinia* enterocolitis is caused by infection with *Yersinia enterocolitica*, a Gram-negative bacillus distributed worldwide. *Yersinia* enterocolitis usually affects the terminal ileum or right colon, but occasionally the left colon. Because the right colon and terminal ileum are frequently involved, full colonoscopy should be considered to confirm *Yersinia* infection [9]. Rutgeerts et al. reported that *Yersinia* enteritis in the terminal ileum is characterized by large ulcers in the form of granular mucosa [10]. Arai et al. also reported multiple granular elevated lesions in *Yersinia* ileitis involving the terminal ileum [11]. *Yersinia* enterocolitis yields inflammatory findings accompanied by granular mucosa of the distal ileum, and is often mistaken for Crohn's disease (CD) because of its location [12][13][14][15]. Therefore, diagnosis of *Yersinia*

enterocolitis should not be made simply by endoscopic findings; other clinical features and clinical findings derived through laboratory tests such as stool tests should be comprehensively considered.

Gastrointestinal (GI) salmonellosis is a disease caused by infection of the GI tract with *Salmonella* species. *Salmonella* mainly affects the distal ileum and the right colon, but in some cases the entire colon may be involved; thus, full colonoscopy should be considered when *Salmonella* infection is suspected, such as *Yersinia* enterocolitis [16]. It is difficult to differentiate *Salmonella* enterocolitis only by endoscopic findings because it yields non-specific acute inflammatory findings, such as mucosal redness, mucosal friability, ulcers, and erosion [17][18]. In severe *Salmonella* enterocolitis involving the whole colon, care must be taken not to confuse it with ulcerative colitis (UC). Moreover, care should be taken not to confuse it with CD when the right colon is severely involved [16].

Shigellosis presents with fever and watery diarrhea, progressing to invasive, hemorrhagic colitis [19]. Upon endoscopy, shigellosis shows mucosal redness, punctate spots, mucosal edema, irregular ulcers, mucosal friability, and exudate [20]. Sometimes in severe shigellosis, the ulcers coalesce and form a circular shape [21]. Although shigellosis mainly affects the left colon, particularly the rectosigmoid colon, it can extend to the proximal part beyond the rectosigmoid colon, and it may present as pancolitis in 15% of cases [20][22]. Shigella can be confused with UC because it shows ulceration endoscopically with diarrhea and bleeding, and the involved area is similar to that in UC.

Enterohemorrhagic *E. coli* enterocolitis (EHEC) can cause hemorrhagic colitis, diarrhea, and hemolytic uremic syndrome [21]. Several studies have reported that inflammation may appear in the entire colorectum, but is more prevalent in the right colon [23][24][25][26]. When severe inflammation occurs, marked swelling, hemorrhage, and dark red erythema may appear in the right colon, which may be similar to the endoscopic findings of ischemic colitis. Moreover, ischemic colitis and EHEC have similar histological findings [27][28][29]. However, they can be differentiated by their common location of involvement. Ischemic colitis usually occurs in the left colon, especially in the watershed area, whereas EHEC enterocolitis occurs more severely in the right colon [21][30].

Pseudomembranous colitis (PMC) is characterized by the presence of numerous yellowish-white plaques forming a pseudomembrane on the colonic mucosa. Endoscopic findings are characterized by multiple yellowish or creamy mucosal plaques [31]. The most common cause of PMC is *Clostridium difficile* [32]. However, it can also be rarely caused by *Clostridium ramosum*, *Entamoeba histolytica, E. coli* O157:H7, *Klebsiella oxytoca*, *Salmonella* species, *Shigella* species, CMV, chemical agents and medications, IBD, and ischemic colitis [33]. *C. difficile*-associated PMC is caused by *C. difficile* toxins, and the use of antibiotics is the greatest risk factor for *C. difficile* overgrowth. PMC usually involves the left colon, but may involve the entire colon in up to approximately one-third of cases [19][21][34]. However, colonoscopy does not always show typical positive findings in pseudomembranous colitis. Bergstein et al. reported that 16 of 29 (55%) patients with confirmed *C. difficile* had endoscopic confirmation of pseudomembrane, and non-specific colitis was found in 4 (14%) [35]. Additionally, Gebhard et al. reported that in the early course of *C. Difficile*-associated PMC, tiny round yellowish spots, different from the usual findings of extensive PMC, could be seen [36]. Colonoscopy can also be used for therapeutic purposes in *C. difficile* infection.

Fecal microbiota transplantation for the treatment of refractory *C. difficile* infection, or for the prevention of recurrence, can be administered via colonoscopy [37].

To diagnose intestinal tuberculosis, tissue sampling is required, so colonoscopy is essential [38][39]. Since intestinal tuberculosis often invades the terminal ileum, the terminal ileum should be observed when performing colonoscopy [40]. Endoscopic findings of intestinal tuberculosis include erosions, aphthous ulcers, circumferential ulcers, round- or irregular-shaped ulcers with circumferential arrangements, multiple nodules, ileocecal deformity, and luminal narrowing [39][41]. Since intestinal tuberculosis tends to involve the ileocecal area and the endoscopic findings are similar to those of CD, care must be taken in making the differential diagnosis. Intestinal tuberculosis more frequently shows a patulous ileocecal valve, scars, and pseudopolyps, and it tends to involve fewer than four segments [42]. Although tissue collection is essential for the diagnosis of intestinal tuberculosis, the probability of confirming intestinal tuberculosis via pathological findings using a biopsy tissue or culture is only 38.7% [43]. Although the confirmation rate via tissue sampling is low, it is also important to confirm the endoscopic findings for the sake of diagnosis.

CMV disease is caused by the reactivation of a latent virus, and is mainly seen in immunocompromised individuals, such as organ transplant recipients [21][44][45]. The GI tract is one of the common organs involved in CMV disease [46]. The diagnostic gold standard for GI CMV disease is the presence of CMV in a tissue sample. However, there may be sampling error and the diagnostic yield is low, so it is not always possible to obtain meaningful results for diagnosis [47][48]. An important endoscopic finding of GI CMV disease is a well-defined ulcer with a punch-out appearance. Occasionally, endoscopic findings may show nonspecific erosions, ulcers, hemorrhagic spots, and granularity and friable mucosa that are difficult to distinguish from UC [49][50][51].

Amoebic colitis is caused by intestinal infection with *Entamoeba histolytica*. Amoebiasis does not cause symptoms in most cases, but approximately 10% of infected people develop symptoms [52]. Colonoscopy can be a good tool for diagnosing amebic colitis. In particular, the microscopic confirmation of trophozoites that phagocytize red blood cells by performing an endoscopic biopsy sample is the most reliable method for diagnosing amebiasis [53]. Endoscopically, amoebic colitis is frequently identified in the cecum or ascending colonm and appears mainly as an ulcerative lesion. The size of the lesion varies from several millimeters to several centimeters, and it shows a clear border with the surrounding normal mucosa and is covered with exudate. In the early stages of the disease, only inflammatory findings, such as mucosal redness, may be seen [53][54]. Tissue biopsy is not diagnostic two-thirds of cases [55][56].

2.2. Inflammatory Bowel Diseases

IBD is classified into CD and UC. Until the 1990s, the treatment goal for IBD was mainly clinical remission. However, as the treatment paradigm has recently changed, the role of endoscopy is becoming more important. An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) published in 2021 suggested endoscopic healing as a long-term target along with normalized quality of life [57]. Endoscopy, especially ileocolonoscopy, is an essential tool for diagnosing IBD, confirming disease activity, assessing treatment effects,

performing colorectal cancer screening, and providing treatment such as endoscopic dilatation [58][59][60][61][62][63][64]. UC and CD show differences in endoscopic findings, and they are very helpful in diagnosis. CD mainly shows segmental involvement, aphthous ulcers, serpentious, longitudinal ulcers, large deep ulcers, rectal sparing, anal or perianal disease, and a cobble stone appearance. Conversely, UC shows a continuous lesion, loss of vascular pattern, granular mucosa, erosion, and rectal involvement [65][66]. Generally, CD can involve the entire GI tract, and UC affects only the colorectum. However, inflammation of the terminal ileum, i.e., backwash ileitis, is found in 10% of patients with diffuse active UC [67]. Since CD often invades the terminal ileum, it is essential to observe the terminal ileum during colonoscopy [66]. Histopathological evaluation through colonoscopic biopsy, especially the identification of granuloma specific to CD, helps to differentiate IBD [68]. However, not all tissue samples of CD show granuloma on histopathological examination. The rate of confirmation of granuloma through endoscopic biopsy in CD is as low as 15% to 36% [66].

Mucosal healing is a strong predictor of an IBD patient's long-term outcome [69][70]. In UC, mucosal healing leads to clinical remission and reduces the risk of colon cancer. In CD, mucosal healing reduces surgery and hospitalization rates [71][72]. **Table 2** summarizes the endoscopic scoring system commonly used in IBD. Endoscopic evaluation is required to evaluate mucosal healing. Since UC occurs only in the colorectum, colonoscopy is essential to evaluate disease activity. Endoscopic severity assessment scoring systems used for UC include the Mayo endoscopic subscore (MES), Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Ulcerative Colitis Colonoscopic Index of Severity (UCCIS). The MES is a part of the Mayo score and is widely used in clinical practice. The MES classifies UC into normal or inactive disease, mild disease (erythema, decreased vascularity, mild friability), moderated disease (marked erythema, absent vascularity, friability, and erosions), and severe disease (spontaneous bleeding and ulceration) [73]. UCEIS is a scoring system that evaluates each of the nine items of vascular pattern, mucosal erythema, mucosal surface, mucosal edema, mucopus, bleeding, incidental friability, contact friability, erosions and ulcers, and extent of erosions or ulcers [74]. UCCIS uses four parameters: granularity, vascular pattern, ulceration, and bleeding/friability [75]. The first endoscopic scoring system for CD was the Crohn's Disease Endoscopic Index of Severity (CDEIS), but it is difficult to use in clinical practice because of its complexity. The subsequent Simple Endoscopic Score for Crohn's Disease assesses the degree of ulceration, ulcerated surface, inflamed surface, and stenosis for five defined bowel segments (the rectum, sigmoid and descending colon, transverse colon, ascending colon, and terminal ileum) to classify the disease activity [76].

Table 2. Endoscopic scoring systems for IBD.

Scoring System	Disease Type	Criteria
MES	UC	0: Normal or inactive disease 1: Mild disease (erythema, decreased vascular pattern, mild friability) 2: Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3: Severe disease (spontaneous bleeding, ulceration)
UCEIS		Combines vascular pattern, bleeding, erosions and ulcers, and evaluates the

Scoring System	Disease Type	Criteria
		severity on a scale of 0 to 8
UCCIS		Evaluates 4 parameters: granularity, vascular pattern, ulceration, and bleeding/friability Score range: 0–12, with higher scores indicating more severe disease
CDEIS	CD	Considers the surface affected by disease, ulcerations, and ulcerated surface Score range: 0–44, with higher scores indicating more severe disease
SES-CD		Evaluates 4 parameters: size of ulcers, ulcerated surface, affected surface, and presence of narrowing Score range: 0–56, with higher scores indicating more severe disease

e activity.

Chronic inflammation of the intestine due to IBD increases the risk of colorectal cancer. The incidence of colorectal cancer in patients with IBD is two- to three-fold [77][78]. The increased risk of colorectal cancer in patients with inflammatory bowel disease can be managed through periodic colonoscopy surveillance. The 2019 BSG and ECCO guidelines recommend starting surveillance 8 years after symptom onset in patients with inflammatory bowel disease with colon involvement. However, if PSC is present, it is recommended to start monitoring at the time of diagnosis [79][80]. In addition, the surveillance interval is classified according to the severity of the disease and is recommended at intervals of 1–5 years. When determining the surveillance interval, the presence of primary sclerosing cholangitis, severity of inflammation, family history, dense pseudopolyps, and dysplasia should be considered [81]. A Cochrane Database systemic review and meta-analysis reported that the surveillance colonoscopy group of patients with IBD showed lower cancer detection (3.2% vs. 1.8%, odds ratio (OR), 0.58; 95% confidence interval (CI), 0.42–0.80, $p < 0.001$), lower colorectal cancer-related mortality (22.3% vs. 8.5%, OR, 0.36; 95% CI, 0.19–0.69, $p = 0.002$), and a higher rate of early-stage colorectal cancer (7.7% vs. 15.5%, OR, 5.40; 95% CI, 1.51–19.30, $p = 0.009$) than the no-surveillance group [82]. Continuous surveillance colonoscopy is required to reduce the increased risk of colorectal cancer in patients with IBD.

MES, Mayo endoscopic score; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; UCCIS, Ulcerative Colitis Colonoscopic Index of Severity; CDEIS, Crohn's Disease Endoscopic Index of Severity; SES-CD, Simple Endoscopic Score for Crohn's Disease.

The surveillance of dysplasia should also be performed in inflammatory bowel disease. The 2019 BSG and ECCO guidelines recommend using high-definition endoscopy rather than standard-definition, and chromoendoscopy rather than white light endoscopy. For chromoendoscopy, the use of methylene blue or indigo carmine is recommended [79][80]. However, chromoendoscopy can be considered impractical for practitioners because it takes a long time and requires several preparations. Therefore, instead of chromoendoscopy, high-definition endoscopy can also be used as a good alternative [83][84]. Previously, biopsies were performed four times every 10 cm when conducting surveillance colonoscopy in patients with IBD, but their effectiveness is controversial. Random biopsy is considered to be problematic because of the low dysplasia detection rate and prolonged procedure time. Moreover, the 2019 BSG and ECCO guidelines recommend target biopsy instead of random biopsy. Therefore, random biopsy can be considered in selected cases [79][80][85]. In past guidelines, surgical proctocolectomy was recommended when dysplasia was identified on surveillance colonoscopy for IBD. However, the recent trend is to attempt endoscopic resection according to the lesion characteristics [83]. Surgical operation is considered for non-visible dysplasia confirmed by random biopsy [86]. On the other hand, macroscopically identified dysplasia lesions can be removed endoscopically. Endoscopic resection should be performed by a skilled therapeutic endoscopist,

and it is determined depending on the shape, size, site, and submucosal invasion of the lesion [86]. Endoscopic resection methods include EMR, ESD, modified EMR (mEMR), and hybrid ESD. It is recommended to perform endoscopic resection when in the endoscopic remission state [81].

IBD is accompanied by various bowel complications, the most representative of which is stricture. Stricture occurs primarily in patients with CD and occurs in up to 33% of patients with CD 10 years after diagnosis [87]. If symptoms occur due to stricture, surgical or endoscopic treatment is required. Since repetitive surgical operations can lead to short bowel syndrome, endoscopic balloon dilatation can replace surgery to preserve the bowel. Endoscopic balloon dilatation should be avoided in patients with fistulas, deep ulcers, or long strictures >5 cm [88][89]. In one study, the technical success rate of endoscopic balloon dilatation was 89% and the clinical success rate was 81% [90]. However, repeated endoscopic dilation is often required because of the high recurrence rate of stricture. Gustavsson et al. performed 776 dilatations in 178 patients with CD. At the 5-year follow-up, only 52% of the patients did not require additional dilatation or only needed one additional dilatation. Complications occurred in 5.3% of patients, and 36% underwent surgery [91]. Ferlitsch et al. reported that after endoscopic dilatation for CD stricture, repeated dilatation was performed in 31% of cases, and surgical resection was performed in 28% [92]. If the length of the stricture is short (<4 cm), stricture of the surgical anastomosis is the most suitable target for balloon dilatation. However, surgical treatment should be considered in cases of multiple stenosis, >4–5 cm, fistula, or abscess [90]. Although strictures are more commonly observed in CD than in UC, if strictures are found in UC patients with a long morbidity period, a biopsy is necessary because there is a risk of dysplasia or colorectal cancer. The characteristics of malignant stricture in UC are as follows: first, it occurs 10–20 years after the onset of UC; second, it is more common in the proximal than in the splenic curve; and third, it is often expressed as a symptom of colonic obstruction [93].

2.3. Neoplasms

Colorectal cancer (CRC) is a major cause of morbidity and mortality throughout the world. It accounts for over 10% of all cancer incidence [94]. It is the third most common cancer worldwide and the second most common cause of death [94]. Most guidelines, including those from the American Cancer Society [95], the US Preventive Services Task Force [96], and the European Society of Gastrointestinal Endoscopy (ESGE) [97], recommend screening for CRC in average-risk individuals beginning at the age of 45 or 50 years. Both colonoscopy and sigmoidoscopy can detect and remove polyps, potentially preventing malignant transformation and decreasing CRC mortality and incidence. To date, four large randomized controlled trials comparing flexible sigmoidoscopy screening with no screening showed reductions in CRC incidence (18–23%) and CRC mortality (22–33%) [98][99][100][101]. These findings provide substantial protection against CRC diagnosis and death, and the benefits can last for up to 17 years [102]. Randomized controlled trials of screening colonoscopy are ongoing, but definitive results will not be available until 2022 or 2026–2027 [103][104][105]. Cohort and case–control studies found an association between lower endoscopy and reduced CRC mortality and incidence. A large prospective cohort study of nearly 89,000 nurses and other healthcare professionals found that, over 24 years of follow-up, colonoscopy was associated with a 68% reduction (95% CI, 0.55–0.76) in CRC-specific mortality compared with no exposure to colonoscopy [106]. Individuals who underwent colonoscopy with polypectomy were found to have a 43% reduction in CRC incidence compared to

those with no lower endoscopy [106]. However, cohort studies probably overestimate the real-world effectiveness of colonoscopy because of the inability to adjust for important factors such as incomplete adherence to testing and the tendency of healthier persons to seek preventive care. In a Canadian case–control study, any colonoscopy was associated with a 37% reduction in the odds of CRC death [107]. Similar case–control studies using the Surveillance, Epidemiology, and End Results (SEER)-Medicare and Veterans Administration data also found approximately 60% reductions in CRC death associated with colonoscopy, with similar differences by site [108][109]. However, these three case–control studies were unable to determine indications for colonoscopy, and excluded colonoscopies performed within 6 months of CRC diagnosis, likely introducing bias. In a meta-analysis conducted with 13 cohorts including 4,713,778 individuals and 16 case–control studies, colonoscopy screening not only reduced the incidence of colorectal cancer by 52% (risk ratio (RR): 0.48, 95% CI, 0.46–0.49), but also reduced colorectal cancer related mortality by 62% (RR: 0.38, 95% CI, 0.36–0.40) [110]. Flexible sigmoidoscopy and colonoscopy are both recommended CRC screening strategies, but their relative effectiveness is unclear. According to the case–control study using the SEER-Medicare database, screening colonoscopy was associated with a greater reduction of 74% (OR 0.26, 95% CI, 0.23–0.30) in CRC mortality compared to screening sigmoidoscopy, which was associated with a 35% reduction (OR 0.65, 95% CI, 0.48–0.89) in CRC mortality. Additionally, screening colonoscopy was found to be more effective in reducing mortality in the distal colon compared to the proximal colon.

The NordICC (Nordic-European Initiative on Colorectal Cancer) study highlights the importance of quality control in population-based colonoscopy screening programs. A significant issue identified in this study is the low quality of colonoscopy screenings, which can affect the effectiveness of these programs in detecting and preventing CRC [111]. The ongoing NordICC study aims to evaluate the long-term performance of colonoscopy screening and the impact of quality control measures. In the next 5 years, the study is expected to yield valuable insights into the effectiveness of various quality indicators in improving colonoscopy screening results [104]. By examining these results, healthcare professionals and policymakers can make informed decisions about implementing and refining population-based colonoscopy screening programs.

Colonoscopy describes the size and shape of neoplasms found during the diagnostic process, and also can estimate the tumor’s malignant potential and invasion depth. Generally, the macroscopic appearance of colonic lesions is described using the Paris classification. According to the Paris classification, among neoplastic lesions with superficial morphology, those taller than the height of the biopsy forcep (2.5 mm) are defined as polypoid, and those that are not are defined as non-polypoid. Polypoid lesions are classified as I, which are further classified as pedunculated (Ip), sessile (Is), and semi-pedunculated (Isp). Nonpolypoids are classified as slightly elevated (IIa), flat (IIb), slightly depressed (IIc), and excavated (III) [112]. Classifying the endoscopic macroscopic type helps to understand the characteristics of the lesion and select an appropriate endoscopic resection method for the lesion. Macroscopic findings are important clues to determine the invasion depth of the lesion. Currently, the indication for endoscopic treatment of colorectal cancer is early colorectal cancer that invades the mucosa or submucosa to <1000 μm [113][114][115]. Therefore, it is necessary to accurately determine the invasion depth of the lesion before endoscopic resection to avoid unnecessary procedures. Representative morphological features suggesting submucosal invasion of colorectal cancer include loss of lobulation, demarcated depression area, stalk swelling,

excavation, fullness, ulcer bleeding, fold convergency, and non-lifting signs [116]. Kudo et al. first proposed a classification method called pit pattern using a magnifying endoscopy and indigo carmine dye [117]. This classification classifies into five types, from type I to type V, and according to each classification, the tissue type and invasion depth of the colorectal tumor can be estimated. As electronic chromoendoscopy can replace chromoagents, the Tumor Narrow Band Imaging (NBI) Interest Group in 2010 proposed the NBI International Colorectal Endoscopic (NICE) classification, which is a method of classifying colorectal lesions according to NBI findings without magnifying endoscopy [118]. Additionally, in 2014, the Japan NBI Expert Team (JNET) proposed the JNET classification using magnifying endoscopy and NBI. The JNET classification divides colorectal lesions into four types (types 1, 2A, 2B, and 3) using surface and vascular patterns, and this is different from the NICE classification, in that the JNET classification can distinguish between benign lesion and mucosal cancer [119].

A subepithelial lesion (SEL) is also a neoplastic lesion that is frequently encountered in clinical practice. SELs can occur in any segment of the colon. As the rate of screening colonoscopy increases, the number of SEL cases is also increasing [120]. SELs can be benign and malignant, so making an accurate diagnosis is very important. For the diagnosis of SELs, first, it is important to confirm the macroscopic findings of the lesion through colonoscopy. Most SELs are lesions < 20 mm, covered by normal mucosa. The color of the surface mucosa varies from normal pinkish to yellowish, bluish, whitish, and reddish. The consistency of the lesion can be assessed by touching it with biopsy forceps. If the cushion sign is positive, it is often a lipoma or lymphangioma. In addition, when pulsation is observed in the lesion, it can be considered as a blood vessel. Rapid growth in size or surface ulceration can be considered as findings suggesting malignancy [121]. An SEL may not be an intraluminal lesion, and may instead be compression caused by an external structure. If the location and pattern of the lesion change through air control or posture change, the possibility of extraluminal compression should be considered. A prospective study reported that when 100 SELs were evaluated, endoscopic identification of the intramural or extramural location of the lesion showed a sensitivity of 98% and a specificity of 64%. This finding suggests that extramural lesions may be mistaken for intramural lesions by endoscopy alone [122]. Therefore, when extramural compression is suspected, performing additional modalities such as endoscopic ultrasonography (EUS) and computed tomography (CT) is helpful for diagnosis. When using EUS, the accuracy of distinguishing between extramural and intramural lesions reaches approximately 90% [122].

EUS is useful for the differentiation of intramural SELs by evaluating the originating layer and echogenicity of the SEL. **Table 3** [123][124] summarizes the layers and echogenicity of representative colonic SELs commonly encountered. In addition to layer and echogenecity, there are clues that are helpful for diagnosis during EUS. First, when there is erosion or ulceration on the surface of the SEL, it is likely a malignancy, such as submucosal tumor like-cancer, metastatic cancer, a neuroendocrine tumor, lymphoma, or a GI stromal tumor. A lipoma has a yellow surface with a positive cushion sign, and when a biopsy is performed, a characteristic naked fat sign is observed. Lymphangioma also has a positive cushion sign, and unlike a lipoma, it has a pale, transparent surface. In addition, a lymphangioma is characterized by anechoic cystic spaces with septations when EUS is performed. It is impossible to completely discriminate all SELs with only EUS. In one study, the concordance between EUS and a histopathologic diagnosis was 79.3% [125]. In summary, to diagnose SEL, the location of the lesion, macroscopic

findings, and EUS findings should be comprehensively considered, and if necessary, additional imaging modalities such as CT and magnetic resonance imaging should be used [124].

Table 3. Characteristic features of colorectal subepithelial tumors.

Type of Lesion	Layer of Origin	EUS Appearance
Benign lesions		
Lipoma	Third	Hyperechoic, homogenous, smooth margin
Lymphangioma	Second, Third	Anechoic with internal septa, serpiginous shape
Leiomyoma	Second, Fourth	Hypoechoic (similar to the muscular layer), homogenous, round or oval, well-circumscribed
Granular cell tumor	Second, Third	Hypoechoic (higher echogenicity compared to the muscular layer), heterogenous, smooth margin
Schwannoma	Third, Fourth	Hypoechoic, homogenous, smooth margin, sometimes with marginal halo
Calcifying fibrous tumor	Second, Third, Forth	Hypoechoic, post-acoustic shadowing with slightly hyperechoic foci inside
Rectal tonsil	Second, Third	Hypoechoic, well-demarcated
Endometriosis	Forth, Fifth	Hypoechoic. Heterogenous (mighht extended into the rectovaginal setum), irregular margin
Lesions with malignant potential		
Neuroendocrine tumor	Second, Third	Hypoechoic or isoechoic, homogenous, smooth margin
GIST—low risk	Second, Fourth	Hypoechoic, round, <3 cm, heterogenous, round, smooth margin
GIST—high risk	Second, Fourth	Hypoechoic, >3 cm, heterogenous with cystic spaces or echogenic foci, irregular margin
MALToma	Second, Third	Hypoechoic, Partial indentation of the submucosa layer

GIST, Gastrointestinal stromal tumor; MALToma, mucosa-associated lymphoid tissue lymphoma; EUS, endoscopic ultrasonography.

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