JSGE 1898 The Japanese Society of Gastroenterology

T (14)

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

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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 T1 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 ≥ 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 ≤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."

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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Executive Committee

Chair: Shinji Tanaka (Department of Endoscopy, Hiroshima University Hospital)

Vice-Chair: Yusuke Saitoh (Digestive Disease Center, Asahikawa City Hospital)

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Original Paper

Digestion

Endoscopic Submucosal Dissection as Total Excisional Biopsy for Clinical T1 Colorectal Carcinoma

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Abstract
Background/Aims: Only the depth of submucosal invasion can be estimated prior to determining the indications for endoscopic submucosal dissection (ESD) as a curative treatment for colorectal carcinoma (CRC). Here we evaluated the outcomes of ESD for clinical T1 CRCs. *Methods:* Of 660 patients who underwent ESD for CRC at the Hiroshima University Hospital between June 2003 and December 2013, we examined the outcomes of 37 (6%; 26 men, 11 women; mean age ± SD, 68 ± 12 years) who underwent ESD as total excisional biopsy for various reasons, in spite of an endoscopic diagnosis of T1 CRC. *Results:* The mean lesion size was 25 ± 14 mm; 14 lesions were protruding and 23 were superficial. The en bloc resection rate was 100% (37/37). The histological en bloc resection rate was 92% (34/37). ESD resulted in a positive vertical margin in 3 cases. Deep submucosal invasion was seen in 3 cases, 2 of which had severe submucosal fibrosis. Although severe submucosal fibrosis was not found in

other cases, pathologic examination of the deepest invasive portion of the tumor revealed poorly differentiated adenocarcinoma. The rates of post-ESD bleeding and perforation were 8% (3/37) and 5% (2/37), respectively. All patients recovered under conservative therapy. No cases of recurrence were noted in patients without additional surgical resection when the lesions satisfied the curative conditions listed in the 2014 Japanese Society for Cancer of the Colon and Rectum guidelines. *Conclusion:* En bloc resection by ESD as total excisional biopsy for clinical T1 CRC is a highly effective treatment and establishes a precise histological diagnosis.

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Introduction

Although lymph node (LN) metastasis typically occurs in approximately 10% of T1 (submucosal invasive) colorectal carcinoma (CRC) cases [1–4], the standard treatment for T1 CRC is surgical resection with regional LNs. According to the 2014 Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines for the treatment of CRC, the criteria for identifying curable T1 CRC after endoscopic resection are well-/moderately dif-

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Table 1. Clinical outcomes of ESD for clinical T1 CRC

Variable	Total (n = 37)	VM+ group (n = 3)	VM– group (n = 34)	p value
En bloc resection rate	37 (100)	3 (100)	34 (100)	n.s.
Histological en block resection rate	34 (92)	0	34 (100)	n.s.
Procedure time, min	60±40	40±6	78±51	n.s.
Delayed bleeding	3 (8)	0	3 (9)	n.s.
Perforation	2 (5)	0	2 (6)	n.s.

Data are expressed as numbers with percentages in parentheses, or means ± SD. n.s. = Not significant.

ferentiated or papillary histologic grade, no vascular invasion, submucosal invasion depth <1,000 μm and budding grade 1* (low grade) [5], because of the very low risk of LN metastasis. Management of T1 CRC should strike a balance between being curative and minimizing the mortality associated with the treatment undertaken. In addition, the need for additional surgical resection must be carefully considered based on the patient's background.

A relatively small number of patients with clinical (c)T1b (submucosal invasion depth ≥1,000 μm) [5] CRC undergo endoscopic submucosal dissection (ESD) rather than surgical resection because, for example, surgical treatment under general anesthesia is contraindicated due to concomitant diseases or the patient refuses surgical treatment. ESD is a reliable method for en bloc resection regardless of the lesion size or location [6–11], and is considered useful for T1 CRC as a total excisional biopsy [8]. Here we retrospectively evaluated the outcomes of cT1b CRCs resected by ESD as total excisional biopsy and the utility of ESD to afford complete resection of the lesions, which is essential for establishing a precise histopathological diagnosis.

Patients and Methods

Among the 660 patients who underwent ESD as treatment for colorectal tumors at the Hiroshima University Hospital between June 2003 and December 2013, we examined the outcomes of 37 consecutive patients (6%) who underwent ESD as total excisional biopsy for various reasons, in spite of an endoscopic diagnosis of cT1b. For treatment planning, magnifying endoscopy and/or endoscopic ultrasonography (EUS) was performed to determine the depth of submucosal invasion in all 37 cases. ESD as total excisional biopsy for T1 CRC is indicated when EUS reveals a dissectible space in the submucosal layer during ESD [8], so we confirmed by EUS prior to ESD whether lesions had a sufficient submucosal layer with a negative vertical cut end. Surgical resection

was not performed in 30 patients because of concomitant disease, in 8 patients due to advanced age, and in 10 patients because they refused surgery (with some overlap).

We compared the clinical outcomes between the vertical margin-positive (VM+) group and the vertical margin-negative (VM–) group (i.e. vertical complete resection). Fibrosis was classified into three grades (F0, F1 and F2) according to the appearance of the layers during submucosal injection of a mixture of sodium hyaluronate and indigo carmine, as described previously [9]. All patients were followed up for 1 year or more.

Results

The mean age ± SD of the 26 men and 11 women enrolled was 68 ± 12 years (range 46–85). The mean lesion size was 25 ± 14 mm (range 6–75); 14 were protruding lesions and 23 were superficial lesions. The en bloc resection rate was 100% (37/37), and the histological en bloc resection rate was 92% (34/37). ESD resulted in VM+ in 3 cases. No differences were observed between the VM+ and VM– groups in clinicopathological features or clinical outcomes (procedure time, grade of fibrosis during submucosal resection, post-ESD bleeding rate and perforation rate; table 1). The 3 VM+ cases had deep submucosal invasion, and ESD revealed severe submucosal fibrosis (F2) in 2 of these cases (table 2). Although no severe submucosal fibrosis was found in the remaining case, pathologic examination of the deepest invasive portion of the tumor revealed poorly differentiated adenocarcinoma. The rates of post-ESD bleeding and perforation were 8% (3/37) and 5% (2/37), respectively. All patients recovered under conservative therapy. In addition, no post-ESD bleeding or perforation was noted in the VM+ group (table 1).

The overall observation period after ESD was 30 months. Six of the 14 patients who were observed met the

Table 2. Characteristics of VM+ cases

Patient No.	Age/sex	Tumor location	Tumor diameter, mm	Macroscopic type	Submucosal fibrosis	Main histologic type	Histologic type of deepest invasion portion	Submucosal invasion depth, μm	Budding grade	Vascular invasion
1	48/male	rectum	15	depressed	F2	well	well	3,000	G1	ly0, v0
2	59/male	ascending colon	30	elevated	F1	mod	poor	1,800	G2	ly0, v0
3	78/female	rectum	20	protruded	F2	mod	poor	6,000	G2	ly1, v0

well = Well-differentiated adenocarcinoma; mod = moderately differentiated adenocarcinoma; poor = poorly differentiated adenocarcinoma.

Table 3. Characteristics of 3 patients with post-ESD recurrence

Patient No.	Dominant histologic type	Histologic type of deepest invasion portion	SM depth, μm	Vascular invasion	Budding grade	Vertical margin	Residual tumor	LN metastasis	Recurrence site	Time to recurrence, months	Survival status
ESD → follow-up											
1	well	poor	1,900	ly0, v0	G3	(–)			liver LN	41	alive
ESD → additional surgery											
2	mod	well	2,500	ly1, v1	G2	(–)	(–)	(–)	lung	5	alive
3	mod	poor	5,000	ly0, v0	G2	(–)	(–)	(–)	pelvis	18	alive

SM = Submucosal; well = well-differentiated adenocarcinoma; mod = moderately differentiated adenocarcinoma; poor = poorly differentiated adenocarcinoma.

JSCCR criteria for identifying curable T1 CRC after ESD, and at present neither local recurrence nor distant/LN metastasis has been observed in any of the 6 patients. Of the other 8 patients followed who did not meet the criteria for curable T1 CRC, 1 developed liver and LN metastasis after 41 months, despite not meeting the criteria for curable T1 CRC. The other 7 patients, who were simply followed for 19 months after ESD, showed neither local recurrence nor distant/LN metastasis. Five of these 7 patients had only deep submucosal invasion as a risk factor for surgery, and the other 2 had one or more indicators other than deep submucosal invasion.

Additional surgical resection was performed in 20 of the 31 patients in whom resection was judged to be incomplete, and 2 exhibited LN metastasis but no residual tumor. At present, 2 of these 20 patients have developed pelvic or metastatic recurrence and 1 patient has died of bladder cancer. No recurrence was found in any of the 3 patients in the VM+ group and additional surgical resection was performed (follow-up period 30 months). Furthermore, no adverse effects were noted in any of the patients who underwent ESD (table 3; fig. 1).

Discussion

ESD performed as total excisional biopsy is not only a therapeutic technique but also an important final diagnostic tool [8]. In particular, complete resection is indispensable for making a precise histopathological diagnosis. According to the JSCCR guidelines for the treatment of CRC [5], only submucosal invasion depth can be predicted prior to treatment; other indicators such as vascular invasion, unfavorable histological differentiation and tumor budding cannot be assessed to help decide the indication for surgical treatment.

In the present study, the en bloc resection rate of ESD was 100% (37/37) and the histological complete resection rate was 92% (34/37). Resection was curative in 16% (6/37) of these T1b CRC patients. In addition, the rate of post-ESD bleeding was 8%, which falls within the range of 0.5–9.5% reported previously for delayed bleeding after colorectal ESD [10]. Moreover, perforation occurred in 2 of our 37 patients (5%), which was in accordance with the findings of other Japanese studies [9, 11].

A collaborative JSCCR study reported a rate of LN metastasis of 0% in nonpedunculated T1 CRC with a submu-

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Fig. 1. Flowchart of post-ESD outcomes for T1 CRC. The classification of patients as curable or noncurable depended on their ability or inability to meet the criteria for curable T1 CRC after ESD.
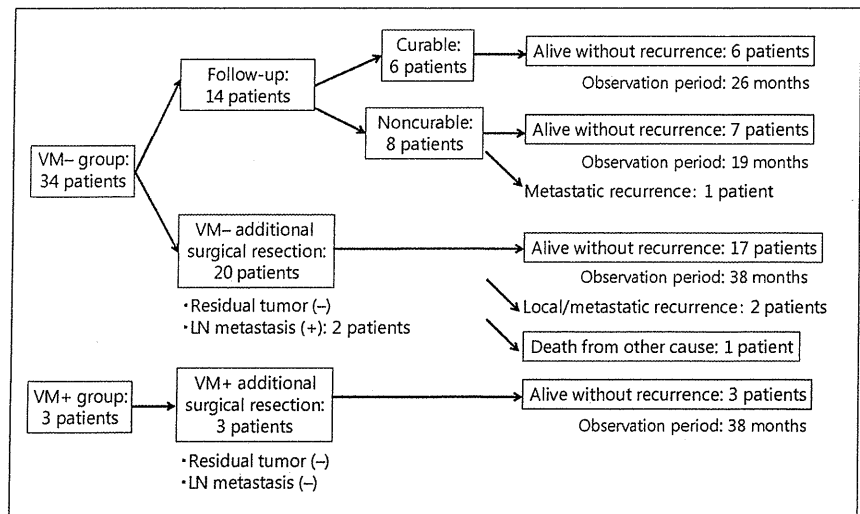
cosal depth <1,000 μm, and in pedunculated T1 CRC with head and stalk invasion to a submucosal invasion depth <3,000 μm with no lymphatic invasion [12]. In contrast, several studies showed that submucosal depth was not significantly related to LN metastasis in patients with T1 CRC [13–15]. We previously reported an incidence of LN metastasis of only 1.2% (95% CI 0.25–3.48%) in T1 CRC without three of the four risk factors (i.e. all but submucosal invasion depth <1,000 μm) for LN metastasis described in the JSCCR guideline [16]. Furthermore, in another study, we suggested the condition of the muscularis mucosae to be an indicator for LN metastasis in T1 CRC [17]. The conditions under which the risk of LN metastasis of T1 CRC is extremely low are becoming clearer by stratifying these risk factors [16–19]. Based on these conditions, it is suggested that ESD as total excisional biopsy for T1 CRC will become increasingly more important in the near future. Histological complete resection of T1 CRC including VM– is indispensable for curative treatment. However, to make this possible, it is important to conduct a preoperative diagnosis by magnifying colonoscopy and EUS. We previously reported that in cases of CRC with an invasion depth ≤1,500 μm, 6% had a significantly lower incidence of positive vertical cut ends than those with an invasion depth >1,500 μm (33%) [20]. These findings indicate that endoscopic mucosal resection for cT1 CRC would not have an important role for total excisional biopsy for all T1 CRCs [20]. However, this study revealed that the histopathological vertical margin was negative in 92% of cases of cT1b CRC treated by ESD.

Compared with endoscopic mucosal resection, ESD is a more difficult technique to perform in the colorectum [21–23]. If a colorectal ESD sample for T1 CRC shows incomplete vertical resection, it is impossible for endoscopists to make the precise assessments of the histopathological findings (e.g. the histologic differentiation, invasion depth and lymphovascular invasion of the lesion) and thus impossible to determine the optimal additional treatment strategy. Furthermore, residual tumors caused by incomplete endoscopic resection were reported to have higher growth potential than they did before resection [24, 25]. Thus, selecting appropriate cases through accurate diagnosis is considered to be essential before ESD as total excisional biopsy for cT1 CRC.

As for the risk of recurrence, Kobayashi et al. [26] reported that even after surgical curative resection with LN dissection, 2.3% of T1 CRC patients developed local and/or metastatic recurrence during a median follow-up period of 7.8 years. On the other hand, the local and/or metastatic recurrence rate after endoscopic resection of T1 CRC was reported to be very low (0–2.3%) in the absence of risk factors for LN metastasis other than submucosal invasion depth [16, 18, 19, 27]. Subsequent surgery is therefore not likely to be absolutely essential in all of these T1 CRC patients. Nevertheless, to reduce the need for unnecessary additional surgeries after endoscopic resection, it is necessary to accurately predict LN metastasis regardless of the pathologic features evident in hematoxylin and eosin-stained sections. In particular, immunohistochemical analysis of molecular markers, both individually and in combination, at the site of the deepest invasive portion

of T1 CRC enables LN metastasis to be predicted regardless of the pathologic risk factors identified by hematoxylin and eosin staining. If the absence of LN metastasis can be predicted, it will be possible to broaden the indications for curative ESD for T1 CRC and to reduce the number of unnecessary additional surgeries after ESD [28].

In the future, it will be necessary to establish a new diagnostic criteria or technique for deciding whether or not en bloc resection is possible, to standardize the ESD techniques for the submucosal layer with a negative vertical cut margin, to create a general strategy for T1 CRC after making a comprehensive decision that takes into account the patient's background and various LN metastasis risks, and to evaluate the long-term outcomes in patients with T1 CRC who undergo ESD as total excisional biopsy.

Conclusion

Our results suggest that en bloc resection by ESD is both a highly effective treatment as total excisional biopsy for cT1 CRC and a means of providing a more precise histological diagnosis.

Disclosure Statement

The authors have no financial conflict of interest.

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Review

Towards safer and appropriate application of endoscopic submucosal dissection for T1 colorectal carcinoma as total excisional biopsy: Future perspectives

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According to the Japanese Society for Cancer of the Colon and Rectum Guidelines 2014 for the Treatment of Colorectal Cancer, cases with T1 colorectal carcinoma should be considered for additional colectomy with lymph node dissection when histologically complete en bloc resection is endoscopically carried out and when one of the four risk factors listed below is present. These four risk factors are: (i) submucosal (SM) invasion depth ≥1000 μm; (ii) positive vascular invasion; (iii) poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous carcinoma; and (iv) grade 2/3 budding at the deepest part of SM invasion. However, the probability of lymph node metastasis is extremely low if none of these risk factors are present, with the exception of SM invasion depth ≥1000 μm. Consequently, it is assumed that there will be an increasing number of cases where no additional surgery is done, or cases of moderate invasive carcinoma in which endoscopic treatment is carried out to achieve an excisional biopsy, for which complete resection is applicable. In these cases, the preoperative diagnosis, resection techniques such as endoscopic submucosal dissection, features of resected specimens, and the accuracy of pathological diagnosis are all extremely important.

Key words: endoscopic submucosal dissection (ESD), lymph node metastasis, recurrence, submucosal colorectal carcinoma, T1 carcinoma

INTRODUCTION

INTRAMUCOSAL COLORECTAL CARCINOMA typically does not metastasize, but lymph node metastasis occurs in approximately 10% of T1 carcinoma cases.[1–9] Therefore, it is important to evaluate its curability and determine whether additional surgery is required after endoscopic resection. In Japan, the Guidelines for the Treatment of Colorectal Cancer were published by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) in 2005/2010,[10] and an evaluation system based on absolute values was established, which involves measuring the submucosal (SM) invasion depth. These guidelines describe in detail both the treatment for T1 colorectal carcinoma and the radical-cure evaluation criteria after endoscopic resection. Previously, only T1 colorectal carcinoma with ultra-shallow SM invasion (≤300 μm) could be judged to have been radically cured after endoscopic resection,[11] although this was subsequently revised to 1000 μm in cases where pathological risk factors such as unfavorable histological type and positive vascular invasion were not detected. The JSCCR Guidelines 2005 have been revised several times.[12] In the latest version (2014),[13] when a positive deep tumor margin is present in resected T1 colorectal carcinoma specimens, colectomy with lymph node dissection must be additionally carried out after endoscopic resection; therefore, the presence of the positive deep tumor margin is the absolute condition for additional surgery. Moreover, additional treatment should be considered (but is not an absolute requirement) when at least one of the following is found: (i) SM invasion depth ≥1000 μm; (ii) positive vascular invasion; (iii) poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous carcinoma; and (iv) grade 2/3 budding at the deepest part of SM invasion. The JSCCR Guidelines 2014 clearly state that additional treatment should be done only after systematically evaluating the predicted curability on the basis of various lymph node metastasis risk factors and the patient's background (wishes, age, physical activity, complications) and after obtaining informed consent from the patient (Fig. 1).
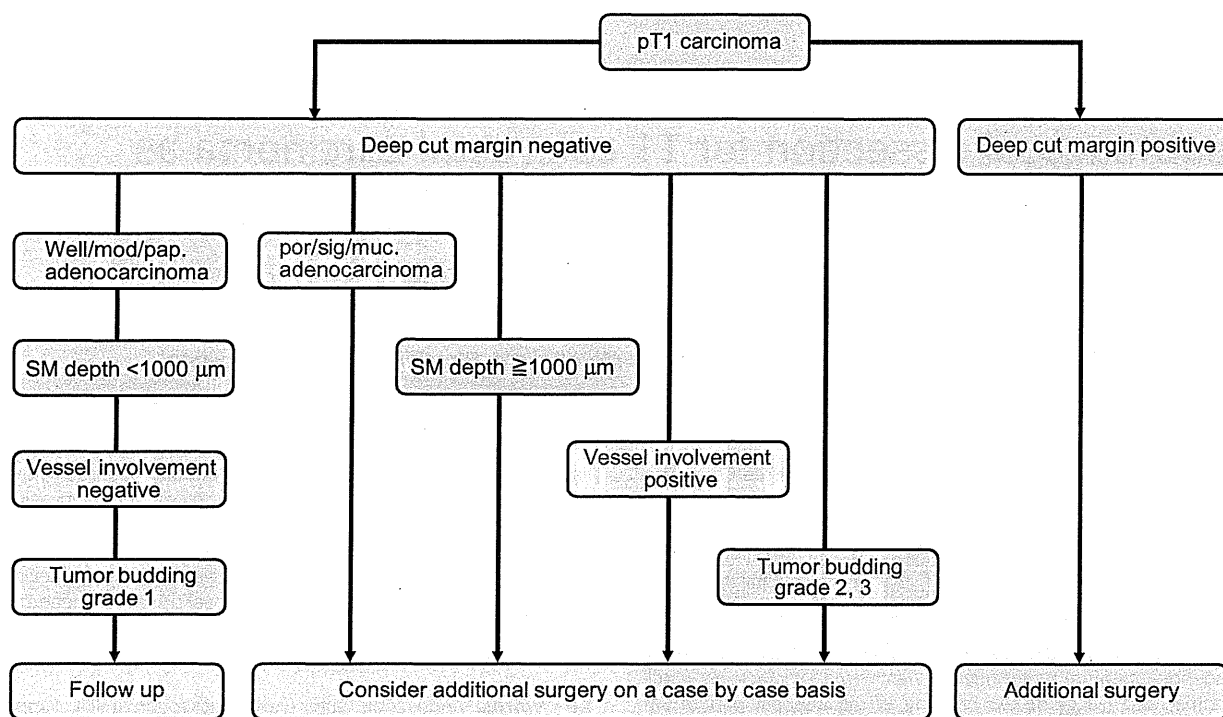
Figure 1 Therapeutic strategy for colorectal submucosal (T1) carcinoma resected endoscopically based on Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the Treatment of Colorectal Cancer 2014.

NEW TWIST IN METASTASIS RISK ASSESSMENT OF ENDOSCOPICALLY RESECTED T1 COLORECTAL CARCINOMA

DATA AVAILABLE FROM a growing number of cases have made it possible to define the conditions under which additional surgery along with lymph node dissection is not absolutely required for endoscopically resected pT1b (SM invasion depth ≥1000 μm) colorectal carcinoma. Nakadoi et al.[14] reported that when neither vascular invasion, poorly differentiated adenocarcinoma, signet ring cell carcinoma, mucinous carcinoma, nor grade 2/3 budding at the deepest part of SM invasion were detected, the lymph node metastasis rate of T1 colorectal carcinoma was approximately 1.2%, regardless of the SM invasion depth. Yoshii et al.[15] reported results similar to those of Nakadoi et al., including prognostic analysis. A research project of the JSCCR considering the stratification of risk factors for metastasis of T1b colorectal carcinoma is ongoing, and results similar to those described above have been obtained (data not shown). Regarding the relationship between the histopathological characteristics and the lymph node metastasis rate of endoscopically resected pT1b colorectal carci-

noma, the JSCCR research project has analyzed many cases after considering parameters including the above-mentioned risk factors for lymph node metastases, patterns of damage to the muscularis mucosae, histological grade, infiltration pattern, histological differentiation at the deepest part of the SM invasion, and macroscopic type. The analytical results will be published in the near future. In the analytical results, the differences in the malignancy of T1 carcinomas located in the rectum below the peritoneal reflection will be compared with those of T1 carcinomas located in other regions.[16]

A surgical operation always poses some risk.[9,16–19] Follow-up research on patients with postoperative T1 carcinoma revealed that the disease recurrence rate in the absence of lymph node metastasis was 0.8% and 4.1% for tumors located in the colon and rectum, respectively.[20] At present, Japan is an aging society, and age along with underlying disease, physical activity, wishes, and the possibility of an artificial anus must be fully considered before carrying out additional surgery. In particular, after rectal surgery for a lesion at the rectum below the peritoneal reflection, problems with the patient's quality of life, such as hypogonadism, dyschezia, and dysuria, may arise. The
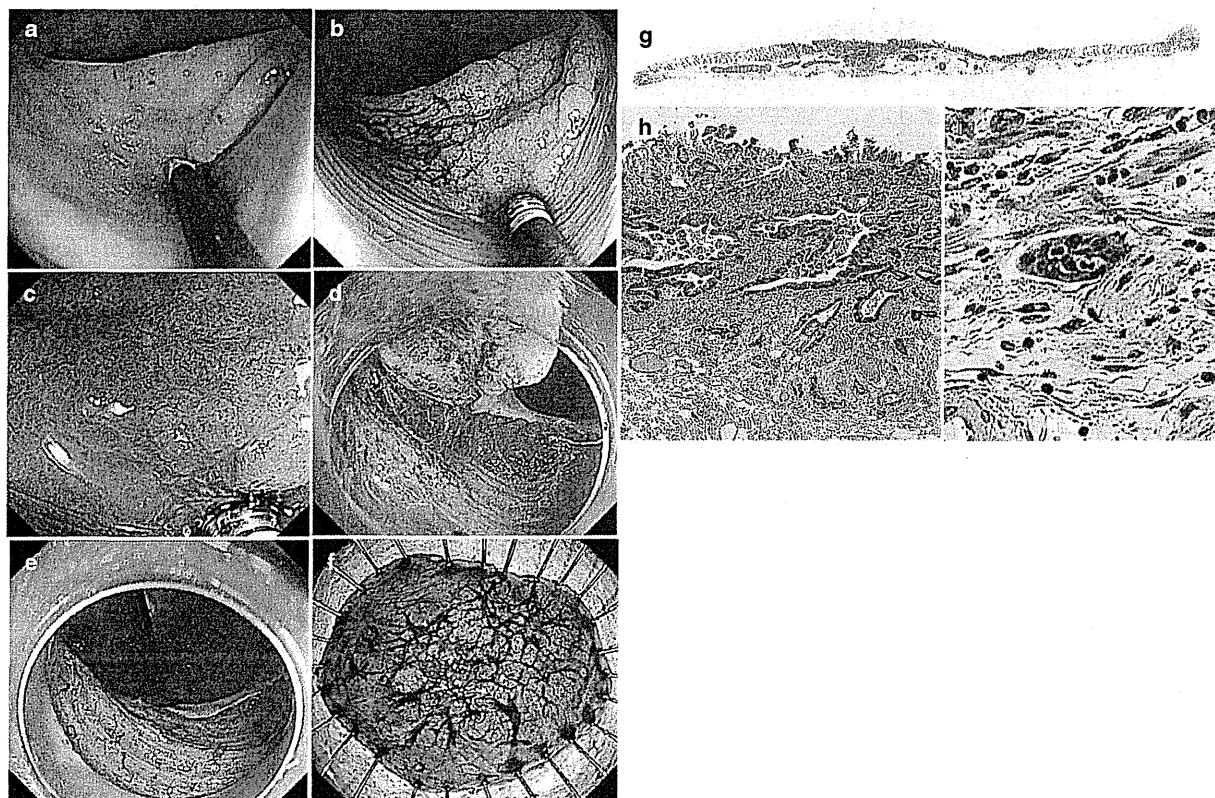
Figure 2 A case of laterally spreading tumor, non-granular type 35 mm in diameter in the sigmoid colon. (a) Standard colonoscopic view. (b) Indigo carmine dye spraying view. (c) Narrow-band imaging magnifying findings show a little irregularity of the surface and vascular pattern. (d,e) Location of the lesion is on the flexure and it is suspected that endoscopic mucosal resection will be difficult. With a preoperative diagnosis of mainly intramucosal colorectal carcinoma, we carried out endoscopic submucosal dissection (ESD) as total excisional biopsy in an en bloc manner. (f) Resected specimen by ESD. (g) Cross-section (hematoxylin-eosin staining). (h,i) Pathological findings of ESD specimen show adenocarcinoma (tub1 >tub2), pT1a (SM depth 800 μm), budding grade: high, lymph vessel involvement positive, tumor cut margin negative (histological complete resection). Middle-power view. This case underwent additional surgery. There was no residual tumor or lymph node metastasis.

'survey of the trend of T1 colorectal cancer treatment' completed by facility members of the JSCCR Guidelines Committee revealed that if the risk of lymph node metastasis was very low, colonoscopists or surgeons themselves did not want to undergo additional surgery (data in submission).

Thus, the previous trend of surgical treatment for T1 colorectal carcinoma in the first instance is being replaced with surgery only after assessing the metastatic risk of endoscopically resected T1 colorectal carcinoma by carrying out an excisional biopsy. In the near future, in addition to the JSCCR project, more detailed definite stratification of lymph node metastasis risk after endoscopic resection will be clarified based on analysis of various

factors with many cases including prognosis estimation (Fig. 2).[21–30]

ENDOSCOPIC SUBMUCOSAL DISSECTION AS A TOTAL EXCISION BIOPSY FOR T1 COLORECTAL CARCINOMA

APPLICATION OF ENDOSCOPIC treatment for early colorectal carcinoma is considered when the size and location of the lesion permits en bloc resection.[10,11,13,31] Endoscopic submucosal dissection (ESD) is a reliable method for en bloc resection regardless of lesion size; it is considered useful for cases of T1 colorectal carcinoma treated with total excisional biopsy.[13] Given the limited
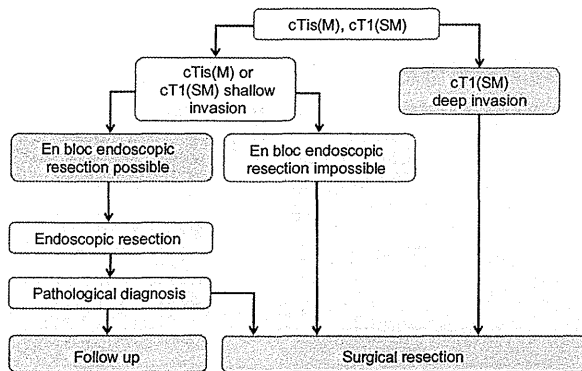
Figure 3 Therapeutic strategy for cTis(M) or cT1(SM) carcinoma based on Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the Treatment of Colorectal Cancer 2014.

accuracy of preoperative diagnosis, histological examination of resected specimens is of particular importance in endoscopic treatment because of the need to achieve precise histological diagnosis.[10,11,13,31] In order to reduce the number of unnecessary additional surgical operations after endoscopic treatment for T1 colorectal carcinoma with negative lymph node metastasis, ESD is first carried out to achieve an excisional biopsy, even if the SM invasion depth is T1b (>1000 μm); the need for additional colectomy is then determined after histological examination of the resected specimens.

JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer[13] state that endoscopic treatment is applicable for early colorectal carcinoma if the lesions are adenoma, cTis mucosal (M) carcinoma, or cT1 carcinoma with shallow SM invasion, regardless of lesion size or macroscopic type (Fig. 3). The Guidelines also state that endoscopic treatment should not be used for cT1 colorectal carcinoma with deep SM invasion. However, as mentioned above, endoscopic treatment is applicable for colorectal carcinoma within a range of SM invasion depths in order to achieve an excisional biopsy if complete en bloc resection is feasible. The relative classification that divides the submucosa into three equal parts (SM1, SM2, and SM3)[32] cannot be used for endoscopically resected specimens, but it can be used as a simple index to determine whether endoscopic resection is applicable for cT1 carcinoma. Because it is likely that an SM3 lesion will be in contact with a muscular layer, and will therefore be likely to become a positive deep-stump, endoscopic treatment should not be used to achieve a total excisional biopsy for these lesions. In contrast, endoscopic treatment can be used for the total excisional biopsy of SM1 and SM2 lesions, which do not directly connect with a muscular layer.

PREOPERATIVE DIAGNOSIS OF T1 COLORECTAL CARCINOMA SUITABLE FOR TOTAL EXCISIONAL BIOPSY

WHEN ENDOSCOPIC TREATMENT is carried out for a colorectal tumor, information regarding tumor size, predicted invasion depth, and histological type is essential. Because there can be many adenomatous lesions in the colon and rectum, preoperative discrimination of adenoma, adenocarcinoma in adenoma, and carcinoma without an adenomatous component is extremely important when selecting an appropriate therapy.[33,34] In order to distinguish these lesions, pit pattern-based diagnosis and magnifying observation by using image-enhanced endoscopy such as narrow band imaging (NBI) and blue laser imaging are useful.[31,35–43] By preoperatively accurately diagnosing the histological diversity in a tumor, piecemeal endoscopic mucosal resection (EMR), ESD, or surgery can be selected for a large lesion. However, to discriminate between SM2 and SM3 colorectal carcinomas and to obtain information about the submucosa, ultrasonic endoscopy is required. Ozawa *et al.* reported that ultrasonic endoscopy is a useful method for evaluating the lesion when complete resection of a T1 colorectal carcinoma is attempted.[44] By considering the area of magnifying findings, such as the major axis of a V_N-type pit pattern region, it might be possible to determine the actual SM invasion depth.[45] Moreover, in addition to discriminating between M and SM colorectal carcinomas, measurement of the actual SM invasion depth and understanding the relationship between an invasive cancerous lesion and a muscular layer are important in determining whether endoscopic total excisional biopsy can be carried out for a lesion. The increasing use of ESD means that the necessity for ultrasonic endoscopy for T1 colorectal carcinoma will greatly increase in the future.

PROBLEMS WITH ESD AS TOTAL EXCISIONAL BIOPSY FOR cT1 COLORECTAL CARCINOMA

AS MENTIONED EARLIER, although endoscopic resection can be used to achieve total excisional biopsy of cT1 colorectal carcinoma regardless of its invasion depth, many problems remain to be resolved. Previous reports concluded that the deepest front of SM invasion actually destroys the vessels and determines the malignancy of T1 colorectal carcinoma. The histological grade of the deepest front is closely related to lymph node metastasis.[8,27,46–48] Therefore, if histologically complete en bloc resection is not carried out, excisional biopsy by ESD for cT1 colorectal carcinoma will have no diagnostic value. For example, if the deep cut margin of a tumor is positive in an ESD specimen,

Table 1 Indications for endoscopic submucosal dissection for colorectal tumors

1 Large sized (>20 mm in diameter) tumors in which en bloc resection using snare endoscopic mucosal resection (EMR) is difficult, although it is indicative for endoscopic treatment:
   • Laterally spreading tumor (LST) of the non-granular (NG) type (LST-NG), particularly those of the pseudo-depressed type
   • Tumors showing VI type pit pattern
   • Carcinoma with submucosal infiltration
   • Large depressed-type tumors
   • Large elevated lesion suspected to be carcinoma.[†]
2 Mucosal tumors with fibrosis caused by prolapse as a result of biopsy or peristalsis of lesions.
3 Sporadic localized tumors in chronic inflammation such as ulcerative colitis.
4 Local residual early carcinoma after endoscopic resection.

[†]Including LST-G, nodular mixed type 1.

additional surgery will be essential[11,13] and, consequently, the cost of treatment and the burden on the patient's finances will increase. Incomplete ESD may leave local residual carcinoma and may increase the risk of metastasis. Moreover, incomplete deep cut margin-positive pT1 colorectal carcinoma cannot be used for future studies to analyze the metastasis risk of T1 colorectal carcinoma.

The most important future goal in the development of excisional biopsy by ESD for cT1 colorectal carcinoma is establishing preoperative diagnostics that can be used to predict whether or not endoscopic complete resection can be achieved. To this end, the relationship between an invasive tumor front and the muscular layer should be examined by using ultrasonic endoscopy, which can allow an image-based diagnosis of transmural invasion. The generalization and quality control of ultrasonic endoscopy including both further technical and mechanical development are then very important. The next task is the generalization and quality control of ESD techniques for complete resection of T1 colorectal carcinoma. Even if en bloc resection of a lesion can be done using ESD, there is a possibility that pathological diagnosis of the SM invasion site cannot be accurately carried out owing to thermal denaturation of the submucosal layer. Hayashi *et al.* reported that risk factors for incomplete resection while using colorectal ESD are SM deep invasion, unfavorable histological type at the deepest site of SM invasion, and a submucosal severe fibrosis.[49] Recently, a similar report has also been published.[50] At present, as the safety of colorectal ESD has already been established,[51] high-quality colorectal ESD needs to be developed. The quality control of colorectal ESD and the precise assessment of resected specimens are also very important.

CONCLUSION

THE JAPANESE SOCIETY of Gastroenterology (JSGE) Clinical Practice Guidelines for Colorectal Polyps[52] and the Japan Gastroenterological Endoscopy Society (JGES) Colorectal ESD/EMR Guidelines[31] recommend the use of ESD for colorectal tumors as shown in Table 1. However, on the basis of new clinicopathological evidence from a growing number of cases, ESD is gradually becoming more commonly used to achieve excisional biopsy of cT1b colorectal carcinoma. If future advances in genomic medicine and molecular pathology allow the development of biomarkers for lymph node metastasis, the number of additional surgical operations for pT1 colorectal carcinoma after ESD can be reduced, which will consequently benefit patients with pT1 colorectal carcinoma. As ESD is less expensive than surgery, this will also reduce medical expenses.

The criteria for attempting a radical cure after endoscopic treatment for T1 colorectal carcinoma will certainly need to be expanded, and it seems very likely that ESD will be used to carry out excisional biopsy. The generalization of endoscopic complete resection techniques such as ESD, the development of new and simpler resection techniques, and the establishment of a system to ensure the quality control of these techniques are required for this. It is also important to determine the optimal method for specimen resection and handling, and to improve the quality control of the precise pathological diagnosis. The establishment of new diagnostic techniques is urgently required for determining whether or not ESD can be used as total excisional biopsy for T1 colorectal carcinoma.

The application of ESD for total excisional biopsy of T1 colorectal carcinoma is predicted to become a standard diagnostic step for these lesions in the 21st century. However, this application is under clinical research, and currently it should be done with caution. At present, only endoscopists who have access to preoperative diagnostics that indicate whether complete en bloc resection can be histologically carried out, and those who have experience of a sufficient number of ESD techniques should use ESD as excisional biopsy for T1 colorectal carcinoma.