Table 3 Emetic risk category for radiation therapy

JSCO emetic risk category	Treated area	
High emetic risk (emetic frequency: >90 %)	Total body	
Moderate emetic risk (emetic frequency: 30–90 %)	Upper abdomen	
Low emetic risk (emetic frequency: 10–30 %)	Lower thorax	Pelvis
	Cranium (radiosurgery)	Craniospinal
Minimum emetic risk (emetic frequency: <10 %)	Head and neck	Extremities
	Cranium	Breast

As for chemotherapy, antiemetic treatments for radiation therapy are critical for successful treatment. Accordingly, the 2004 MASCC and 2006 ASCO guidelines indicate the emetic risk categories for specific targeted tissues, and recommend prophylactic emetic regimens based on these risk classifications. The risk of radiation-induced nausea and vomiting is categorized according to the percentage of patients who experience emesis. Moreover, whole body and upper abdominal radiation therapy are likely to cause greater emesis, and the frequency of nausea and vomiting increases with larger total doses and target tissue volumes [29, 30].

CQ13. Do antiemetic treatments differ in equivalent regimens from those in standard regimens containing specific key agents?

Recommendation (Grade C1): the emetic risk should be assessed on the basis of the agent with the highest emetic risk, even for similar chemotherapeutic regimens that comprise several agents.

Most clinically used chemotherapeutic regimes include several drugs, although many variations of standard chemotherapeutic regimens containing similar key agents. Thus, it is important to assess the emetic risks of regimens according to the emetic risks of each agent in isolation.

CQ14. What clinical factors and patient backgrounds affect CINV?

Recommendation (Grade C1): treatment and patient factors affect the emetic risks of CINV. Treatment factors include emetogenicity and dosages of chemotherapeutic agents, and tissue targets and volumes of radiation therapy. Relevant patient factors include age, gender, and alcohol consumption.

The frequency and intensity of emesis from CINV are affected by numerous factors, including specific chemotherapeutic agents, regimens, dosages, schedules, routes of administration, and tissue targets and volumes for radiation therapy. In addition, patient factors such as age [31], gender [31, 32], alcohol consumption [33], and experience of nausea gravidarum affect the emetic effects of CINV. The NCCN guideline also suggests that bowel obstruction, vestibulopathy, brain metastasis, electrolyte dysbolism, uremia, opioid use, gastric atony, and mental disorders are potential risk factors for emesis. Accordingly, management of treatment-related emesis is well-established with consensus, whereas patient-oriented factors remain unclear.

CQ15. How should CINV be managed in pediatric patients with malignancies?

Recommendation (Grade C1): multidisciplinary management using $5HT_3$ receptor antagonists, corticosteroid, and other antiemetic agents control the emetic effects of CINV, even for pediatric patients.

In the last three decades, advances in cancer treatment, for example high dose methotrexate, cytarabine, cyclophosphamide, and hematinic stem cell transplantation, have led to long term prognoses for $\geq$70 % of pediatric patients with malignancies. However, there are only a few reports with high level evidence about antiemetic treatment in pediatric patients from western populations [34–36]. Accordingly, they are treated with modified dosage on the basis of results of clinical trials on adult patients. Proper antiemetic treatments also enable pediatric patients to receive cancer chemotherapy without decline in QOL.

CQ16. Is it possible to discriminate nausea from anorexia, pyrosis, and dyspepsia? Which diseases produce symptoms of nausea and vomiting?

Recommendation (Grade B): no definitive evidence distinguishes nausea from anorexia, pyrosis, and dyspepsia. However, proton pump inhibitors (PPI) and H2 blockers are recommended for patients with these symptoms.

Recommendation (Grade C1): antiemetic agents should be used on the basis of accurate assessment of patient conditions.

Symptoms of anorexia, pyrosis, and dyspepsia are caused by several factors related to digestive dysfunction, and are frequently accompanied with nausea and other symptoms. Therefore, nausea induced by chemotherapy has not been strictly distinguished from other symptoms of digestive dysfunction. Nonetheless, PPI and H2-blockers are recommended as optional treatments for these symptoms [37].

In addition to treatments for CINV, patients with malignancies may suffer from nausea and vomiting as a result of the following conditions:

- Partial or complete bowel obstruction
- Vestibulopathy

- Brain metastasis
- Electrolyte dysbolism (hypercalcemia, hyponatremia, and hyperglycemia)
- Uremia
- Other combinations of drugs, including opioids
- Gastric atony
- Anticipatory nausea and vomiting

CQ17. How are different forms of agents appropriately selected and used?

Recommendation (Grade B): patients should self-manage the use of oral agents. However, in circumstances in which nausea and vomiting prevent patients from taking oral treatments, optional intravenous administration should be considered.

Antiemetic agents are available in a variety of formulations for oral, rectal, intravenous, and intramuscular administration. A meta-analysis of randomized control trials showed equivalence of oral and intravenous $5HT_3$ receptor antagonists [38]. However, the cost effectiveness and convenience of administration of oral agents are superior to those of intravenous agents, particularly when administered as tablets that disintegrate orally. Nonetheless, intravenous agents may improve treatment adherence among pediatric patients.

CQ18. For which antiemetic drugs are pharmacokinetic interactions observed?

Recommendation (Grade B): it is essential that aprepitant is used carefully to avoid interactions with co-administered drugs, including some chemotherapeutic agents. Moreover, strict dose control of combined drug regimens according to patient conditions and disease backgrounds is critical.

Because aprepitant induces and inhibits the cytochrome P450 enzymes 3A4 (CYP3A4) and 2C9 (CYP2C9) it can alter plasma concentrations of co-administered drugs by interacting with these critical drug-metabolizing enzymes [39]. Chemotherapeutic agents that are metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosphamide, imatinib, vinorelbine, vinblastine, and vincristine. Although doses were not adjusted for several chemotherapeutic agents used concurrently with aprepitant in phase III trials, these drugs should be used with caution [40, 41] because aprepitant interacts with several non-chemotherapeutic drugs, including warfarin, dexamethasone, and methylprednisolone. Concurrent use of aprepitant temporarily reduces prothrombin time–international normalized ratio (PT–INR) for patients receiving regimens that contain warfarin, necessitating anticoagulant monitoring for these patients [42]. Aprepitant also increases AUCs of the corticosteroids dexamethasone and methylprednisolone, necessitating appropriate reductions of corticosteroid doses (CQ7) [39]. However, to ensure anti-cancer effects, steroid doses should not be reduced in chemotherapeutic regimens for malignant lymphoma that include corticosteroid, despite concomitant use of aprepitant. Moreover, concurrent use of the CYP3A4 inhibitors ketoconazole, itraconazole, and erythromycin may increase aprepitant AUCs, whereas the CYP3A4 inducers carbamazepine, rifampicin, and phenytoin may reduce plasma levels of aprepitant.

CQ19. How are the effects of antiemetic treatment evaluated?

Recommendation (Grade A): the effects of antiemetic treatment should be assessed at every visit for outpatients, and within 24 h after administration of chemotherapy for admitted patients.

Recommendation (Grade C1): strict assessments require patients to report their conditions to medical staff by using self-reporting systems.

No definitive evidence or consensus has been published for assessment of antiemetic treatments. However, successful anticancer treatment depends on optimum patient assessments, and nausea and vomiting are observed for 31 and 20 % of cancer patients, respectively [43]. Accordingly, the 2009 NCCN guidelines for palliative care recommend optimum screening for supportive care of all oncology patients according to their symptoms throughout the entire clinical course. Moreover, the RAND Cancer Quality-Assessing Symptoms Side Effects and Indicators of Supportive Treatment Project recommends symptom evaluations for all cancer patients, at every outpatient visit, and within 24 h of hospital admission. The 2009 NCCN Clinical Practice Guidelines for Antiemetics in Oncology suggest that prevention of nausea and vomiting is a primary objective. Hence, prophylactic treatment is mandatory for $\geq$4 days, because the emetic risks of CINV continue for several days under conditions of highly or moderately emetogenic cancer chemotherapy [44]. Moreover, complete responses were reportedly not achieved for acute and delayed emesis, despite optimum prophylactic treatment [40].

Differential diagnosis of the causes of emesis are necessary during clinical evaluations (CQ14, 16). However, common terminology criteria for adverse events (CTCAE) may remain useful when chemotherapeutic regimens are applied, and are based on objective assessments by medical staff rather than subjective assessments by patients. Nonetheless, applicable patient directed subjective evaluations include the numerical rating scale (NRS), the visual analog scale (VAS), the verbal rating scale (VRS) and the Wong–Baker face rating scale. In addition, index of nausea, vomiting and retching (INVR) [44], Morrow assessment of nausea and emesis (MANE) [45], and functional living index-emesis (FLIE) scores [46] are also applicable as tools for evaluating longitudinal changes in emesis and the ensuing effects on quality of life.

CQ20. How is occlusive ileus managed in cancer patients with advanced and metastatic status, including carcinomatous peritonitis?

Recommendation (Grade A): reduction of gastrointestinal pressure using a nasogastric tube or percutaneous gastrostomy is recommended. In addition, intraperitoneal injection of octreotide is recommended as a drug therapy for carcinomatous peritonitis.

Recommendation (Grade C1): such salvage surgery as bowel bypass may also be effective for patients who are not in a critical condition and have expectations of comparatively long survival. However, endoscopic stents are recommended to resolve symptoms of simple intestinal obstruction for patients with poor prognosis.

Bowel obstruction among patients with advanced metastatic disease reduces quality of life and causes difficulty in the continuation of anticancer treatments. Conservative treatments are usually used for such patients, because of poor prognosis as a result of advanced oncological status. However, 50 % of colon cancer patients and 6–34 % of gynecologic cancer patients suffer from benign bowel obstructions [47], so accurate diagnoses is required.

CQ21. How are opioid-induced nausea and vomiting managed?

Recommendation (Grade B): emesis that is induced by opioid use should be managed by use of antiemetic treatments, although opioid rotation or changes in routes of administration may be considered.

Recommendation (Grade C1): prophylactic antiemetic treatments during opioid therapy may be useful despite the lack of high-level evidence of efficacy and safety.

The WHO ladder strongly recommends opioid use for oncological pain and cites high-level evidence of efficacy and safety. Moreover, three opioid receptors, the δ and κ receptors for emetogenic functions and the μ receptor for antiemetic functions, have been characterized. Patients frequently suffer from constipation, sleepiness, nausea, and vomiting on initiation of opioid therapy. However, antiemetic treatments for opioid-induced emesis are important for successful pain control among cancer patients. Moreover, differential diagnosis of other causes is important in patients suffering from emesis after opioid treatments (CQ16). Nonetheless, opioid-induced emesis is usually relieved within a few days of opioid administration.

Discussion

The purpose of these practice guidelines is to disseminate treatment recommendations for daily practice according to CQ relating to medications. Thus, 21 CQ pertaining to antiemetic therapy, including prophylactic and retrospective antiemetic treatments, were generated. In this literature review, most of the evidence was collected from foreign studies reporting high-level evidence that was acceptable for Japanese cancer patients. Therefore, these recommendations for standard therapy, depending on the grade of recommendation, were made on the basis of systematic review and meta-analysis of antiemetic therapy. Consequently, the CQs and their recommendations were similar to those published in previous guidelines that have been used globally. However, most reported evidence fails to consider ethnicity and Japanese health-care systems. Thus, after release of the guidelines, their penetration and dissemination to Japanese medical practitioners was evaluated. To this end, current use of antiemetic treatment in Japan was analyzed on the basis of data obtained from a nationwide questionnaire. Response was 88 % and use of the guidelines 78 % (in press).

Conclusion

In this manuscript we present, in English, of the 2010 JSCO clinical practice guidelines for antiemesis. High concordance with other antiemetic guidelines reflected their evidence-based nature. After release of these guidelines, high recognition and penetration was achieved for antiemetic medicine in Japan, thus contributing to effective antiemetic therapy for Japanese patients with malignancies.

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Inter-Rater Agreement of Sputum Cytology for Lung Cancer Screening in Japan

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Background: *To compare lung cancer detection rate by sputum cytology, we need some assurance that the estimates do not vary widely if different observers evaluate the same specimens. The aim of this study was to determine inter-rater agreement of sputum cytology diagnoses.*
Methods: *Slides of sputum cytology from 150 subjects were selected from a pool of slides held by six of the laboratories that had participated in a population-based lung cancer screening program over the last ten years in Japan. The cytotechnologists in these laboratories had considerable experience with sputum cytology. Each case was re-evaluated six times. Cases that were diagnosed as the same category by all six laboratories were selected as consensus cases to serve as standardized sputum cytology cases. Thirty-seven cytotechnologists with various levels of experience in sputum cytology then re-evaluated these consensus cases. Inter-rater agreement was calculated by kappa statistics including Fleiss' kappa.*
Results: *All pairs of interlaboratory agreement for the 150 cases showed statistically significant kappa values, most pairs showing substantial agreement. Fleiss' kappa value across the six laboratories was 0.5. Fourteen cases were identified as the consensus cases, and the agreement among observers with less experience of sputum cytology showed significantly lower than the agreement among those with considerable experience (Fleiss' kappa value 0.27 vs. 0.45, $P < 0.05$). Moreover, cytotechnologists with less experience under-diagnosed the slides significantly more often than those with considerable experience.*
Conclusion: *When the observers have considerable experience with sputum cytology, inter-observer agreement is good.* Diagn. Cytopathol. 2015;43:545–550. © 2015 Wiley Periodicals, Inc.

Key Words: sputum cytology; lung cancer screening; quality assurance; interrater agreement; kappa statistics; Fleiss'; kappa

A joint committee of the Japan Lung Cancer Society and the Japanese Society of Clinical Cytology has discussed quality assurance for sputum cytology in a population-based lung cancer screening program that has been running for more than 30 years in Japan.[1–3] Screening is offered to residents aged more than 39 years and comprises annual chest X-rays for all screenees plus sputum cytology for screenees with a more than 30 pack-year smoking history. Each prefecture in Japan has managed this program for their residents, designated cytology laboratories in each prefecture assessing the sputum cytology of screenees.

Recently, it has been debated whether all such laboratories have similar capabilities in sputum cytology diagnosis because there is considerable inter-prefectural variability in lung cancer detection rate by sputum cytology in this screening program. However, to date, inter-rater agreement of sputum cytology has not been studied in Japan, except for one small study[4] in which five laboratories evaluated sputum cytology slides of only eleven cases without statistical analysis.

Thus, we designed this study, in which standardized sputum cytology cases were selected and agreement of

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SPECIAL ARTICLE

Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer

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Abstract Colorectal cancer is a major cause of death in Japan, where it accounts for the largest number of deaths from malignant neoplasms among women and the third largest number among men. Many new methods of treatment have been developed during recent decades. The Japanese Society for Cancer of the Colon and Rectum Guidelines 2014 for treatment of colorectal cancer (JSCCR Guidelines 2014) have been prepared as standard treatment strategies for colorectal cancer, to eliminate treatment disparities among institutions, to eliminate unnecessary treatment and insufficient treatment, and to deepen mutual understanding among health-care professionals and patients by making these guidelines available to the general public. These guidelines have been prepared as a result

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The Japanese Society of Gastroenterology

SPECIAL ARTICLE

Evidence-based clinical practice guidelines for management of colorectal polyps

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Abstract
Background Recently in Japan, the morbidity of colorectal polyp has been increasing. As a result, a large number of cases of colorectal polyps that are diagnosed and treated using colonoscopy has now increased, and clinical guidelines are needed for endoscopic management and surveillance after treatment.
Methods Three committees [the professional committee for making clinical questions (CQs) and statements by Japanese specialists, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee by moderators] were organized. Ten specialists for colorectal polyp management extracted the specific clinical statements from articles published between 1983 and September 2011 obtained from PubMed and a secondary database, and developed the CQs and statements. Basically, statements were made according to the GRADE system. The expert panel individually rated the clinical statements using a modified Delphi approach, in which a clinical statement receiving a median score greater than seven on a nine-point scale from the panel was regarded as valid.
Results The professional committee created 91CQs and statements for the current concept and diagnosis/treatment of various colorectal polyps including epidemiology, screening, pathophysiology, definition and classification, diagnosis, treatment/management, practical treatment, complications and surveillance after treatment, and other colorectal lesions (submucosal tumors, nonneoplastic polyps, polyposis, hereditary tumors, ulcerative colitis-associated tumor/carcinoma).
Conclusions After evaluation by the moderators, evidence-based clinical guidelines for management of colorectal polyps have been proposed for 2014.

Keywords Colorectal polyp · Colorectal tumor · Polyposis · GRADE system

The original version of this article appeared in Japanese as "Daicho Polyp Sinryo Guidelines 2014" from the Japanese Society of Gastroenterology (JSGE), published by Nankodo, Tokyo, 2014. Please see the article on the standards, methods, and process of developing the Guidelines (doi: 10.1007/s00535-014-1016-1). The members of the Working Committee are listed in the Appendix in the text.

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Introduction

In Japan, following the westernization of eating habits and with aging of the population, the morbidity of colorectal carcinoma and associated mortality are both increasing. Indeed, it has been said that the 21st century is the era of the large intestine. As the number of cases of colorectal polyps that are diagnosed and treated via colonoscopy has now increased, clinical guidelines are needed for endoscopic management and surveillance after treatment. In April 2012, the National Health Insurance system began offering coverage for expenses incurred for colorectal endoscopic submucosal dissection (ESD). Accordingly, appropriate selection between ESD and endoscopic

mucosal resection (EMR) has become more important. In this regard, the Japanese Society of Gastroenterology (JSGE) has established "evidence-based clinical guidelines for management of colorectal polyps" (hereafter referred to as "the Guidelines"). Although the title of the Guidelines mentions colorectal polyps, they include all types of localized colorectal lesions, including superficial neoplastic lesions, early carcinoma, and polyposis.

The Guidelines Creation Committee and Evaluation Committee were established prior to drafting the Guidelines. The Japanese Gastroenterological Association, Japanese Society of Gastrointestinal Cancer Screening, the Japan Gastroenterological Endoscopy Society (JGES), the Japan Society of Coloproctology (JSCP), and the Japanese Society for Cancer of the Colon and Rectum (JSCCR), which are cooperative societies, recommended members to be assigned to these two committees.

In the creation of the Guidelines, the Guidelines Creation Committee drafted clinical questions (CQs) that covered: (1) epidemiology; (2) screening; (3) pathophysiology, definition, and classification; (4) diagnosis; (5) treatment and management; (6) practical treatment; (7) complication and surveillance after treatment; and (8) other colorectal lesions (submucosal tumors, nonneoplastic polyps, polyposis, hereditary tumors, ulcerative colitis-associated tumor/cancer). The Evaluation Committee evaluated the drafts of the CQs, and 91 CQs were established. For each CQ, a document retrieval style was created, and systematic document retrieval was performed by searching PubMed and Igaku Chuo Zassi for articles published between January 1983 and September 2011. For insufficient or unobtainable documents, manual searching was also performed. Subsequently, a structured abstract was created, and both a statement and an explanation were written. The Guidelines Creation Committee determined the grades of recommendations and the levels of evidence after deliberation using the Delphi method. As mentioned in a previous publication [1], the Guidelines were created in accordance with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. This draft was evaluated and amended by the Evaluation Committee, which was then presented to members of the JSGE. After obtaining public comments, these comments were discussed, and a final version of the Guidelines was created.

The contents on tumor diagnosis and endoscopic treatment described in the Guidelines partially overlap with those of the previously published 2014 JSCCR Guidelines for the Treatment of Colorectal Cancer [2] and the Colorectal ESD/EMR Guidelines (JGES) [3]. In addition, the committees for these three guidelines closely cooperated with each other to ensure their consistency. Concerning the contents of the Guidelines, this paper mainly introduces CQs for the treatment of colorectal polyps.

Clinical questions (CQ) and statements

CQ. What are the indications for endoscopic resection with respect to the size of adenomas?

- Endoscopic resection should be used for lesions ≥6 mm in size (Recommendation 2 [100 %], level of evidence C). However, endoscopic resection should also be used for diminutive lesions ≤5 mm, flat and depressed lesions, as well as for those indistinguishable from carcinoma (Recommendation 2 [100 %], level of evidence D).

Comment: It is strongly recommended that endoscopic resection be used for lesions ≥6 mm in size because the incidence of carcinoma is higher in lesions ≥6 mm than in those ≤5 mm, and because it is often difficult to distinguish between benign adenomas and carcinomas by colonoscopy alone [4, 5].

According to a study in the UK, if the relative risk for carcinoma in lesions ≤5 mm is considered 1, it increases to 7.2, 12.7, and 14.6 in lesions sized 6–10 mm, 11–20 mm, and >20 mm, respectively. Therefore, all colonic lesions ≥6 mm should be either resected or ablated [4]. From the results of meta-analyses, polypectomy [4] and EMR [6]/ESD [7] can be considered the preferred less invasive treatments for colorectal neoplasia [8, 9]. However, for flat and depressed lesions, endoscopic resection is recommended, since the incidence of carcinoma is even higher in lesions that are ≤5 mm in size than in polypoid lesions [6, 10].

CQ. How should diminutive adenomas that are ≤5 mm in size be managed?

- Diminutive polypoid lesions should be followed up (Recommendation 2 [100 %], level of evidence C). However, endoscopic resection should be performed for diminutive flat and depressed lesions that are difficult to distinguish from adenomas or carcinomas (Recommendation 2 [100 %], level of evidence D).

Comment: Hyperplastic diminutive lesions ≤5 mm in size are acceptable for being followed up by colonoscopy. In diminutive polypoid adenomas ≤5 mm, at least in principle, follow-up is acceptable in the absence of colonoscopic findings suggestive of carcinoma. Flat and depressed lesions suspected of being adenoma or carcinoma on colonoscopy are preferably treated by endoscopic resection. Colonoscopic findings suspicious for carcinoma include the following: (1) expansive appearance (protrusion and overextension of the lesion and/or surrounding normal mucosa such as a submucosal tumor); (2) depressed surface; (3) rough appearance (rough surface without shine); (4) normal mucosa of the border of the tumor in

sessile lesions; and (5) type V pit pattern (irregular or disappearance of surface structure). To confirm these findings, chromoendoscopy or magnifying colonoscopy is recommended [11, 12]. Diminutive lesions should be followed up with annual colonoscopy for 3 years [13, 14].

A cohort study on diminutive colorectal lesions reported that there is little change in either the size or shape of lesions after 2–3 years of follow-up [13]. The incidence of carcinoma in diminutive colorectal lesions in Western countries is reported to range from 0.03 to 0.05 %. According to a large-scale cohort study, the overall incidence of polypectomy-related complications is 0.7 % with a perforation rate of 0.1 % (one per 1,000 resections). In addition, to decrease unnecessary risks for healthy individuals and lower overall costs, endoscopic resection should not be performed for all diminutive colorectal lesions ≤5 mm [15, 16].

After resection of colorectal neoplasia, yearly follow-up by colonoscopy is recommended until all colorectal polyps including diminutive lesions have been completely excised, and every 3 years thereafter [14, 17].

CQ. How should hyperplastic polyps be managed?

- Follow-up is recommended for hyperplastic polyps ≤5 mm detected in the recto-sigmoid region (Recommendation 2 [100 %], level of evidence D). Endoscopic resection should be performed for lesions ≥10 mm detected in the right side of the colon, as they are difficult to discriminate from sessile serrated adenoma/polyps (SSA/P) (Recommendation 2 [100 %], level of evidence D).

Comment: Typical hyperplastic polyps presenting as whitish flat lesions ≤5 mm in the recto-sigmoid region should be followed up, as there have been no reports on the association of these lesions with adenoma [18, 19]. Colonoscopy every 10 years is recommended in the case of hyperplastic polyps according to the guidelines of the AGA/ASGE. Endoscopic resection should be used for lesions ≥10 mm in size in the right side of the colon, as they are difficult to distinguish from SSA/P; the incidence of carcinoma in such lesions has been reported to be 9.4 % [20].

According to the results of 1,800 cases in two large studies on chemoprevention, the risk of hyperplastic polyps is significantly higher (OR 3.67; $p < 0.001$) in patients with hyperplastic polyps detected at initial examination. Moreover, the risk of relapse of adenomatous polyps is also significantly higher (OR 2.08; $p < 0.01$) in patients with adenomatous polyps detected at initial examination. On the other hand, there is no correlation between the risk of adenoma and detection of hyperplastic polyps at initial examination or between adenomatous polyps and the presence of hyperplastic polyps [18, 19]. It has been hypothesized that adenomatous and hyperplastic polys may have different etiology, since the presence of the former has no correlation with the latter, and vice versa [18, 19].

However, one report has suggested that hyperplastic polyps in the recto-sigmoid region may indicate malignant lesions in the proximal colon, since *BRAF* mutations have been detected in hyperplastic polyps, although additional investigations are needed to clarify potential correlations between hyperplastic polyps and SSA/P [18, 19].

CQ. How should serrated lesions of the colorectum be treated?

- Serrated lesions of the colorectum include sessile serrated adenoma/polyp (SSA/P), traditional serrated adenoma (TSA), and hyperplastic polyp (HP). The former two lesions have potential to develop to adenocarcinoma and thus are recommended to treat (Recommendation 2 [100 %], level of evidence D).

Comment: Serrated lesions of the colorectum include SSA/P, TSA, and HP. SSA/P and TSA may undergo malignant transformation to adenocarcinoma and should thus be treated. SSA/P is associated with *BRAF* mutations and the CpG island methylator phenotype (CIMP), and is considered a precursor lesion of colorectal carcinoma with microsatellite instability [21]. Recent studies have reported that the rate of progression to carcinoma in SSA/P ranges from 1.5 to 20 % [22]. Aggressive resection should be performed for SSA/P [23].

TSA is a protruding lesion with distinct redness that is commonly found in the left side of the colon and rectum. Histologically, TSA is considered to potentially progress to carcinoma, similar to SSA/P. Treatment is therefore indicated for TSA, and resection is indicated for TSA ≥5 mm in diameter, similar to common adenomas. As for SSA/P, most studies recommend that lesions ≥10 mm in diameter should be resected [24–26]. HP may be a precursor lesion of SSA/P and/or TSA. Treatment is not indicated for HP ≤5 mm in diameter.

CQ. What therapy is indicated for laterally spreading tumors (LST)?

- The therapeutic choice between piecemeal EMR and ESD for a large LST should be based on the LST subtype, and use of magnifying endoscopy and endoscopic ultrasonography as appropriate (Recommendation 2 [100 %], level of evidence C).

Comment: LSTs are classified into two types according to morphology: granular type (LST-G) and non-granular type (LST-NG) [27]. Each type has two subtypes. The former consists of a "homogenous type" and a "nodular mixed type", while the latter consists of a "flat elevated type" and

a "pseudo-depressed type". Most LST-Gs are considered adenomatous lesions. Among homogenous-type LST-Gs, the incidence of carcinoma or submucosal invasion is extremely low [28, 29]. Large nodule in a nodular mixed-type LST-G, where submucosal invasion tends to be present [30], should be resected en bloc [31]. An adenomatous LST-G homogenous type can be resected by piecemeal EMR [32]. A flat elevated-type LST-NG should be treated according to preoperative diagnosis. For pseudo-depressed-type LST-NGs, en bloc resection should be performed, since these tumors have a high probability of multifocal submucosal invasion independent of their size or pit pattern [30, 31]. In summary, the indications for ESD or piecemeal EMR are based on the LST subtype; magnifying endoscopy and endoscopic ultrasonography are used as needed.

CQ. What are the indications for endoscopic resection of early colorectal carcinoma?

- An early colorectal carcinoma (Tis/T1) should be treated endoscopically when the possibility of lymph node metastasis is extremely low and en bloc resection is possible (Recommendation none, level of evidence level C).

Comment: There are no reports of lymph node metastasis in intramucosal (Tis) carcinomas, while lymph node metastasis occurs in approximately 10 % of submucosal invasive (T1) carcinomas [33, 34]. Therefore, endoscopic resection is recommended in a Tis or Tl carcinoma that has a low probability of lymph node metastasis. Endoscopic resection is both a therapeutic and important diagnostic method that can be used for total excisional biopsy. Complete resection with a negative vertical margin is indispensable for cure after endoscopic resection of a T1 carcinoma. Endoscopic resection of T1 carcinomas is associated with a risk of positive vertical margins. It is thus necessary to completely resect the carcinoma and ensure that horizontal and vertical margins are negative, enabling both precise pathological diagnosis and curative potential [2].

CQ. What pathological findings do indicate additional surgery after endoscopic resection for early colorectal carcinoma?

- T1 carcinoma with a tumor-positive vertical margin is an absolute indication. T1 carcinoma with an unfavorable histologic grade or submucosal invasion of $\geq$1,000 μm, or vascular invasion or grade 2/3 tumor budding should be considered for additional surgery with lymph node dissection (Recommendation none, level of evidence C).

Comment: Lymph node metastasis is found in 6.8–17.8 % of T1 carcinomas [2, 35, 36]. In principle, T1 carcinoma should be treated by surgery with lymph node dissection. The risk factors for lymph node metastasis in T1 carcinoma include depth of submucosal invasion [2, 35, 37–42], histological grade [2, 35, 37, 39–42], budding grade [2, 35, 36, 43], and vascular invasion [2, 35–44]. According to the 2014 guidelines by the JSCCR (Japanese Society for Cancer of the Colon and Rectum) for the treatment of colorectal carcinoma, among the carcinomas treated by endoscopic resection, T1 carcinomas with a tumor-negative vertical margin, favorable histologic grade with a submucosal invasion depth of <1,000 μm, and absence of vascular invasion with tumor budding grade 1 (low grade) could be followed up, while T1 carcinomas that do not meet these criteria should be considered for additional surgery with lymph node dissection. It may possible to reduce the number of patients undergoing unnecessary additional surgical resection considering the above risk factors [2, 37–39, 45, 46]. Even if the risk for lymph node metastasis after endoscopic treatment cannot be considered zero, a comprehensive assessment of the pathologic findings after endoscopic resection, patient age, physical activity levels, comorbidities, and any potentially undesirable consequences of the resection such as urinary and excretory disorders or the need for colostomy is needed.

CQ. In which types of colorectal tumors is it acceptable to perform piecemeal EMR?

- Definite adenoma or Tis carcinoma based on preoperative diagnosis are acceptable for piecemeal EMR. However, rates of local recurrence with piecemeal resection are high, and thus caution is advised (Recommendation 2 [100 %], level of evidence C).

Comment: In principle, en bloc resection should be used for suspicious or definite carcinoma, since the specimen obtained by complete en bloc resection should be pathologically examined in detail. On the basis of precise preoperative diagnosis with magnifying endoscopy, adenomatous lesions or focal carcinoma in adenomas $\geq$2 cm in diameter, for which en bloc snare EMR is not indicated, can be completely resected using deliberate piecemeal EMR to avoid segmentation of the carcinomatous area without compromising pathological diagnosis [2]. Although the local recurrence rate associated with piecemeal resection is high compared with that after en bloc resection [31, 32, 47–52], most local recurrent lesions are adenomas. Cure is possible with additional endoscopic treatment for local recurrent intramucosal lesions [47, 49, 52, 53]. In contrast, ESD allows complete en bloc resection regardless of lesion size. However, colorectal ESD is

technically more difficult and requires considerable experience.

CQ. What are the indications for endoscopic submucosal dissection?

- (1) Tumors requiring endoscopic en bloc resection, for which the snare technique is difficult to use; (2) intramucosal tumors accompanied by submucosal fibrosis, induced by biopsy or peristalsis of the lesion; (3) sporadic localized tumors that occur as a result of chronic inflammation; and (4) local residual early carcinoma after endoscopic resection are among the indications for ESD (Recommendation none, level of evidence C).

Comment: The Colorectal ESD Standardization Implementation Working Group proposed a draft entitled Criteria of Indications for Colorectal ESD [31]. It specifically states that colorectal ESD is indicated for tumors requiring endoscopic en bloc resection when it is difficult to use the snare technique, such as LST-NG (especially the pseudo-depressed type), tumors with a type VI pit pattern, shallow submucosal invasive carcinoma, large depressed tumors, and large elevated lesions that are probably malignant (large nodular lesions such as LST-G). Other lesions such as intramucosal tumors accompanied by submucosal fibrosis induced by biopsy or peristalsis of the lesion, sporadic localized tumors that occur as a result of chronic inflammation such as ulcerative colitis, and local residual early carcinoma after endoscopic resection, are also included in the indications for ESD. A cure rate of 83–88 % has been reported using ESD for local residual early carcinoma after endoscopic resection [54, 55]. In Japan, colorectal ESD has been covered by national health insurance since April 2012. It is indicated in early colorectal carcinomas, early carcinomas that are 2–5 cm in diameter. However, there were no significant differences in the outcome of colorectal ESD between lesions 2–5 cm in diameter and those $\leq$5 cm in diameter based on a prospective cohort study by the Japan Gastroenterological Endoscopy Society (JGES). Considering payments by national health insurance, no limitations on lesion size have been required for colorectal ESD.

CQ. Is biopsy essential for choosing the therapeutic strategy for colorectal lesions?

- This will depend on the characteristics of individual lesions. It is acceptable to decide a therapeutic strategy for colorectal lesions without biopsy (Recommendation 2 [100 %], level of evidence C).

Comment: Endoscopic procedures, especially magnifying endoscopy such as pit pattern diagnosis or image-enhanced endoscopy, avoid unnecessary biopsy for colorectal tumors. Biopsy should not be performed in polypectomy or EMR, as it increases medical expenses. In addition, it is clinically insignificant to randomly obtain biopsies for protruding lesions, as most are adenoma or carcinoma in adenoma. However, biopsy for a lesion suspected to be T1 carcinoma may acceptable, since histological information is helpful for planning the therapeutic strategy. Biopsy for superficial lesions (flat or depressed lesions) should not be performed prior to endoscopic resection, as it causes false-positive non-lifting signs due to submucosal fibrosis after injection during EMR [56]. It is important to understand whether the lesion is indicated for endoscopic resection through standard or magnifying endoscopic observation.

CQ. How is the choice made from among polypectomy, EMR, and ESD for colorectal tumors?

- Polypectomy is indicated for pedunculated or semi-pedunculated polyps, and EMR is indicated for sessile polyps or superficial lesions. ESD is indicated for lesions requiring endoscopic en bloc resection, although the lesions cannot be resected en bloc by snare techniques (Recommendation 2 [100 %], level of evidence C).

Comment: The choice of technique for endoscopic resection should be based on tumor morphology and size. Polypectomy is normally indicated for pedunculated or adenomatous semi-pedunculated polyps, while EMR is suitable for sessile, semi-pedunculated, or superficial tumors that are likely to be carcinoma [6, 57]. ESD allows complete en bloc resection regardless of the size of the lesion [28, 31, 58, 59]. Colorectal ESD is thus indicated for lesions requiring endoscopic en bloc resection when it is difficult to use the snare technique [31]. Moreover, en bloc resection is particularly indicated for depressed tumors or pseudo-depressed-type LST-NGs, as these tumors have a high incidence of submucosal invasion [28, 29]. In contrast, piecemeal EMR is acceptable for LST-G homogenous-type, since it is associated with a very low incidence of submucosal invasion [31]. EMR or ESD should be preferred over polypectomy for suspected submucosal invasive (T1) carcinoma.

CQ. Does colorectal carcinoma incidence decrease by endoscopic removal of colorectal adenoma?

- It is generally believed that the incidence of colorectal carcinoma decreases following endoscopic removal of colorectal adenomas, at least in Western countries, although there is limited data in Japan (Recommendation none, level of evidence B).

Comment: In 1993, the National Polyp Study (NPS) Workgroup reported that endoscopic removal of all

colorectal adenomatous polyps is associated with a decrease in the incidence of colorectal carcinoma from 76 to 90 % [60]. Since then, endoscopic removal of all adenomas during colonoscopy was strongly recommended in Western countries. In contrast, some Japanese endoscopists have reported that endoscopic polypectomy of all adenomas (especially for diminutive polyps) may not be effective in decreasing the incidence of colorectal carcinoma. Moreover, there is limited data in Japan. Regarding this CQ, two issues should be considered, namely the prevalence of carcinoma based on the size of the lesions and the interval of surveillance after endoscopic polypectomy. Regarding the former, in 1995, Sawada and Hiwatashi reported that the prevalence of carcinoma in patients with diminutive (<5 mm) polyps was 1.2 % (98.8 % were benign adenoma) [61]. While this proportion appears to be higher than that reported in Western countries (0.03–0.05 %), this discrepancy may be related to differences in pathological definitions. Nonetheless, the prevalence of carcinoma in patients with diminutive polyps is rather low. On the other hand, a single screening/surveillance colonoscopy session may not identify all polyps. Moreover, there are many reports concerning the clinical importance of de novo carcinoma. We note that a single colonoscopy with polyp removal is not a flawless procedure, and in particular, poor bowel preparation may be associated with a lower reported incidence of colorectal carcinoma [62–64]. Based on these points, it can be assumed that carcinoma can be prevented by endoscopic removal of polyps.

CQ. How should surveillance colonoscopy be planned after endoscopic removal of colorectal adenoma?

- Follow-up colonoscopy should be performed within 3 years after polypectomy (Recommendation 2 [100 %], level of evidence B).

Comment: The National Polyp Study (NPS) Workgroup recommended an interval of at least 3 years after colonoscopic removal of newly diagnosed adenomatous polyps and follow-up examination [65]. According to the European guidelines [66] and modified US guidelines [67], the most suitable interval for surveillance colonoscopy is recommended based on the number of adenomas, maximum size of polyps, and histopathological findings (including the presence of high-grade dysplasia) of resected lesions. As general guidance, patients with several (in European guidelines: <4, in US guidelines <9) small adenomas (low-grade dysplasia) <10 mm should undergo surveillance colonoscopy at 3 years following polypectomy. In contrast, patients with only one or two small low-grade adenomas should undergo routine screening (i.e., FOBT) according to the European guidelines, and surveillance colonoscopy after 5–10 years according to the US guidelines. Moreover, according to these guidelines, patients with many adenomas (>10) or high-grade dysplasia (known as intramucosal cancer in Japan) should undergo more intensive surveillance colonoscopy. In Japan, the decision to follow these guidelines is uncertain because management of diminutive adenoma (<5 mm) has not been established. In brief, endoscopists in the West attempt to remove all adenomas, whereas there is no uniform Japanese approach (removal or follow-up) for diminutive adenomas, and controversy remains in Japan [68–72]. The present guidelines, therefore, recommend the following based on data from a retrospective study carried out by the Japan Polyp Study Workgroup [73]: "Follow-up colonoscopy should be performed within 3 years after polypectomy."

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Appendix

Members of the Working Committee who created and evaluated the "Evidence-based clinical guidelines for management of colorectal polyps", JSGE

Director Responsible

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Guideline

JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection

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Colorectal endoscopic submucosal dissection (ESD) has become common in recent years. Suitable lesions for endoscopic treatment include not only early colorectal carcinomas but also many types of precarcinomatous adenomas. It is important to establish practical guidelines in which the preoperative diagnosis of colorectal neoplasia and the selection of endoscopic treatment procedures are properly outlined, and to ensure that the actual endoscopic treatment is useful and safe in general hospitals when carried out in accordance with the guidelines. In cooperation with the Japanese Society for Cancer of the Colon and Rectum, the Japanese Society of Coloproctology, and the Japanese Society of Gastroenterology, the Japan Gastroenterological Endoscopy Society has recently compiled a set of colorectal ESD/endoscopic mucosal resection (EMR) guidelines using evidence-based methods. The guidelines focus on the diagnostic and therapeutic strategies and caveat before, during, and after ESD/EMR and, in this regard, exclude the specific procedures, types and proper use of instruments, devices, and drugs. Although eight areas, ranging from indication to pathology, were originally planned for inclusion in these guidelines, evidence was scarce in each area. Therefore, grades of recommendation were determined largely through expert consensus in these areas.

Key words: colorectal tumor, early colorectal carcinoma, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), guidelines

INTRODUCTION

AT PRESENT, WE can select various techniques in endoscopic treatment for colorectal tumors. Basically, complete en bloc resection is indicated for early colorectal carcinoma regardless of tumor size. Although endoscopic submucosal dissection (ESD) has made it possible, colorectal ESD is technically more difficult to carry out than upper-gastrointestinal ESD and, hence, it is essential to prevent complications such as perforation. However, among epithelial colorectal tumors that can be treated by endoscopic treatment, there are many adenomatous lesions that may be regarded as precarcinomatous in addition to early carcinomas. Therefore, accurate and qualitative preoperative diagnosis of lesions and the selection of appropriate treatment on the basis of a precise diagnosis are essential.

In this capacity the Guidelines Committee of the Japan Gastroenterological Endoscopy Society (JGES) drafted the Colorectal ESD/EMR Guidelines (hereinafter referred to as the Guidelines) with the aim of ensuring the appropriate clinical introduction of colorectal ESD in relation to endoscopic mucosal resection (EMR). These guidelines focus on the diagnostic and therapeutic strategies and stipulations before, during, and after EMR and ESD and do not contain specific information about the procedures, types and proper use of instruments, devices, and drugs. In the Guidelines, differences between colorectal EMR and ESD, preoperative diagnosis, and perioperative care are also described on the basis and strength of clinical evidence.

We created the Guidelines in accordance with the Procedures for the Evaluation, Selection, and Publication of

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Japanese Clinical Practice Guidelines in Medical Information Network Distribution Service (MINDS) 2007,[1] taking into account levels of evidence and grades of recommendation with regard to evaluating evidence-based medicine (Table 1), as reported previously.[2] Although eight areas, ranging from indication to pathology, were originally planned for inclusion in the guidelines, evidence in each area was scarce, which has resulted in the grades of recommendation being mostly determined through expert consensus.

We established six categories for evaluation, as follows: indications, techniques, complications, treatment outcome (recurrence, metastasis, and prognosis), postoperative follow up, and pathology. For each clinical question (CQ), systematic document retrieval was done by searching PubMed and *Igaku Chuozasshi* for articles published from 1985 to 2012. For insufficient or unsearchable documents, hand searching was also done. The retrieved documents were evaluated, and pertinent documents were adopted. Subsequently, a statement and an explanation were created for each CQ. Members of the Guidelines Creation Committee set the levels of evidence and the grades of recommendations in their responsible fields by using the MINDS Grade of Recommendations, as described above. For the created statements, nine members of the Guidelines Creation Committee voted by using the Delphi method, as reported previously.[2]

Table 1 Levels of evidence and grades of recommendations: MINDS Grade of Recommendations

Levels of evidence
I: Systematic review/meta-analysis
II: Several randomized controlled trials
III: Non-randomized controlled trial
IVa: Analytical epidemiological study: cohort study
IVb: Analytical epidemiological study: case–control study, cross-sectional study
V: Descriptive study (case report and case series)
VI: Opinions of special committees and individual experts that are not based on patient data
Grades of recommendations
A: Strong scientific evidence exists and the therapy is strongly recommended
B: Scientific evidence exists and the therapy is recommended
C1: No scientific evidence exists but the therapy is recommended
C2: No scientific evidence exists and the therapy is not recommended
D: Scientific evidence of ineffectiveness or danger exists and the therapy is not recommended

MINDS, Medical Information Network Distribution Service.

INDICATION FOR ENDOSCOPIC OR SURGICAL TREATMENT

Basic principles

WHEN EARLY COLORECTAL carcinoma is diagnosed, the patient is recommended to undergo endoscopic or surgical treatment (level of evidence: IVb, grade of recommendation: B). When surgical treatment was carried out, the 5-year survival rate of colorectal carcinoma was reported to be 94.3% for stage 0 and 90.6% for stage I. Curability was reported to be 92.7% when endoscopic treatment was carried out.[3] Thus, excellent results could be obtained from both surgical treatment and endoscopic treatment.[4,5]

In cases where the risk exceeds the benefit of endoscopic treatment, such as when a patient's general condition is extremely poor, it is recommended to abandon the treatment (level of evidence: V, grade of recommendation: C1). In particular, the application of endoscopic treatment to elderly patients (≥65 years) must be carefully considered. Many elderly patients have poor general condition and suffer from comorbidities. The frequency of complications associated with endoscopic treatment is high in these patients.[6] In contrast, some reports have indicated that endoscopic treatment could be safely carried out even for elderly patients.[7,8] For very elderly patients (≥85 years), endoscopic treatment should be done only when the expected advantage is likely to outweigh the risk of complications associated with the resection, while also considering the average life expectancy, comorbidities, and body age of the patient.

When carrying out endoscopic treatment, a patient's general condition and medications must be verified, and informed consent must be obtained (level of evidence: VI, grade of recommendation: C1). Before carrying out endoscopic treatment, a patient's comorbidities and medications must be thoroughly evaluated. In particular, hemorrhage may develop when a patient taking an antithrombotic agent (anticoagulant or antiplatelet) undergoes endoscopic treatment without discontinuing the drug, whereas a cerebrocardiovascular event may occur if the patient discontinues the medication. After evaluating both risks, the decision should be made regarding whether the patient should continue to take the medication. If drug discontinuation is decided, the optimal timing for drug discontinuation and resumption must be carefully evaluated.[2] The risk of thromboembolism differs depending on the status of the patient's underlying disease, and the type and time of placement of artificial valves or stents. The risk of hemorrhage differs depending on the kind of endoscopic examination and treatment. Both ESD and EMR are considered to have a high risk of hemorrhage.

As a general rule, written informed consent (IC) for carrying out endoscopic treatment must be obtained from the patient. The IC form must contain the following items: (i) name and condition of the patient's disease; (ii) reasons for recommending endoscopic treatment; (iii) actual details of the procedure to be carried out; (iv) expected outcomes; (v) predicted risks; (vi) alternative methods that could substitute for endoscopic treatment and information on the comparison; and (vii) prognosis if the patient does not undergo endoscopic treatment.[9] When it is difficult to sufficiently communicate with a patient, IC must be obtained from an appropriate representative. With regard to the use of sedation during endoscopic treatment, it is advisable to obtain IC in which the expected effect and risk of complications are completely explained in a written document.

Indication for endoscopic treatment

Non-carcinoma

Resection is recommended for adenomas ≥6 mm in size. Resection is recommended for superficial depressed-type lesions (type 0–IIc) even when the lesion is ≤5 mm in size. Typical hyperplastic polyps ≤5 mm in size that are present in the distal colon may be left untreated (level of evidence: IVb, grade of recommendation: B). Among adenomas and early carcinomas, the carcinoma rate of protruded-type and superficial elevated-type lesions ≤5 mm in size is low, and these adenomas are very unlikely to become a T1 (submucosal [SM]) carcinoma. However, the rate of SM invasion (i.e. the T1 [SM] carcinoma rate of lesions >6 mm) increases as the size of the lesion increases.[10–15] Despite an extensive search of the literature, we could find no clear evidence regarding the carcinoma rate and prognosis of microlesions ≤5 mm in size in cases where it is left untreated. Some studies reported that colorectal adenomas ≤5 mm in size that had been followed for several years showed minimal changes.[16–18] Therefore, prompt treatment is not required for protruded-type and superficial protruded-type adenomas ≤5 mm in size. Superficial depressed-type lesions exhibit a certain carcinoma rate and a certain rate of SM invasion even when their size is ≤5 mm.[10,11,13,14] Although adenomas themselves are benign, it is expected that their removal will prevent the development of colorectal carcinoma.[19,20] Most colorectal neoplasms are adenomas,[9] and these adenomas can be cured by using EMR or piecemeal EMR techniques.[21,22] For some neoplasms, endoscopic treatment is technically difficult to carry out depending on the site or size of the lesion.

According to genetic-pathological analyses, some colorectal carcinomas are assumed to develop from serrated lesions through the so-called serrated pathway. However, the natural history and carcinoma rate of serrated lesions have not been sufficiently elucidated. The risk for colorectal carcinoma is reported to be high in patients with sessile serrated adenoma/polyp (SSA/P).[23–27] However, data on how often and how fast carcinoma development occurs within the SSA/P itself have been insufficient.[28–32] Large or dysplastic SSA/P has the potential of developing into a carcinoma. In contrast, the possibility of carcinoma development is considered to be extremely low for typical hyperplastic polyps ≤5 mm in size present in the distal colon or rectum.[33]

Carcinoma

Among early colorectal carcinomas (Tis/T1), lesions with little possibility of lymph node metastasis and higher expectancy of curability with en bloc resection on the basis of the size and the location are usually treated endoscopically because such cases are expected to be curable. Obvious clinical T1b carcinomas (submucosal invasion depth ≥1000 μm) are usually treated surgically. When endoscopic treatment is carried out for colorectal carcinomas, en bloc resection is the principal approach; however, piecemeal resection is also acceptable when the possibility of submucosal invasion can be definitively excluded and if the treatment is appropriately carried out (level of evidence: IVb, grade of recommendation: B).

In early colorectal carcinomas, lymph node metastasis is difficult to predict. In contrast, invasion depth can be very precisely predicted when image-enhanced endoscopy, magnifying endoscopy, and/or endoscopic ultrasonography (EUS) are used concurrently (discussed below).

Among the endoscopic treatments, ESD is the most suitable method for en bloc resection.[34–40] Piecemeal EMR may make it difficult to establish a pathological diagnosis of the invasion depth and to determine a free resection margin. The number of resected pieces must be minimized, and the region suspected to contain a carcinoma should not be sectioned. With a larger tumor size and a greater number of resected pieces, the local recurrence rate increases.[41–43] When carrying out piecemeal EMR, magnifying endoscopic observation, which is the best way to identify the carcinomatous part of the lesion, should be carried out before the treatment, and the carcinomatous area should not be sectioned. Otherwise, it would be difficult to evaluate the invasion depth or vessel invasion, and an additional treatment such as lymph node dissection might not be done even when it is necessary in case of submucosal invasive carcinoma.

Laterally spreading tumors (LST) are classified into granular type (LST-G) and non-granular type (LST-NG). In LST-NG, the pseudo-depressed type (PD), which is expressed as IIc+IIa or IIa+IIc according to the Japanese Classification of Colorectal Carcinoma,[44] is associated with multifocal invasion, the foci of which are often difficult to predict. In addition, LST-NG (PD) is frequently associated with fibrosis. Therefore, in many cases, EMR is not suitable for LST-NG (PD).[45] Considering the high possibility of deep submucosal invasion in LST-NG (PD), whether the lesion is indicated for surgical operation or for endoscopic treatment should be carefully considered. To determine the indication

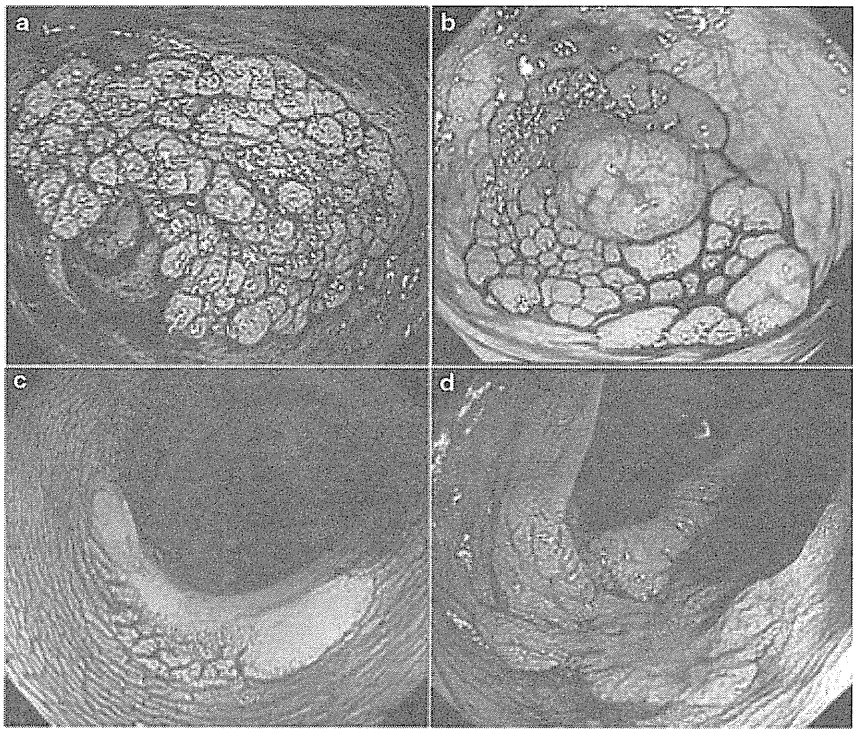

Figure 1 Subtypes of laterally spreading tumors (LST) (classification should be done on the basis of images obtained by using indigocarmine dye spraying). (a) Homogeneous type: LST-G (Homo). (b) Nodular mixed type: LST-G (Mix). (c) Flat-elevated type: LST-NG (F). (d) Pseudo-depressed type: LST-NG (PD). LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor non-granular type.

for ESD or EMR for LST, overall judgment based on the subclassification of LST (Fig. 1) and on the pit pattern diagnosis by using magnifying observation is useful.[46] The details of evaluating lesions for the ESD technique are presented in a draft proposed by the Colorectal ESD Standardization Implementation Working Group (Table 2).[34,35,38,47,48]

PREOPERATIVE DIAGNOSIS

Distinction between adenoma and adenocarcinoma

BEFORE CARRYING OUT colorectal ESD or EMR, it is important to distinguish between adenoma and adenocarcinoma in order to determine whether the lesion is benign or malignant and to characterize the marginal demarcation of the lesion. In the large intestine, adenoma and 'carcinoma in/with adenoma' lesions are often detected in addition to early carcinomas without adenoma. Therefore, not only the malignancy of an entire lesion but also the carcinomatous and adenomatous parts of the lesion must be correctly assessed and distinguished. Consequently, therapeutic strategies such as the use of ESD or EMR, selection of piecemeal EMR, and a deliberate planned sectioning line can be determined.[49]

When image-enhanced endoscopy and magnifying observation are used, a distinction between adenoma and

Table 2 Indications for ESD for colorectal tumors†

Lesions for which endoscopic en bloc resection is required
1) Lesions for which en bloc resection with snare EMR is difficult to apply
- LST-NG, particularly LST-NG (PD)
- Lesions showing a V_I-type pit pattern
- Carcinoma with shallow T1 (SM) invasion
- Large depressed-type tumors
- Large protruded-type lesions suspected to be carcinoma‡

2) Mucosal tumors with submucosal fibrosis§
3) Sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis
4) Local residual or recurrent early carcinomas after endoscopic resection

†Partially modified from the draft proposed by the Colorectal ESD Standardization Implementation Working Group.
‡Including LST-G, nodular mixed type.
§As a result of a previous biopsy or prolapse caused by peristalsis of the intestine.
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor non-granular type; PD, pseudo-depressed; SM, submucosal.