green reflectance to distinguish neoplastic from non-neoplastic areas based on differences in the intensity of the autofluorescence and green reflectance spectra. The utility of this system for diagnosing bronchial SCC has already been confirmed.[28–30] As AFI might prove useful for the diagnosis of SCC of the esophagus and pharynx, we decided to evaluate the visualization of such lesions comparing the AFI system to white light endoscopy (WLE).

Methods

AFI videoendoscope system

We conducted a prospective study to evaluate visualization of esophageal and pharyngeal SCC using AFI videoendoscopy, which is a new illumination system that allows for real-time WLE, but also makes it possible to switch to AFI endoscopy by the press of a single button on the scope handle.[25–27] This system includes a sequential green and blue light source (XCLV-260HP) and a high-resolution videoendoscope (GIF-FQ260Z). The endoscope has two high-quality charged coupled devices (CCD): one for high-resolution WLE and the other for high-resolution AFI.

In the AFI mode, the image is composed of two parts: autofluorescence emitted by blue light excitation (390–470 nm) and green reflectance (540–560 nm). When exposed to blue light excitation, some endogenous biological substances (e.g. collagen, elastin, flavin and nicotinamide adenine dinucleotide) in the submucosal layer emit autofluorescence with longer wavelengths. A barrier filter is placed in front of the AFI CCD to allow only the passage of light with a wavelength between 500–630 nm, thereby cutting off the blue light excitation. The sequentially detected images from autofluorescence and green reflectance are integrated by an image processor into a real-time, pseudo-color AFI image.

Neoplastic areas involve a thickening of the mucosal layer and increased hemoglobin so such areas emit weaker autofluorescence compared to non-neoplastic areas. During endoscopy using the AFI mode, non-neoplastic areas appear to be green in color whereas neoplastic areas are purple or magenta.

Patients

Thirty-two consecutive patients with superficial esophageal SCC and 11 patients with superficial pharyngeal SCC that had been previously diagnosed in other hospitals were enrolled in this pilot study. Endoscopists in the other hospitals used WLE as well as LC and/or narrow band imaging (NBI) videoendoscopy,[22,31–33] but not AFI videoendoscopy to diagnose the lesions which were all histologically confirmed as being SCC. Those 32 patients with esophageal SCC and 11 patients with pharyngeal SCC were then referred to our hospital for treatment of their lesions.

Endoscopic examinations

In order to more precisely diagnose the extent of the SCC lesions and their invasive depth for determination of the optimal method of treatment, endoscopic examinations were carried out using an AFI videoendoscope system by one highly experienced endoscopist (I.O.) familiar with the AFI technique. This endoscopist was provided with information received from the previous hospitals concerning the lesions, including their locations, number and endoscopic images. Written informed consent was obtained from all patients before their examinations.

First, routine endoscopic examinations were carried out using the WLE mode of the AFI videoendoscope system to identify abnormal mucosal areas in the esophagus and pharynx. If abnormal mucosal areas were identified, photographs which depicted the lesion in the center of the endoscopic monitor were taken of the WLE view. We then examined the esophagus and pharynx by switching to the AFI mode. If a demarcated area purple or magenta in color on a green background was observed, SCC of the esophagus or pharynx was suspected and photographs were taken of the AFI view as described previously. In addition, LC and NBI videoendoscopy were also carried out to diagnose lesions more precisely, but LC was not used in the pharynx. Finally, biopsy specimens were taken from the areas that were suspected of being SCC of the esophagus and pharynx.

Evaluation of esophageal and pharyngeal SCC visualization

During the endoscopic examinations referred to above, the endoscopist (I.O.) took pictures of abnormal mucosal areas and a representative collection was then assembled of both WLE and AFI images of the superficial esophageal and pharyngeal SCC lesions. After the endoscopic examinations, the other three endoscopists with extensive experience in the detection of SCC of the esophagus and pharynx (Y.S., H.I., H.S.) blindly evaluated the superficial lesions histologically diagnosed as SCC in terms of the visualization quality of both the WLE and AFI images without reference to any information concerning the nature of the lesions. The visualizations were evaluated on a three-tier scale: visible, illegible and invisible. A 'visible lesion' was defined as a lesion that was clearly detected by WLE or AFI and definitely diagnosed endoscopically as an esophageal or pharyngeal SCC. An 'illegible lesion' was defined as a lesion that could barely be identified by WLE or AFI, but could not be differentiated endoscopically from a non-neoplastic lesion. An 'invisible lesion' was defined as a lesion that could not be recognized by WLE or AFI and could not be diagnosed endoscopically as SCC. The percentage of visible lesions identified using WLE and AFI, respectively, was then calculated, and the ability of AFI and WLE to visualize esophageal and pharyngeal SCC was compared. In addition, the interobserver agreement on the visualization of superficial lesions was assessed.

Histological assessment and definition of superficial cancers

We subsequently carried out ER or surgery on the superficial esophageal and pharyngeal SCC lesions. Histological assessment of the resected esophageal specimens was based on the Vienna classification.[34] Category 4 lesions under the Vienna classification are either high-grade dysplasia (category 4.1.) or carcinoma in situ (category 4.2.), whereas category 5 lesions are intramucosal carcinoma (category 5.1.), submucosal carcinoma or beyond (category 5.2.). Superficial esophageal cancer is defined as a lesion in which tumor invasion is limited within the intramucosal and submucosal layers corresponding to categories 4 and 5 in the Vienna classification.[35]

According to the Japan Society for Head and Neck Cancer,[36] a superficial pharyngeal lesion is defined as one in which vertical invasion is comparatively shallow and visual changes do not indicate an advanced cancer. This rather vague definition suggests that vertical invasion is limited to the epithelium or just beneath the epithelium, but does not extend to the muscle layer. The stratified layer of the pharynx is not equivalent to that of the gastrointestinal tract, however, due to the absence of muscularis mucosae in the pharynx, so the Vienna classification was not used for histological assessment of resected pharyngeal specimens.

Statistical analysis

McNemar's test and Fisher's test were used for statistical analysis using the standard computer software statistical package SPSS for Windows (SPSS, Release 6.0, SPSS Inc., Chicago, IL, USA, 1993). A P value < 0.05 was considered significant. Interobserver agreement was also calculated using Kappa statistics.

Results

We identified a total of 39 superficial esophageal SCC lesions in the 32 patients. ER was subsequently carried out on 26 of those patients with 31 lesions, whereas surgical treatment was carried out on the remaining six patients with eight lesions. The lesions were diagnosed according to depth of invasion (categories 4.2. or 5.1./category 5.2. of the Vienna classification: 34/5); macroscopic type (flat/elevated: 36/3) and tumor size (less than half the circumference of the lumen/half the circumference of the lumen or greater: 23/16).

A total of 20, 11 and eight of those lesions were considered as being visible, illegible and invisible, respectively, using WLE compared to 31, three and five lesions, respectively, with AFI. The percentage of visible lesions was 79% with AFI and 51% with WLE ($P < 0.05$) (Fig. 1). In terms of interobserver agreement on the visualization of superficial esophageal SCC, there was higher agreement with AFI than with WLE (AFI ($\kappa = 0.46$) and WLE ($\kappa = 0.31$)). In addition, AFI revealed 12 lesions in the esophagus that were not adequately visualized by WLE with such lesions limited to the mucosa ($P = 0.26$) and tending to be smaller (less than half circumference) in size ($P = 0.72$) (Fig. 2).

In addition, a total of 12 superficial pharyngeal SCC lesions were identified in 11 patients. ER was subsequently carried out on eight of those patients with nine lesions and surgical treatment was carried out on the other three patients with three lesions. These lesions were diagnosed according to depth of invasion (carcinoma in-situ/subepithelial invasion): 6/6) and macroscopic type (flat/elevated: 7/5). Based on the WLE images, four, five and three lesions were considered as being visible, illegible and invisible, respectively, in comparison to nine, three and 0 lesions, respectively, using AFI. The percentage of visible lesions was 75% with AFI and 33% with WLE ($P = 0.13$) (Fig. 3).

Representative conventional WLE and corresponding AFI pictures of SCC in the middle thoracic esophagus and SCC in situ of the hypopharynx are shown, respectively, in Figures 4a,b and 5a,b.

Discussion

Based on these results, the AFI videoendoscope system was better at visualizing superficial esophageal and pharyngeal SCC compared to conventional WLE. In particular, AFI significantly improved the visualization of esophageal SCC and was able to better recognize mucosal and smaller esophageal SCC lesions that were difficult to visualize using WLE. Although visualization of pharyngeal SCC using AFI was also better than with WLE, the difference between the two techniques was not significant. Therefore, these results suggest that the AFI system may be more useful for early diagnosis of SCC of the esophagus and pharynx compared to WLE.

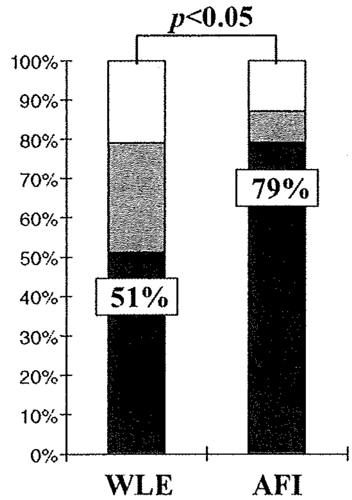

Figure 1 Visualization of superficial esophageal squamous cell carcinoma (SCC) by autofluorescence imaging (AFI) and white light endoscopy (WLE). Percentage of visible lesions was 79% with AFI and 51% with WLE ($P < 0.05$). P value was calculated using McNemar's test. □ Invisible; ▒ Illegible; ■ Visible.

The AFI videoendoscope system presently available combines a high-quality white light videoendoscope system with an autofluorescence and green reflectance-imaging mode.[23-27] This system provides superior image quality compared to earlier AFI systems using fiber-optic endoscopy. Neoplastic tissue can be distinguished using this system based on differences in the intensity of the autofluorescence and green reflectance spectra. The usefulness of this latest system has been confirmed in the diagnosis of bronchial SCC.[28-30] Recently, Uedo *et al.* reported that the AFI system has an advantage over standard WLE in the diagnosis of early esophagogastric cancers including five early esophageal SCC lesions with image quality being acceptable.[25] Kara *et al.* further reported that endoscopic video AFI may improve the detection of early neoplasia in patients with Barrett's esophagus.[26] In addition, it has been reported that autofluorescence laryngoscopy was useful in the early diagnosis of laryngeal cancer.[37] Although the value of the newest AFI videoendoscope system has been recognized in a number of studies, there are few reports on its effectiveness in the early diagnosis of SCC of the esophagus and pharynx. Therefore, this research indicating that AFI may be of potential use in this area is especially important.

The early detection of superficial SCC of the esophagus by conventional WLE continues to be difficult[5,7] because there are few morphological changes, but LC improves the endoscopic visualization and frequently makes it possible to diagnose esophageal

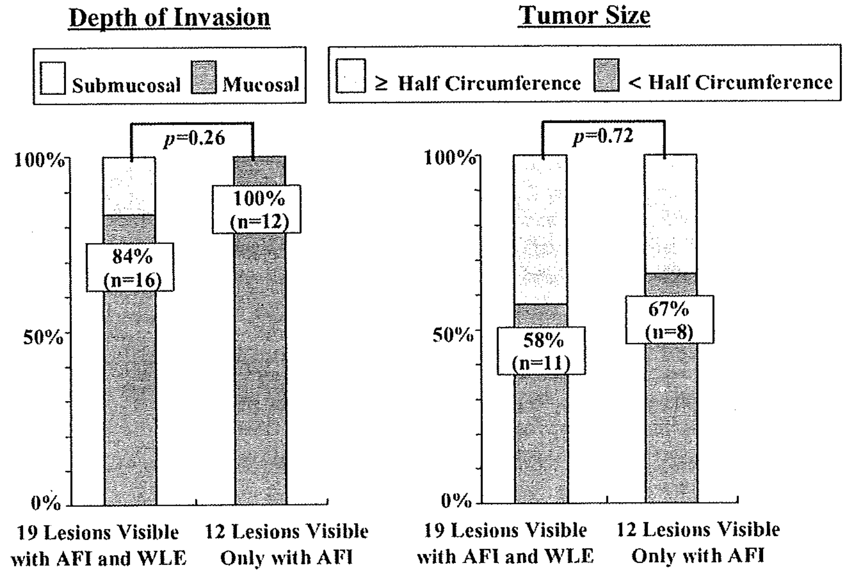

Figure 2 Clinicopathological features of lesions visible by autofluorescence imaging (AFI) only compared with lesions visible by both white light endoscopy (WLE) and AFI. *P* values were calculated using Fisher's test.

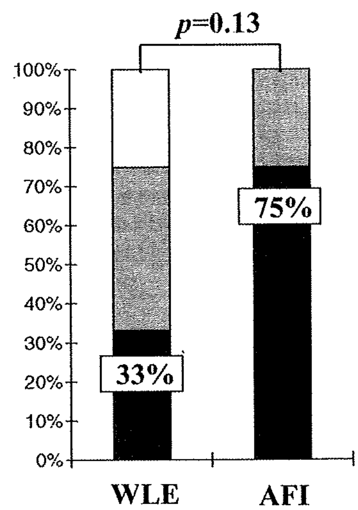

Figure 3 Visualization of superficial pharyngeal squamous cell carcinoma (SCC) by autofluorescence imaging (AFI) and white light endoscopy (WLE). Percentage of visible lesions was 75% with AFI and 33% with WLE ($P = 0.13$). *P* value was calculated using McNemar's test. □ Invisible; ▒ Illegible; ■ Visible.

SCC at an early stage.[7–9] Unfortunately, Lugol staining often causes mucosal irritation during examinations leading to retrosternal pain and discomfort,[10–14] although final rinsing with thiosulfate solution can ease such irritation.

Despite the fact that gastrointestinal endoscopists now have a better chance of finding pharyngeal cancers, the majority are not detected until an advanced stage with a resultant poor prognosis because it is so difficult to detect such lesions using conventional WLE.[17,22] Regrettably, there are few diagnostic techniques for the detection of pharyngeal SCC at an early stage partly because LC cannot be carried out in the pharynx.

Consequently, the development of a new, non-invasive diagnostic modality is highly desirable not only for esophageal SCC, but also for pharyngeal SCC where Lugol staining is not feasible. The AFI system could play an important role in the future diagnosis of such cancers, because it appears to improve the endoscopic visualization of esophageal and pharyngeal SCC without any of the disadvantages associated with LC.

The NBI system is another novel non-invasive optical imaging technique that has shown promising results in the diagnosis of esophageal and pharyngeal SCC.[22,31–33] In addition, NBI with magnification can reveal the superficial mucosal structure of such SCC lesions including any morphological change in capillary vessels enabling it to distinguish between neoplastic lesions and inflammatory conditions and it is also helpful in predicting histological depth.[22,31–33] Several reports have further shown that NBI may improve recognition of mucosal and vascular patterns in Barrett's esophageal mucosa and identification of early neoplasia in Barrett's esophagus.[27,38–40] A proof-of-principle study on diagnosing early neoplasia in patients with Barrett's esophagus in which AFI results were used as a red-flag to identify suspicious areas followed by NBI with magnification for confirmation of suspected superficial lesions indicated that detailed NBI evaluation after initial AFI examination reduced the false-positive rate of AFI.[27,40] Although the usefulness of both the NBI and AFI systems has been recognized in a number of studies, there have been no published reports as yet actually comparing detection of esophageal and pharyngeal SCC using AFI and NBI. Therefore, we intend to conduct a prospective study to evaluate the usefulness of AFI compared to NBI for the diagnosis of SCC of the esophagus and pharynx.

It seems reasonable to conclude from our study that the AFI videoendoscope system can increase the possibility of early diagnosis of SCC of the esophagus and pharynx because of improved endoscopic visualization, but it should be noted that this was only an uncontrolled pilot trial with a small number of patients. Furthermore, the endoscopic examinations in our study were

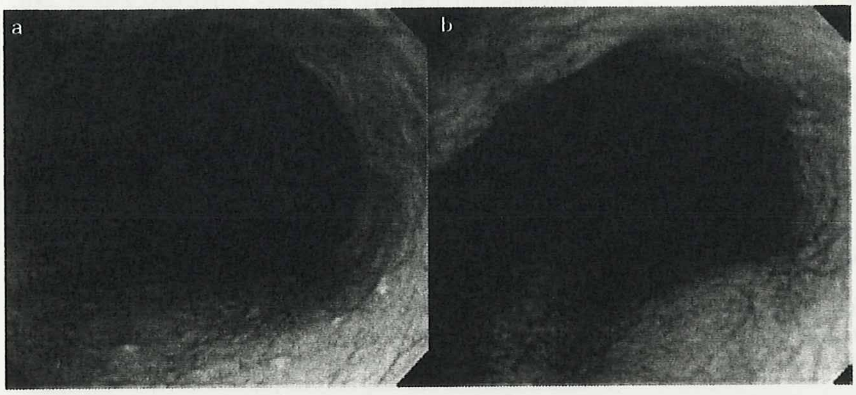

Figure 4 Squamous cell carcinoma (SCC) in the middle thoracic esophagus (mucosal invasion: Category 4.2. of the Vienna classification; flat type; less than half circumference). (a) Conventional white light endoscopy (WLE) showed a slightly reddish area that was evaluated as being illegible. (b) Autofluorescence imaging (AFI) endoscopy showed a clearly demarcated area magenta in color that was evaluated as being visible.

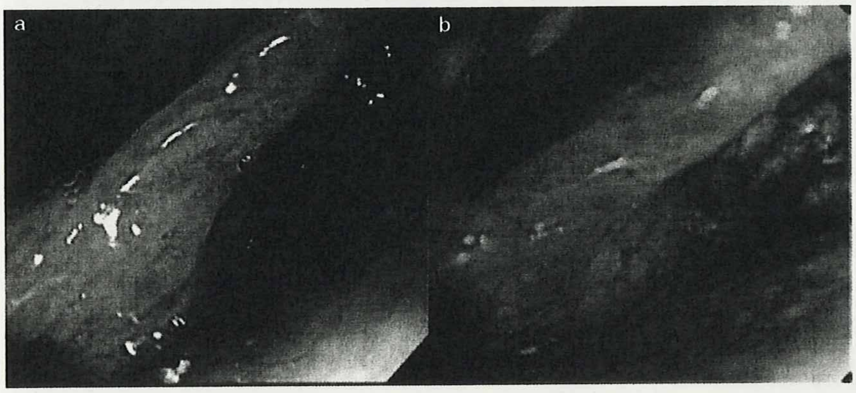

Figure 5 Squamous cell carcinoma (SCC) in situ of the right hypopharynx. (a) Conventional white light endoscopy (WLE) showed a slightly elevated area that was evaluated as being illegible. (b) Autofluorescence imaging (AFI) endoscopy showed a clearly demarcated area magenta in color that was evaluated as being visible.

conducted using WLE first followed by AFI, so the AFI results may have been more favorable as well as possibly being biased simply because the endoscopist had seen at least some of the lesions initially with WLE, although the visualization of the lesions using WLE and AFI was blindly evaluated by the other three endoscopists. The results, therefore, should be interpreted cautiously. In retrospect, we probably should have randomly carried out half of the endoscopic examinations using WLE first followed by AFI and the other half using AFI first followed by WLE.

It has been reported that visualization of some tumors and distinguishing neoplastic lesions from non-neoplastic areas, including inflammatory changes, continues to be difficult even when using the latest AFI system because of resolution limitations that sometimes result in false-positive findings. However, as we only evaluated visualization of previously diagnosed esophageal and pharyngeal SCC, it is possible that our AFI results are better than when both neoplastic and non-neoplastic lesions are included. Although maneuverability of the AFI videoendoscope was almost the same as that of a conventional videoendoscope, it also took several seconds longer to complete the AFI mode change.[25]

Therefore, a prospective, randomized controlled trial involving a large number of patients with not only SCC of the esophagus and pharynx, but also non-neoplastic lesions should be conducted to more fully evaluate the feasibility and efficacy of using the AFI system in the diagnosis of these lesions. Both image quality and maneuverability of the AFI system will also need to be improved before this recently developed technology can be accepted for general clinical use.

In conclusion, the results of the present study suggest that the AFI videoendoscope system may be more useful for the early diagnosis of SCC of the esophagus and pharynx because of improved visualization of such lesions compared to WLE.

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References

1 Isono K, Sato H, Nakayama K. Results of a nationwide study on the three-field lymph node dissection of esophageal cancer. *Oncology* 1991; **48**: 411–20.

2 Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann. Surg.* 2000; **232**: 225–32.

3 Inoue H. Treatment of esophageal and gastric tumors. *Endoscopy* 2001; **33**: 119–25.

4 Takeshita K, Tani M, Inoue H *et al.* Endoscopic treatment of early oesophageal or gastric cancer. *Gut* 1997; **40**: 123–7.

5 Yoshinaka H, Shimazu H, Fukumoto T, Baba M. Superficial esophageal carcinoma: a clinicopathological review of 59 cases. *Am. J. Gastroenterol.* 1991; **86**: 1413–18.
6 Kumagai Y, Makuuchi H, Mitomi T *et al.* A new classification system for early carcinoma of the esophagus. *Dig. Endosc.* 1993; **5**: 139–50.
7 Sugimachi K, Ohno S, Matsuda H, Mori M, Kuwano H. Lugol-combined endoscopic detection of minute malignant lesions of the thoracic esophagus. *Ann. Surg.* 1988; **208**: 179–83.
8 Yokoyama A, Ohmori T, Makuuchi H *et al.* Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. *Cancer* 1995; **76**: 928–34.
9 Dawsey SM, Fleischer DE, Wang GQ *et al.* Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus. *Cancer* 1998; **83**: 220–31.
10 Aoyama N, Akaike S, Koizumi H *et al.* Questionnaire investigating side effects of Lugol staining [in Japanese]. *Jpn. J. Gastroenterol. Surg.* 1983; **16**: 939–40.
11 Park JM, Lee IS, Kang JY *et al.* Acute esophageal and gastric injury: complication of Lugol's solution. *Scand. J. Gastroenterol.* 2007; **42**: 135–7.
12 Thuler FP, de Paulo GA, Ferrari AP. Chemical esophagitis after chromoendoscopy with Lugol's solution for esophageal cancer: case report. *Gastrointestinal. Endosc.* 2004; **59**: 925–6.
13 Kameyama H, Murakami M, Shimizu Y *et al.* The efficacy and diagnostic significance of sodium thiosulphate solution spraying after iodine dyeing of the esophagus. *Dig. Endosc.* 1994; **6**: 181–6.
14 Kondo H, Fukuda H, Ono H *et al.* Sodium thiosulfate solution spray for relief of irritation caused by Lugol's stain in chromoendoscopy. *Gastrointestinal. Endosc.* 2001; **53**: 199–202.
15 Shimizu Y, Tsukagoshi H, Fujita M *et al.* Head and neck cancer arising after endoscopic mucosal resection for squamous cell carcinoma of the esophagus. *Endoscopy* 2003; **35**: 322–6.
16 Matono S, Sueyoshi S, Tanaka T *et al.* Clinical analysis of esophageal cancer associated with other primary malignancies [English abstract]. *Jpn. J. Gastroenterol. Surg.* 2004; **37**: 633–9.
17 Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP, Mendenhall WM. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. *J. Clin. Oncol.* 2001; **19**: 1358–62.
18 Kraus DH, Zelefsky MJ, Brock HA, Huo J, Harrison LB, Shah JP. Combined surgery and radiation therapy for squamous cell carcinoma of the hypopharynx. *Otolaryngol Head Neck Surg.* 1997; **116**: 637–41.
19 Wahlberg PC, Andersson KE, Biorklund AT, Möller TR. Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. *Head Neck* 1998; **20**: 714–9.
20 Johansen LV, Grau C, Overgaard J. Hypopharyngeal squamous cell carcinoma treatment results in 138 consecutively admitted patients. *Acta Oncol.* 2000; **39**: 529–36.
21 Eckel HE, Staar S, Volling P, Sittel C, Damm M, Jungehuelsing M. Surgical treatment for hypopharynx carcinoma: feasibility, mortality, and results. *Otolaryngol. Head Neck Surg.* 2001; **124**: 561–9.
22 Muto M, Nakane M, Katada C *et al.* Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. *Cancer* 2004; **101**: 1375–81.
23 Haringsma J, Tytgat GN, Yano H *et al.* Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. *Gastrointest. Endosc.* 2001; **53**: 642–50.
24 Georgakoudi I, Jacobson BC, Van Dam J *et al.* Fluorescence, reflectance, and light-scattering spectroscopy for evaluating dysplasia in patients with Barrett's esophagus. *Gastroenterology* 2001; **120**: 1620–9.
25 Uedo N, Iishi H, Tatsuta M *et al.* A novel videoendoscopy system by using autofluorescence and reflectance imaging for diagnosis of esophagogastric cancers. *Gastrointestinal. Endosc.* 2005; **62**: 521–8.
26 Kara MA, Peters FP, ten Kate FJW, Van Deventer SJ, Fockens P, Bergman JJ. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. *Gastrointest. Endosc.* 2005; **61**: 679–85.
27 Kara MA, Peters FP, Fockens P, ten Kate FJW, Bergman JJ. Endoscopic video-autofluorescence imaging followed by narrow band imaging for detecting early neoplasia in Barrett's esophagus. *Gastrointestinal. Endosc.* 2006; **64**: 176–85.
28 Sutedja TG, Codrington H, Risse EK *et al.* Autofluorescence bronchoscopy improves staging of radiographically occult lung cancer and has an impact on therapeutic strategy. *Chest* 2001; **120**: 1327–32.
29 Hoshino H, Shibuya K, Chiyo M *et al.* Biological features of bronchial squamous dysplasia followed up by autofluorescence bronchoscopy. *Lung Cancer* 2004; **46**: 187–96.
30 Chiyo M, Shibuya K, Hoshino H *et al.* Effective detection of bronchial preinvasive lesions and early lung cancer by a new autofluorescence imaging bronchovideoscope system. *Lung Cancer* 2005; **48**: 307–13.
31 Gono K, Yamazaki K, Doguchi N *et al.* Endoscopic observation of tissue by narrow-band illumination. *Opt. Rev.* 2003; **10**: 211–15.
32 Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. *Gastrointest. Endosc.* 2004; **59**: 288–95.
33 Nonaka S, Saito Y. Endoscopic diagnosis of pharyngeal carcinoma by NBI. *Endoscopy* 2008; **40**: 347–51.
34 Schlemper RJ, Riddell RH, Kato Y *et al.* The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251–5.
35 The Japanese Society for Esophageal Diseases. *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus.* Tokyo: Kanehara, 2002.
36 Japan Society for Head and Neck Cancer. *General Rules for Clinical Studies on Head and Neck Cancer.* Tokyo: Kanehara, 2005.
37 Arens C, Reubner D, Woenkhaus J, Leunig A, Betz CS, Glanz H. Indirect fluorescence laryngoscopy in the diagnosis of precancerous and cancerous laryngeal lesions. *Eur. Arch. Otorhinolarygol.* 2007; **264**: 621–6.
38 Kara MA, Ennahachi M, Fockens P, ten Kate FJW, Bergman JJ. Detection and classification of the mucosal and vascular patterns (mucosal morphology) in Barrett's esophagus by using narrow band imaging. *Gastrointest. Endosc.* 2006; **64**: 155–66.
39 Kara MA, Peters FP, Rosmolen WD *et al.* High-resolution endoscopy plus indigo carmine chromoendoscopy or narrow band imaging: a prospective randomized cross-over study in patients with Barrett esophagus. *Endoscopy* 2005; **37**: 929–36.
40 Curvers WL, Singh R, Song LM *et al.* Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. *Gut* 2008; **57**: 167–72.

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ORIGINAL ARTICLE

Local recurrence after endoscopic resection of colorectal tumors

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Abstract
Background and aims Local recurrence frequently occurs after endoscopic resection of large colorectal tumors. However, appropriate intervals for surveillance colonoscopy to assess local recurrence after endoscopic resection have not been clarified. The aim of the present study was to determine local recurrence rates following en-bloc and piecemeal endoscopic resection and establish appropriate surveillance colonoscopy intervals based on retrospective analysis of local recurrences.
Materials and methods A total of 461 patients with 572≥ 10-mm lesions underwent endoscopic resection and follow-up. We retrospectively compared local recurrence rates on lesion size, macroscopic type, and histological type after en-bloc resection (440 lesions) and piecemeal resection (132 lesions). Cumulative local recurrence rates were analyzed using the Kaplan–Meier method.
Results Local recurrence occurred for 34 lesions (5.9%). Local recurrence rates for the en-bloc and piecemeal groups was 0.7% (3/440) and 23.5% (31/132), respectively ($P<0.001$). The difference between the two groups was distinct in terms of lesion size, macroscopic type, and histological type. Of the 34 local recurrences, 32 were treated endoscopically and two cases required additional surgery. The 6-, 12-, and 24-month cumulative local recurrence rate of the en-bloc group was 0.24%, 0.49%, and 0.81%. Then the 6-, 12-, and 24-month cumulative local recurrence rate for the piecemeal group was 18.4%, 23.1%, and 30.7%.
Conclusion Local recurrence occurred more frequently after piecemeal resection than en-bloc resection. However, almost all cases of local recurrences could be cured by additional endoscopic resection, so piecemeal resection can be acceptable treatment.

Keywords Colorectal tumors · Colonoscopy · Neoplasm recurrence · Follow-up studies

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Introduction

Endoscopic resection is used to treat early colorectal tumors around the world. However, the high frequency of local recurrence after piecemeal resection for large colorectal tumors is a serious problem [1–6]. Based on national polyp study [7], the appropriate interval for surveillance colonoscopy after endoscopic resection of adenomatous polyps is 3 years. However, the appropriate intervals after incomplete endoscopic resection has not yet been clarified. In the present study, we retrospectively analyzed the local recurrence frequency after en-bloc and piecemeal endoscopic resection for colorectal neoplasms ≥10 mm in size in large number of follow-up cases. We also analyzed clinicopathologic features and treatment of local recurrences. Our goal was to establish appropriate surveillance colonoscopy programs after endoscopic resection for colorectal tumors based on our retrospective analysis of local recurrence.

Table 1 The clinicopathologic characteristics

	En-bloc (n=440)	Piecemeal (n=132)
Follow-up (months)	22 (1–57)	18 (1–54)
Size (mean, mm)	13.9 (10–40)	23.3 (10–45)
Location		
(Rb/Ra/Rs/S/D/T/A/C)	23/23/32/140/39/73/81/29	12/4/8/20/6/25/29/28
Macroscopic type		
Protruding	324	26
Flat elevated	114	100
Depressed	2	6
Pathological type		
Adenoma	181	35
M-ca	253	88
SM-ca	5	8
Unevaluated	1	1

Rb lower rectum, *Ra* upper rectum, *Rs*: rect-sigmoid colon, *S* sigmoid colon, *D* descending colon, *T* transverse colon, *A* ascending colon, *C* cecum, *M-ca* intramucosal carcinoma, *SM-ca* submucosal invasive carcinoma

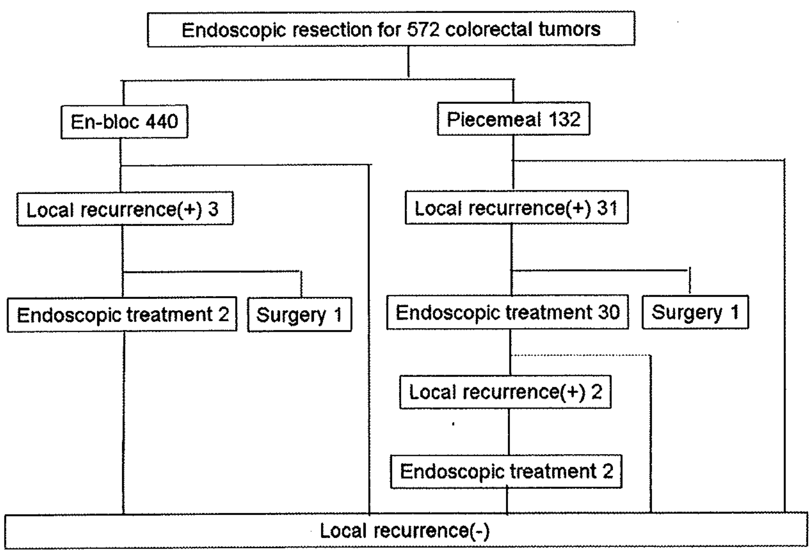
Materials and methods

A total of 461 patients (311 men, 150 women), with 572≥10-mm lesions underwent endoscopic resection and were followed up endoscopically between January 1998 and March 2002 at the National Cancer Center Hospital (Tokyo, Japan). Patients that required additional surgical treatment immediately after endoscopic resection and in whom follow-up colonoscopy could not be performed were excluded from the study. Clinical and pathological records were retrospectively analyzed. The mean patient age was 63.8 years (range 19–89). Of 572 lesions, 440 (76.9%) were removed en-bloc and 132 (23.1%) were removed by piecemeal. The clinicopathologic characteristics of the en-bloc and piecemeal groups are shown in Table 1. There was no difference in the follow-up period for the groups. For the piecemeal group, the mean size of the lesion was 23.3 mm. For the en-bloc group, the mean size of the lesion was 13.9 mm. The rates of rectal lesions were about 20% in both groups. In the piecemeal group, the dominant macroscopic type was flat-elevated. In the en-bloc group, the dominant macroscopic was protruded. We compared the local recurrence rates in the two groups by lesion size, macroscopic type, and histological type. Furthermore, we analyzed the clinicopathologic features and treatments of cases with local recurrence. All patients provided informed consent prior to endoscopic resection.

Endoscopic technique

Good bowel preparation is essential for detection and detailed observation of lesions. We used 2 L of polyethylene glycol electrocyte solution on the day of examination. We used conventional or magnifying video colonoscopies (CF200I, CF-Q240I, CF-200Z, CF-Q240ZI, PCF-230, PCF-Q240ZI; Olympus Optical, Tokyo, Japan). Scopolamine butyl bromide was administered intravenously unless contraindicated. The initial dose was 10 mg and was increased as required. If necessary, the conscious sedation was maintained with intravenous boluses of midazolam or pethidine. We routinely used chromoendoscopy with 0.2% indigo carmine dye to accentuate the lesion contours [8]. This procedure was useful for determining the area of endoscopic resection and detecting local recurrence at the site of resection. Furthermore, we used a magnifying endoscope with 0.2% indigo carmine or 0.05% crystal violet to estimate the depth of invasion in the target lesion [8] and to detect the residual tumor immediately after

Fig. 1 A chart of 572 colorectal tumors followed up after endoscopic resection



endoscopic resection. Macroscopically, at the margins, lesions can be classified into three major groups: protruding type including sessile (Is), semi-pedunclated (Isp), pedunclated (Ip); flat-elevated type including IIa, IIa+IIc, and Is+IIa; and depressed type including IIc. The indication for endoscopic resection is lesion invasion depth limited to the mucosa and shallow submucosa. After the visible lesion was completely removed, 0.2% indigo carmine was sprayed over the area and the area was magnified. Residual tumor was removed with hot biopsy forceps. We performed all endoscopic treatments in a single session.

Histological examination

All tissue was retrieved for histological evaluation. Removed specimens were fixed in 10% formalin for 24 h and embedded in paraffin wax. Serial sections (3 μm) were stained with hematoxylin and eosin. Two or more pathologists specializing in gastroenterology made histological diagnoses including histological type, invasion depth, vessel invasion, and surgical margin. In the present study, histological type was classified into three groups: adenomas, mucosal carcinomas (M-ca), and submucosal carcinomas (SM-ca).

A principle of additional surgical treatment

Patients that were (1) diagnosed with deep SM-ca >1,000 μm, (2) positive for vessel invasions, (3) positive for poorly differentiated adenocarcinoma at the sites of invasion, and (4) positive for vertical margins were judged to require additional surgical treatment with resection of regional lymph nodes. Cases that were judged to have positive or indistinct for lateral margins were followed up endoscopically.

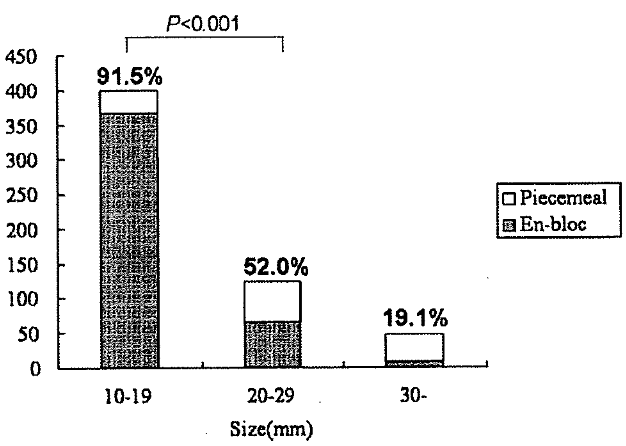


Fig. 2 En-bloc resection rates by lesion size

Table 2 Local recurrence rates by the lesion size

Size (mm)	10–19	20–29	30+	Total
En-bloc	0.8%* (3/366)	0%* (0/65)	0% (0/9)	0.7% (3/440)
Piecemeal	14.7% (5/34)	21.7% (13/60)	34.2% (13/38)	23.5% (31/132)
Total	2.0% (8/400)	10.4% (13/125)	27.7% (13/47)	5.9% (34/572)

*$P<0.001$

Statistical analysis

Local recurrence rates were compared with a chi-square test. Cumulative local recurrence rates were analyzed with the Kaplan–Meier method. Comparison of local recurrence rates were analyzed with log rank test. All statistical analysis was performed with Stat Mate Ver.3 for Windows (ATMS Tokyo, Japan). Calculated P values <0.05 were considered statistically significant.

Results

Local recurrence occurred in 34 lesions (5.9%) of 572 lesions. The local recurrence rates in en-bloc and piecemeal groups was 0.7% (3/440) and 23.5% (31/132, chi-square, $P<0.001$; Fig. 1). The en-bloc resection rates of lesions (Fig. 2) decreased in proportion to increase in size (chi-square; $P<0.001$). The local recurrence rates by lesion size are shown in Table 2. Based on lesion size, local recurrence rates of the en-bloc group were significantly lower than those of the piecemeal group (10–19 and 20–29 mm, chi-square, $P<0.001$). Based on macroscopic type, local recurrence rates of the en-bloc group were significantly lower than those in the piecemeal for protruding and flat-elevated types (chi-square, $P<0.001$; Table 3). Based on histological type, local recurrence rates of the en-bloc group were significantly lower than those of the piecemeal group for adenoma and M-ca (chi-square, $P<0.001$; Table 4).

Table 3 Local recurrence rates by macroscopic type

Type	Protruding	Flat elevated	Depressed	Total
En-bloc	0%* (0/324)	2.6%* (3/114)	0% (0/2)	0.7% (3/440)
Piecemeal	19.2% (5/26)	24.0% (24/100)	33.3% (2/6)	23.5% (31/132)
Total	1.4% (5/350)	12.6% (27/214)	25.0% (2/8)	5.9% (34/572)

*$P<0.001$

Table 4 Local recurrence rates by histological type

Type	Adenoma	M-ca	SM-ca	Unevaluated	Total
En-bloc	1.1%* (2/181)	0.4%* (1/253)	0% (0/5)	0% (0/1)	0.7% (3/440)
Piecemeal	17.1% (6/35)	26.1% (23/88)	25% (2/8)	0% (0/1)	23.5% (31/132)
Total	3.7% (8/216)	7.0% (24/341)	15.4% (2/13)	0% (0/2)	5.9% (34/572)

M-ca intramucosal carcinoma, *SM-ca* submucosal invasive carcinoma
*$P<0.001$

Twenty-eight of the 34 lesions with local recurrence were detected by the first follow-up colonoscopy that occurred at a median of 114 days (range 74–471) after resection. Local recurrence was detected in the remaining six lesions at the second or subsequent colonoscopy that occurred at a median of 726 days (range 337–910). For four of the six local recurrences that were missed by the first colonoscopy, the colonoscopy was performed within 3 months of resection.

The cumulative rate of local recurrence using the Kaplan–Meier method is shown in Fig. 3. The 6-, 12-, and 24-month cumulative local recurrence rate of the en-bloc group was 0.24%, 0.49%, and 0.81%. The 6-, 12-, and 24-month cumulative local recurrence rate for the piecemeal group was 18.4%, 23.1%, and 30.7%. Local recurrences were significantly frequent in the piecemeal group (log rank test, $P<0.001$). Therefore, we considered the proper first follow-up interval for the piecemeal group to be 6 months. The treatment for local recurrence endoscopic resection was performed in 32 cases (94.1%), and almost all of them were performed in a single session (mean 1.1, range 1–2; Fig. 1). Neither bleeding nor perforation occurred during endoscopic treatment. Two patients required additional surgery (Fig. 1), and the finding was intramucosal carcinoma without lymph node metastasis. The rate of additional surgery after endoscopic en-bloc and piecemeal resection was 0.23% (1/440) and 0.75% (1/132).

Discussion

Endoscopic resection for an early colorectal tumor has been used throughout the world since the 1970s [9, 10]. An endoscopic mucosal resection (EMR) with submucosal saline injection technique [1, 11–14] allowed us to remove a large colorectal tumor that appeared to be not only sessile but also flat and depressed. However, local recurrences frequently occurred after endoscopic piecemeal resection for large sessile tumors, which is a serious problem. Previous studies have reported the rate of local recurrence following piecemeal resection to be 25–50% [1, 2, 6]. Consequently, a combination of snare polypectomy and argon plasma coagulator (APC) [4, 5] or YAG laser [3, 15] was attempted to reduce local recurrence. One randomized controlled study demonstrated that there were fewer local recurrences with APC than without APC (1/10 vs. 7/11) [5]. However, the randomized group consisted of the patients in whom initial polypectomy was apparently complete, and local recurrence frequently occurred despite APC in patients with incomplete polypectomies (6/13). On the other hand, Palma et al. [15] reported that YAG laser reduced remnant tumor in ≥40-mm adenomas. However, the number of treatments with the YAG laser were frequently as many as three, which is a disadvantage of the method. The effort to reduce the local recurrence of piecemeal resection has stalled.

In pathologic staging, it is often difficult to evaluate the surgical margins and invasion depth after piecemeal removal of lesions because specimens may be difficult to reconstruct [16]. On the other hand, surgical margins and invasion depth are easily assessed after en-bloc resection

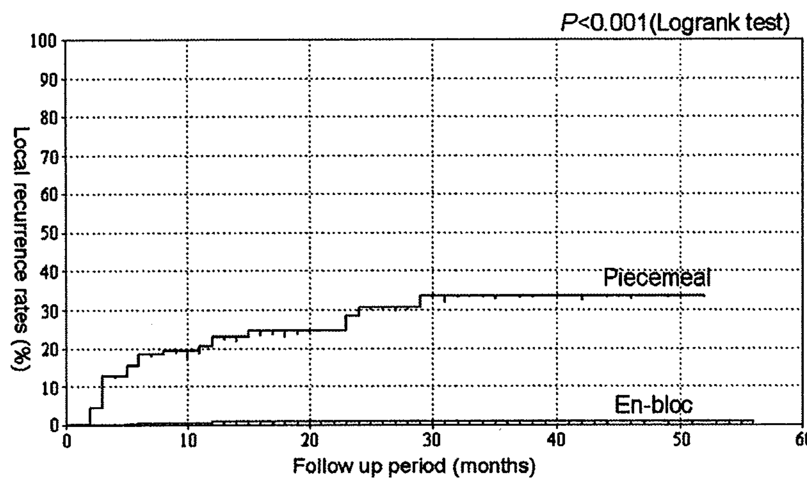


Fig. 3 Cumulative local recurrence rates after endoscopic resection (Kaplan–Meier method)

[16]. Moreover, one can easily evaluate the lateral margin after an en-bloc procedure by immediate observation of the retrieved specimen.

Could the en-bloc method reduce local recurrence after endoscopic resection? In the present study of 572 colorectal tumors that were endoscopically resected, local recurrence occurred for 34 lesions (5.9%). Furthermore, the local recurrence rate for the en-bloc group was significantly lower (0.7%) than that for the piecemeal group (23.5%; $P < 0.001$). The difference was maintained in subgroups with different lesion sizes (i.e., 10–19 vs. 20–29 mm). We could rationalize that the 10- to 19-mm lesions in which local recurrence occurred were difficult to locate, and therefore, we could not perform en-bloc resection.

Localization of the lesion in the large bowel is an important factor for the detection of remnant tumor immediately after endoscopic resection. Moreover, neither the macroscopic nor the histological type affected the local recurrence rate. Therefore, en-bloc resection appears to be an important factor for reducing local recurrences. Iishi et al. [17]. reported that of 56 large sessile colorectal polyps, the local recurrence after an en-bloc resection was less than that after piecemeal resection (0% vs. 50%). We confirmed this result in a large number of cases in the present study, and we added a detailed analysis for each factor. Although we routinely use magnifying observation of artificial ulcer's edges after endoscopic resection, local recurrence rate of the piecemeal group was significantly higher than the en-bloc group. We speculate this reason that there were micro-residual lesions made by intra-plural snaring method in the center of artificial ulcers, which were difficult to diagnose by observation of ulcer edges. Moreover, higher local recurrence rate might be caused by detailed detection during follow-up colonoscopy using magnified observation.

For the part of large rectal lesions, transanal endoscopic microsurgery (TEM) was considered for an alternative therapy for endoscopic resection. Local recurrence rates (0–10%) of TEM were reported [18], and these were better than our data of endoscopic piecemeal resection. However, TEM required experienced techniques and special instruments, and some complications such as incontinence and urinary retention which never arose in endoscopic resection occur [18].

Recently, several Japanese endoscopists [19, 20] developed novel techniques for large en-bloc resection, endoscopic submucosal dissection (ESD). Gotoda et al. [19] reported EMR on two rectal tumors using an insulation-tipped knife with which they cut the normal mucosa surrounding the target lesions before snaring. Yamamoto et al. [20] successfully removed a 40-mm rectal laterally spreading tumor with submucosal injection of a large amount of sodium hyaluronate. They also cut normal mucosa surrounding the target lesions with a needle knife before snaring. There are several problems with these novel techniques, including technical difficulty, the inability to determine the rate of perforation, and long procedure time. For those reasons, ESD is not widely used.

Based on our result, local recurrence is rare following en-bloc resection. Therefore, the 3- to 5-year interval for surveillance colonoscopy suggested by the national polyp study [7] and the guidelines of the American Gastroenterological Association (AGA) [21] should be appropriate after en-bloc resection. Definite surveillance intervals after incomplete resection have not been proposed by the AGA [21]. In our piecemeal resection group, local recurrence increased gradually from 18.4% at 6 months to 30.8% at 24 months. Based on those findings, an earlier surveillance colonoscopy (e.g., 3 months) would have missed local recurrence. Therefore, a 6-month interval for surveillance colonoscopy after piecemeal resection seems appropriate. That interval will provide accurate diagnosis of local recurrences >50% of the time.

The limitations of our study include using retrospective analysis and being non-randomized. Prospective randomized controlled studies are necessary for determining the appropriate interval for surveillance colonoscopy after piecemeal resection.

In our study, only two instances of local recurrence required additional surgery; the remainder were treated with additional endoscopic resection. We consider piecemeal resection an acceptable treatment until the efficacy and safety of large en-bloc resection are established.

In the future, an effective injection fluid or snare should be developed for safer and larger en-bloc resection based on conventional EMR procedures. We recently injected 10% glycerin solution into the submucosa during EMR, which resulted in a better en-bloc resection rate compared to normal saline [22]. Furthermore, we should make an effort to establish an ESD technique while paying a great deal of attention to safety.

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References

1. Nivatvongs S, Snover DC, Fang DT (1984) Piecemeal snare excision of large sessile colon and rectal polyps: is it adequate? Gastrointest Endosc 30:18–20
2. Walsh RM, Ackroyd FW, Shellito PC (1992) Endoscopic resection of large sessile colorectal polyps. Gastrointest Endosc 38:303–309

3. Hintze RE, Adler A, Veltzke W (1995) Endoscopic resection of large colorectal adenomas: a combination of snare and laser ablation. Endoscopy 27:665–670
4. Zlatanic J, Waye JD, Kim PS, Baiocco PJ, Gleim GW (1999) Large sessile colonic adenomas: use of argon plasma coagulator to supplement piecemeal snare polypectomy. Gastrointest Endosc 49:731–735
5. Brooker JC, Saunders BP, Shah SG, Thapar CJ, Suzuki N, Williams CB (2002) Treatment with argon plasma coagulation reduces recurrence after piecemeal resection of large sessile colonic polyps: a randomized trial and recommendations. Gastrointest Endosc 55:371–375
6. Waye JD (2001) Endoscopic mucosal resection of colon polyps. Gastrointest Endosc Clin N Am 11:537–548
7. Winawer SJ, Zauber AG, O'brien MJ (1993) Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. N Engl J Med 328:901–906
8. Fujii T, Hasegawa RT, Saitoh Y (2001) Chromoscopy during colonoscopy. Endoscopy 33:1036–1041
9. Wolff WI, Shinya H (1973) Polypectomy via the fiberoptic colonoscopy. N Engl J Med 288:329–332
10. Christie JP (1977) Colonoscopic excision of large sessile polyps. Am J Gastroenterol 67:430–438
11. Karita M, Tada M, Okita K (1992) The successive strip biopsy partial resection technique for large early gastric and colon cancers. Gastrointest Endosc 38:174–178
12. Kudo S (1993) Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy 25:455–461
13. Yokota T, Sugihara K, Yoshida S (1994) Endoscopic mucosal resection for colorectal neoplastic lesions. Dis Colon Rectum 37:1108–1111
14. Bedogni G, Bertoni G, Ricci E (1986) Colonoscopic excision of large and giant colorectal polyps. Technical implications and results over eight years. Dis Colon Rectum 29:831–835
15. Palma GD, Caiazzo C, Matteo ED, Capalbo G, Catanzano C (1995) Endoscopic treatment of sessile rectal adenomas of Nd: YAG laser therapy and injection-assisted piecemeal polypectomy. Gastrointest Endosc 41:553–556
16. Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N (2003) Endoscopic mucosal resection. Gastrointest Endosc 57:567–579
17. Iishi H, Tatsuta M, Iseki K (2000) Endoscopic mucosal resection with submucosal saline injection of large sessile colorectal polyps. Gastrointest Endosc 51:697–700
18. Casadesus D (2006) Transanal endoscopic microsurgery: a review. Endsocopy 38:418–423
19. Gotoda T, Kondo H, Ono H (1999) A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. Gastrointest Endosc 50:560–563
20. Yamamoto H, Koiwai H, Yube T (1999) A successful single-step endoscopic resection of a 40 millimeter flat-elevated tumor in the rectum: endoscopic mucosal resection using sodium hyaluronate. Gastrointest Endosc 50:701–704
21. Winawer S, Fletcher R, Rex D (2003) Colorectal cancer screening and surveillance: clinical guidelines and rationale. Update based on new evidence. Gastroenterology 124:544–560
22. Uraoka T, Fujii T, Saito Y (2005) Effectiveness of glycerol as a submucosal injection for EMR. Gastrointest Endosc 61:736–740

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ORIGINAL ARTICLE – COLORECTAL CANCER

Successful Complete Cure En-Bloc Resection of Large Nonpedunculated Colonic Polyps by Endoscopic Submucosal Dissection: A Meta-Analysis and Systematic Review

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ABSTRACT

Background. Endoscopic submucosal dissection (ESD) has emerged as one of the techniques to successfully resect large colonic polyps en bloc. Complete resection prevents the patient from going through transabdominal colonic resection. We sought to evaluate the proportion of successful en-bloc and complete cure en-bloc resection of large colonic polyps by ESD.

Methods. Studies that use ESD technique to resect large colonic polyps were selected. Successful en-bloc resection was defined as resection of the polyp in one piece. Successful complete cure en-bloc resection was defined as one piece with histologic disease-free-margin polyp resection. Articles were searched in Medline, PubMed, and Cochrane control trial registry. Pooled proportions were calculated by both fixed and random-effects model.

Results. The initial search identified 2,120 reference articles; 389 relevant articles were selected and reviewed. Data were extracted from 14 studies ($n = 1{,}314$) that met the inclusion criteria. The mean ± standard error size of the polyps was 30.65 ± 2.88 mm. Pooled proportion of en-bloc resection by the random-effects model was 84.91% (95% confidence interval, 77.82–90.82) and complete cure en-bloc resection was 75.39% (95% confidence interval, 66.69–82.21). The fixed-effects model was not used because of the heterogeneity of studies.

Conclusions. ESD should be considered the best minimally invasive endoscopic technique in the treatment of large (>2 cm) sessile and flat polyps because it allows full pathological evaluation and cure in most patients. ESD offers an important alternative to surgery in the therapy of large sessile and flat polyps.

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Endoscopic submucosal dissection (ESD), which was pioneered in Japan for the treatment of early gastric cancers, has now been applied to the colorectum. ESD has an advantage over other endoscopic techniques in that it allows en-bloc removal of large (>2 cm) colonic lesions.[1] ESD uses an electrosurgical cutting device to purposely dissect the deeper layers of the submucosa to remove neoplastic mucosal lesions.

ESD has an advantage over the older technique of endoscopic mucosal resection in that its effectiveness is not limited by the size of the lesion or its configuration. Multiple electrosurgical knives have been used, from a conventional needle knife to other modified accessories.[1–3]

Adenomas represent the single most important premalignant lesions of the colorectum. Pedunculated adenomas are easily removed by loop snare. However, this technique frequently results in piecemeal removal when applied to sessile and flat polyps.[4] ESD has been found to be particularly useful for the removal of sessile or flat adenomatous lesions.[2,3] En-bloc removal is advantageous because it allows full histological evaluation of the complete resection and is associated with a lower recurrence rate when compared with piecemeal removal.[3,5]

With such an important difference in treatment and prognosis between en-bloc versus piecemeal resection, it is important to evaluate the proportion of successful en-bloc and complete cure en-bloc resection of large colonic polyps by ESD. Because of this inconsistency, as well as the clinical importance of ESD for treatment and prognosis, we performed a meta-analysis to evaluate the proportion of successful en-bloc and complete cure en-bloc resection of large colonic polyps by ESD.

METHODS

Study Selection Criteria

Studies that used the ESD technique to resect large colonic polyps were selected. Successful en-bloc resection was defined as resection of the polyp in one piece. Successful complete cure en-bloc resection was defined as one piece with histologic disease-free-margin polyp resection.

Data Collection and Extraction

Articles were searched in the following databases: Medline (through PubMed, an electronic search engine for published articles and Ovid), Japanese Language Literature, PubMed, Ovid journals, Cumulative Index for Nursing and Allied Health Literature, ACP journal club, DARE, International Pharmaceutical Abstracts, old Medline, Medline nonindexed citations, OVID Healthstar, and Cochrane Central Register of Controlled Trials (CENTRAL). Both English- and Japanese-language literature was searched. The search was performed for studies published in the years 1966 to June 2008. The search terms used were ESD, endoscopic submucosal dissection, colon polyps, lateral spreading tumors, large polyps, nonpolypoid colon lesions, flat colon polyps, and flat adenomas. Two authors (S.P. and Y.K.) independently searched and extracted the data into an abstraction form. Any differences were resolved by mutual agreement.

Quality of Studies

Clinical trials designed with a control and treatment arms can be assessed for quality of the study. A number of criteria have been used to assess this quality of a study (e.g., randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome).[6,7] There is no consensus on how to assess studies without a control arm. Hence, these criteria do not apply to studies without a control arm.[7] Therefore, for this meta-analysis and systematic review, studies were selected on the basis of completeness of data and inclusion criteria.

Statistical Methods

This meta-analysis was performed by calculating pooled proportions (i.e., pooled proportion of en-bloc resection and complete cure en-bloc resection). First the individual study, proportions of successful resection were transformed into a quantity by Freeman–Tukey variant of the arcsine square root–transformed proportion. The pooled proportion was calculated as the backtransform of the weighted mean of the transformed proportions; inverse arcsine variance weights were used for the fixed-effects model, and DerSimonian–Laird weights were used for the random-effects model.[8,9] Forrest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forrest plots indicates the assigned weight to that study. The heterogeneity among studies was tested by Cochran's Q-test on the basis of inverse variance weights.[10] If the P value is >.10, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested by the Begg–Mazumdar bias indicator.[11] Also, funnel plots were constructed to evaluate potential publication bias by means of the standard error and diagnostic odds ratio.[12,13]

RESULTS

Initial search identified 2,120 reference articles; from these, 389 relevant articles were selected and reviewed. Data were extracted from 14 studies (n = 1,314) that met the inclusion criteria.[3,14–26] The search results are shown in Fig. 1. The mean ± standard error size of the polyps was 30.65 ± 2.88 mm. There were 1,105 successful en-bloc resections.

Pooled proportion of successful en-bloc resection by the random-effects model was 84.91% (95% confidence interval, 77.82–90.82). The Forrest plot in Fig. 2 depicts the individual study proportion of successful en-bloc resection in relation to the pooled estimate. The pooled proportion for successful complete cure en-bloc resections

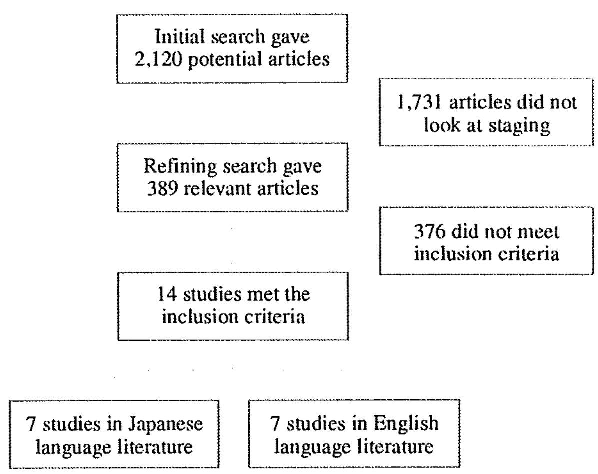

FIG. 1 Search results

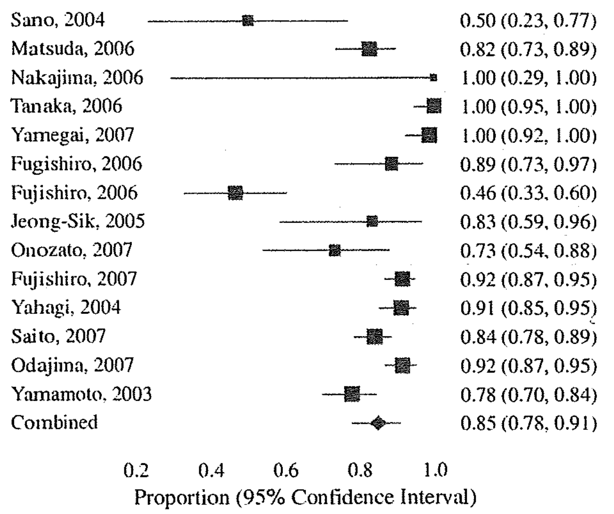

FIG. 2 Forrest plot showing successful en-bloc resection

by the random-effects model was 75.39% (95% confidence interval, 66.69–82.21). Figure 3 shows a Forrest plot depicting the individual study successful cure en-bloc resection in relation to the pooled estimate. The fixed-effects model was not used because of the heterogeneity of studies.

Subgroup analysis was performed by grouping studies according to the study population. This was done because the expertise required to perform procedures might affect the outcome. Studies were grouped into two groups: <100 patients and >100 patients. The proportion for successful en-bloc and successful cure en-bloc resections are shown in Table 1. The proportions shown in Table 1 were obtained by the random-effects model.

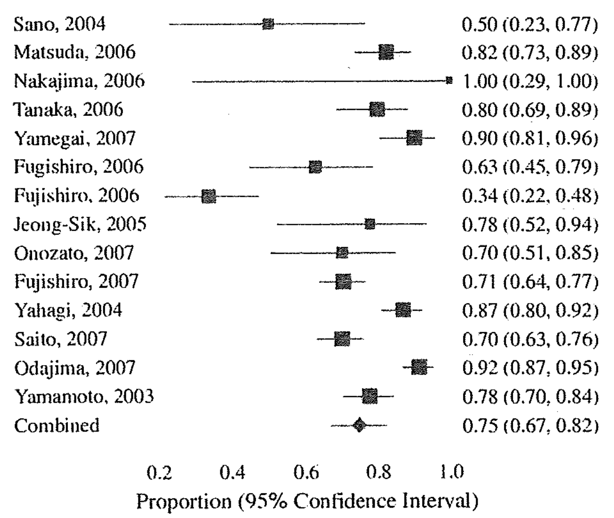

FIG. 3 Forrest plot showing successful complete cure en-bloc resection

The publication bias calculated by Begg-Mazumdar bias indicator for successful en-bloc resection gave a Kendall's tau b value of −.31 ($P = .14$), and for successful cure en-block resection, it was −.16 ($P = .38$). The funnel plot in Fig. 4 shows the publication bias for successful cure en-bloc resection.

DISCUSSION

Most colorectal cancers develop from adenomas. The risk of high-grade dysplasia and cancer has been found to increase with the size of the lesion.[27] Although traditional loop snare polypectomy has been found to be effective to treat large pedunculated neoplasias, its effectiveness in the therapy of sessile and flat polyps has been disappointing, frequently requiring piecemeal resection and additional procedures or therapies.[28,29] Surgical therapy of these large sessile and flat lesions continues to be an important alternative to endoscopic therapy, especially in the Western world.[30]

Although the procedure was initially developed to treat early gastric cancers, ESD has been found to be effective in the therapy of large (>2 cm) benign colorectal neoplastic lesions and early colorectal malignancy. ESD has an advantage over traditional loop snare polypectomy and endoscopic mucosal resection in that its effectiveness is not constrained by the size of the snare or by the configuration of the lesion.[1,3]

Our meta-analysis revealed that ESD en-bloc resection is achieved in 84.91% of lesions, and clear vertical and lateral margins are achieved in 75.39%. These results compare well to en-bloc resections achieved by conventional polypectomy snare, which have been reported to be between 7% and 34% for the treatment of large sessile polyps.[4,29] Our meta-analysis also reveals that experience with ESD plays an important role in achieving a better en-bloc resection and en-bloc cure. Studies with >100 lesions reported a pooled successful en-bloc resection of 87.77%, and clear vertical and lateral margins were achieved in 79.67%. In studies with <100 lesions, the pooled successful en-bloc resection drops to 82.6%, and clear vertical and lateral margins were achieved in 71.2%.

A limitation of this meta-analysis is that there was heterogeneity among studies; we thus used the random-effects model instead of the fixed-effects model. However, to overcome any potential bias, we looked into the world literature, which included articles published in Japanese. We think that our results are a true reflection of the status of ESD in the therapy of large polyps of the colon.

ESD is an innovative technique for resection of large nonpedunculated polyps of the colon, and we think that it should be considered the best minimally invasive

TABLE 1 Pooled proportion of successful en-bloc and cure en-bloc resection based on study size

Study size	No. of studies	Successful en-bloc resection, % (95% CI)	Complete cure en-bloc resection, % (95% CI)
<100 patients	9	82.60 (66.45–94.22)	71.23 (57.17–83.46)
>100 patients	5	87.77 (85.55–89.84)	79.67 (76.97–82.25)

95% CI, 95% confidence interval

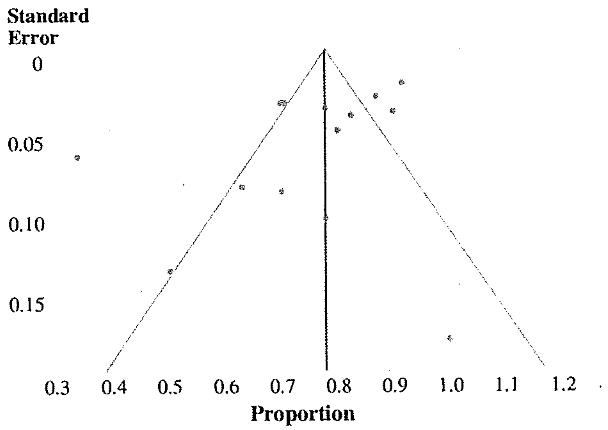

FIG. 4 Funnel plot showing publication bias for successful complete cure en-bloc resection

endoscopic technique in the treatment of large (>2 cm) sessile and flat polyps because it allows full pathological evaluation and cure in most patients. In addition, improvement in techniques and equipment are likely to improve complete cure en-bloc resection. ESD offers an important alternative to surgery in the therapy of large sessile and flat polyps.

REFERENCES

1. Antillon MR, Bartalos CR, Miller ML, et al. En bloc submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: expanding the frontiers of endoscopic surgery. *Gastrointest Endosc.* 2008;67:332–7.
2. Hurlstone DP, Atkinson R, Sanders DS, et al. Achieving R0 resection in the colorectum using endoscopic submucosal dissection. *Br J Surg.* 2007;94:1536–42.
3. Saito Y, Uraoka T, Matsuda T, et al. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections. *Gastrointest Endosc.* 2007;66: 966–73.
4. Church JM. Avoiding surgery in patients with colorectal polyps. *Dis Colon Rectum.* 2003;46:1513–6.
5. Conio M, Repici A, Demarquay JF, et al. EMR of large sessile colorectal polyps. *Gastrointest Endosc.* 2004:60:234–41.
6. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1–12.
7. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283:2008–12.
8. Stuart A, Ord JK. Kendall's advanced theory of statistics. 6th ed. London: Edward Arnold; 1994.
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–88.
10. Deeks JJ. Systematic reviews of evaluations of diagnostic and screening tests. In: Egger M, Smith GD, Altman DG, editors. Systematic reviews in health care: meta-analysis in context. London: BMJ Books; 2001.
11. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50:1088–101.
12. Sterne JAC, Egger M, Davey-Smith G. Investigating and dealing with publication and other biases in meta-analysis. *Br Med J.* 2001;323:101–5.
13. Sterne JAC, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol.* 2001;54:1046–55.
14. Fujishiro M, Yahagi N, Nakamura M, et al. Endoscopic submucosal dissection for rectal epithelial neoplasia. *Endoscopy.* 2006;38:493–7.
15. Fujishiro M, Yahagi N, Kakushima N, et al. Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. *Clin Gastroenterol Hepatol.* 2007;5: 678–83.
16. Fujishiro M, Yahagi N, Nakamura M, et al. Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. *Gastrointest Endosc.* 2006;63:243–9.
17. Sano Y, Machida Y, Fu KI, et al. Endoscopic mucosal resection and submucosal dissection method for large colorectal tumors. *Dig Endosc.* 2004;16(Suppl):S93–6.
18. Matsuda T, Saito Y, Uraoka T, et al. Therapeutic strategy for laterally spreading tumors (LSTs) in the colorectum. *Syokaki Naisikyo.* 2006;18:1151–7.
19. Odajima S, Fujishiro M, Kadoshima N, et al. ESD of lateral spreading polyps. *Syokakino Rinsyo.* 2007;10:60–5.
20. Yamamoto H, Sunada K, Kita H, et al. Reliable en-bloc resection by submucosal dissection EMR using sodium hyaluronate ard small-caliber tip transparent hood. *Syokaki Naisikyo.* 2003;7:933–8.
21. Nakajima K, Miyazaki S, Aoki T, et al. Result of endoscopic resection and treatment strategy including operation for colorectal adenoma and early cancer of 20 mm or more in diameter. *Progr Dig Endosc.* 2006;68:67–72.
22. Tanaka S, Oka S, Kaneko I, et al. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. *Gastrointest Endosc.* 2007;66:100–7.
23. Yahagi N, Fujishiro M, Omata M. Endoscopic submucosal dissection of colorectal lesion. *Dig Endosc.* 2004;16:S178–81.
24. Onozato Y, Kakizaki S, Ishihara H, et al. Endoscopic submucosal dissection for rectal tumors. *Endoscopy.* 2007;39:423–7.
25. Tamegai Y, Saito Y, Masaki N, et al. Endoscopic submucosal dissection: a safe technique for colorectal tumors. *Endoscopy.* 2007;39:418–22.
26. Byeon JS, Jo JY, Choi KD, et al. Combination of endoscopic submucosal dissection and snare resection in colorectal lesions. *J Gastroenterol Hepatol.* 2005;20(Suppl 2):A246–7.

27. Odom SR, Duffy SD, Barone JE, Ghevariya V, McClane SJ. The rate of adenocarcinoma in endoscopically removed colorectal polyps. *Am Surg.* 2005;71:1024–6.
28. Doniec JM, Lohnert MS, Schniewind B, et al. Endoscopic removal of large colorectal polyps: prevention of unnecessary surgery? *Dis Colon Rectum.* 2003;46:340–8.
29. Stergiou N, Riphaus A, Lange P, et al. Endoscopic snare resection of large colonic polyps: how far can we go? *Int J Colorectal Dis.* 2003;18:131–5.
30. Pokala N, Delaney CP, Kiran RP, Brady K, Senagore AJ. Outcome of laparoscopic colectomyfor polyps not suitable for endoscopic resection. *Surg Endosc.* 2007;21:400–3.

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CURRENT STATUS AND FUTURE PERSPECTIVE OF ENDOSCOPIC TREATMENT FOR COLORECTAL NEOPLASIA

ENDOSCOPIC SUBMUCOSAL DISSECTION IN THE COLORECTUM: PRESENT STATUS AND FUTURE PROSPECTS

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Endoscopic submucosal dissection (ESD) can successfully resect early stage gastrointestinal tumors, but colorectal ESDs are not widely performed, even by Japanese endoscopists, because of several negative factors. Besides being considerably more difficult in terms of technical demands, colorectal ESDs involve a longer procedure time and have a higher complication rate compared to gastric ESDs. In addition, most colorectal lesions are adenomas or intramucosal cancers that despite their large size that can be curatively treated by endoscopic mucosal resection including piecemeal resection.

There is, however, no doubt about ESD having a major therapeutic advantage in being able to achieve a higher en-bloc resection rate resulting in enhanced curability and more accurate histopathological assessment. Continued improvement in the technical skills of endoscopists, further refinement of such devices as electrical surgical knives and a special colonoscope as well as the development of more effective submucosal injection solutions and new traction systems are expected to facilitate easier, faster and safer colorectal ESD procedures in the relatively near future.

Key words: colorectum, endoscopic submucosal dissection (ESD), perforation, thin endoscope assisted-ESD (TEA-ESD), training.

INTRODUCTION

Endoscopic submucosal dissection (ESD) can successfully resect early stage gastrointestinal tumors *en bloc* including large lesions and lesions with submucosal fibrosis and ulceration scarring.[1–9] The acceptance of ESD for treating early gastric cancer has steadily increased in many Japanese medical centers, but colorectal ESDs are not widely performed by endoscopists in Japan because of a greater level of technical difficulty, longer procedure times and a higher risk of complications, such as perforations, compared to gastric ESDs.[5,10–16]

This review focuses on the present status of colorectal ESD, taking into account recent advances as well as future prospects for this very promising procedure, with continued improvement in technical skills and further refinement and development of new endoscopic devices, materials and techniques.

TECHNICAL ISSUES ASSOCIATED WITH COLORECTAL ESD

Lack of education and training programs

There are no education and training programs for colorectal ESD in Japan at the present time. The first author, for example, is the only endoscopist currently capable of performing this procedure at his hospital.

Given the increased level of technical difficulty involved in colorectal ESD and the complete lack of any existing education and training programs, it is, therefore, strongly recommended that endoscopists obtain the requisite experience by performing a sufficient number of gastric ESDs before attempting colorectal ESD. We recommend at least 20 such gastric ESDs as a minimum and the initial colorectal ESDs should be performed in the rectum because rectal lesions are technically less difficult to treat endoscopically with a lower risk of perforation.

Longer procedure time

The reported procedure times for colorectal ESDs have ranged between 70 and 110 minutes.[10,12–14] The actual time required depends on a number of factors, of course, particularly an individual lesion's characteristics, but it is generally regarded that colorectal ESD requires more time than gastric ESD.

The graph in Fig. 1 indicates the relationship between procedure time and lesion size in our hospital. Although it seems obvious, the necessity of longer procedure times as lesion size increased was clearly indicated with a high correlation coefficient.

Perforation

The narrow angulated lumen and thinner wall in the colorectum make it difficult to control the endoscope and resect

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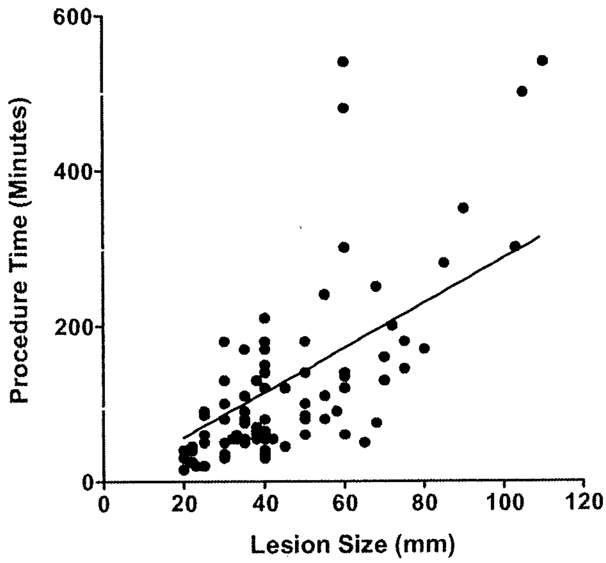

Fig. 1. Relationship between lesion size and procedure time at our hospital. The endoscopic submucosal dissection procedure took longer as lesion size increased, with a correspondingly high correlation coefficient (0.6386, $P < 0.001$).

safely during colorectal ESD. Perforation is a serious complication requiring immediate management especially in the colorectum because of the greater possibility of peritonitis due to the presence of fecal fluid.

When colorectal ESDs were initially being performed, the perforation rate was reported to have been approximately 10%.[17,18] More recent reports from medical centers specializing in ESDs, however, have indicated better results attributable to improved technical ability and the refinement of new endoscopic devices and techniques.[19]

Endoscopic submucosal dissection specialists have also mastered effective complication management methods such as the use of endoclips.[17,20] Successful endoscopic closure of perforations and the administration of antibiotics following ESD procedures have now made it possible to conservatively treat most patients with perforations, and emergency surgery has become quite rare.

MINIMIZING NEGATIVE FACTORS

In order to reduce the effect of these negative factors, further refinement of such devices as electrical surgical knives and a special colonoscope in addition to the development of improved submucosal injection solutions and better traction systems will be necessary.

Combination use of electrical surgical knives

Early ESD pioneers developed various surgical knives, but most endoscopists now performing colorectal ESD combine the use of different electrical surgical knives during the actual procedure. Using a combination of various electrical surgical knives is preferred because it shortens the procedure time while ensuring a higher level of safety in virtually all situations.

The combined use of a Flex knife (Olympus Co., Tokyo, Japan) and a Hook knife (Olympus)[5,8,13] and a Flush knife (FTS, Omiya, Japan) together with a Hook knife[9] have both been reported previously. We primarily use a bipolar current needle knife (B-knife, Zeon Medical Inc., Tokyo, Japan),[10–12,16,21] which has been specifically designed so high-frequency current sent to the muscle layer is reduced for better control and safer use with the current flowing back from the knife towards the sheath tip, in combination with an insulation-tipped knife (IT knife; Olympus) to shorten the procedure time[10,12] and/or a Mucosectom (PENTAX Co., Tokyo, Japan)[7] for safer dissection of submucosal fibrosis and ulceration scar tissue with satisfactory clinical treatment outcomes.

Among 137 ESDs performed between April 2006 and October 2008 in our hospital, the en-bloc resection rate was 91%, the median procedure time was 75 minutes and the mean size of resected specimens was 43 mm. Perforations that occurred in 3% of all cases could be successfully managed using endoclips without the necessity for surgical treatment.

Thin endoscope assisted-ESD

We developed a thin endoscope assisted-ESD (TEA-ESD) traction system to improve direct visualization of the submucosal layer cutting line.[16] This procedure is performed (Fig. 2) with a primary gastroscope and a second thinner endoscope, 6.5 mm in diameter, each of which is operated by a different endoscopist. After a circumferential incision and partial exfoliation have been completed, an endoclip is attached to the edge of the exfoliated mucosa. The thinner endoscope is then inserted into the lumen and a snare is used to grasp the positioned endoclip and pull the lesion away from the muscle layer. Traction direction is easily controlled because of the flexibility of the thinner endoscope and direct cutting line visualization is maintained by retracting the submucosal layer tissue resulting in a safe dissection.

As a result of improved direct visualization having been achieved with the TEA-ESD traction system, it is expected that continued use of this technique will result in both reducing the perforation rate and shortening the colorectal ESD procedure time. We are now prospectively performing TEA-ESDs to remove laterally spreading tumors >20 mm located in the rectum and sigmoid colon to evaluate the safety and efficacy of this procedure.

Special colonoscope for colorectal ESD

Recently, a special 10.5 mm-diameter pediatric type EMR/ESD colonoscope with a water-jet function (PCF-260J1; Olympus) has become available in Japan facilitating even safer and more efficient ESD colorectal procedures. This colonscope's small caliber, shorter bend at the top and increased flexibility make it easier to use the retroflex position in the narrow colorectal lumen. Water is supplied through the accessory channel when the endoscopist simply steps on a foot switch. The water-jet function helps to improve direct cutting line visualization and identify any bleeding points without the necessity of taking various devices like an electrical surgical knife or coagulation forceps

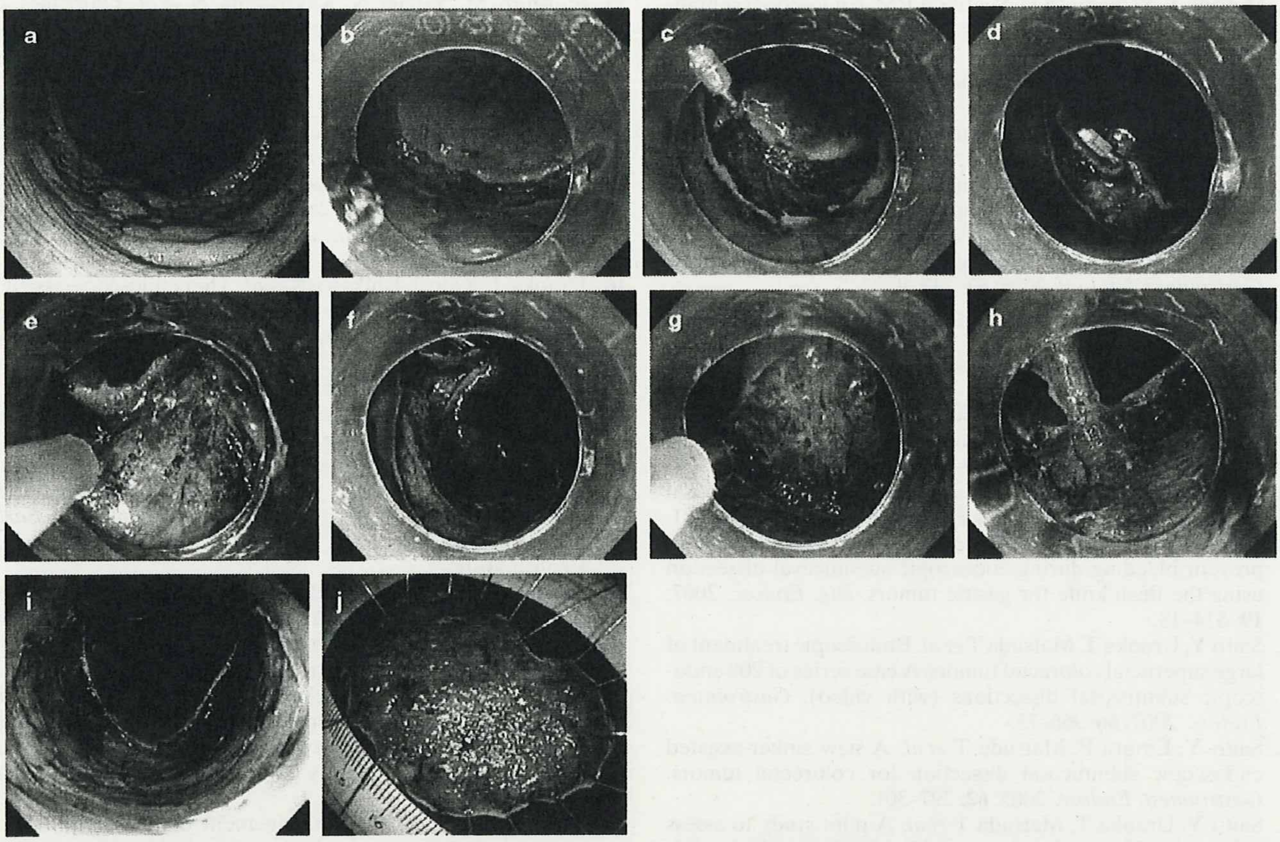

Fig. 2. Thin endoscope assisted-endoscopic submucosal dissection (TEA-ESD) Technique. (a) Laterally spreading tumor 50 mm in diameter located in lower rectum. (b) After submucosal injection, we performed circumferential incision and partial exfoliation. (c) Endoclip attached to edge of exfoliated mucosa. (d) Second thinner endoscope inserted into lumen and snare introduced through working channel grasped endoclip and pulled lesion away from muscle layer. (e) Thinner endoscope provided sufficient traction. (f) Thinner endoscope facilitating sufficient traction easily controlled by flexible endoscope. (g) Submucosal dissection safely and successfully performed by TEA-ESD. (h) Final stage of TEA-ESD. (i) Successful en-bloc resection without complication. (j) Histopathological diagnosis revealed well-differentiated adenocarcinoma, M, lymphovascular invasion (-) and cut end (-).

in and out during the procedure. Use of this function should contribute to shorter procedure times and safer submucosal dissections.

FUTURE PROSPECTS

Further refinements in colorectal ESD devices and techniques are expected to be standardized in the future. Colonoscopes will have enhanced features such as greater flexibility and be multifunctional including the ability to release and retract multiple devices instantly. Control of electrical surgical knives and traction forceps will also be considerably more flexible than with the devices currently in use.

In order to assist endoscopists in acquiring the necessary colorectal ESD skills more efficiently, the development of a simulation system involving an ESD training model such as the stomach of a pig is important. Eventually, a robotic system with remote control of newly developed devices and techniques may be feasible.

There is no doubt about ESD being a significant advancement in therapeutic endoscopy with the major advantage of being able to achieve a higher en-bloc resection rate resulting in enhanced curability and more accurate histopathological assessment. While still in the developmental stages at the present time, it is certainly conceivable that colorectal ESD could become the standard procedure for treating large lesions and lesions with submucosal fibrosis and ulceration scarring as continued advances are made that facilitate easier, faster and safer procedures in the relatively near future.

CONFLICT OF INTEREST

No conflict of interest has been declared by T Uraoka, Y Kawahara, J Kato, Y Saito or K Yamamoto.

REFERENCES

1. Ohkuwa M, Hosokawa K, Boku N *et al.* New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; **33**: 221–6.
2. Oda I, Gotoda T, Hamanaka H *et al.* Endoscopic submucosal dissection for early gastric cancer: Technical feasibility, operation time and complications from a large consecutive series. *Dig. Endosc.* 2005; **17**: 54–8.

3. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J. Gastroenterol.* 2006; **41**: 929–42.
4. Yamamoto H, Kawata H, Sunada K *et al.* Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. *Endoscopy* 2003; **35**: 690–4.
5. Fujishiro M, Yahagi N, Nakamura M *et al.* Successful outcomes of a novel endoscopic treatment for GI tumors: Endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. *Gastrointest. Endosc.* 2006; **63**: 243–9.
6. Oka S, Tanaka S, Kaneko I *et al.* Endoscopic submucosal dissection for residual/local recurrence of early gastric cancer after endoscopic mucosal resection. *Endoscopy* 2006; **38**: 996–1000.
7. Kawahara Y, Takenaka R, Okada H. Risk management to prevent perforation during endoscopic submucosal dissection. *Dig. Endosc.* 2007; **19**: S9–13.
8. Yahagi N, Fujishiro M, Omata M. Endoscopic submucosal dissection of colorectal lesion. *Dig. Endosc.* 2004; **16**: S178–81.
9. Toyonaga T, Nishino E, Dozaiku T *et al.* Management to prevent bleeding during endoscopic submucosal dissection using the flush knife for gastric tumors. *Dig. Endosc.* 2007; **19**: S14–18.
10. Saito Y, Uraoka T, Matsuda T *et al.* Endoscopic treatment of large superficial colorectal tumors: A case series of 200 endoscopic submucosal dissections (with video). *Gastrointest. Endosc.* 2007; **66**: 966–73.
11. Saito Y, Emura F, Matsuda T *et al.* A new sinker-assisted endoscopic submucosal dissection for colorectal tumors. *Gastrointest. Endosc.* 2005; **62**: 297–301.
12. Saito Y, Uraoka T, Matsuda T *et al.* A pilot study to assess safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection under conscious sedation. *Gastrointest. Endosc.* 2007; **65**: 537–42.
13. Fujishiro M, Yahagi N, Kakushima N *et al.* Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. *Clin. Gastroenterol. Hepatol.* 2007; **5**: 678–83.
14. Tanaka S, Oka S, Kaneko I *et al.* Endoscopic submucosal dissection for colorectal neoplasia: Possibility of standardization. *Gastrointest. Endosc.* 2007; **66**: 100–7.
15. Uraoka T, Saito Y, Matsuda T *et al.* Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. *Gut* 2006; **55**: 1592–7.
16. Uraoka T, Kato J, Ishikawa S *et al.* Thin endoscope-assisted endoscopic submucosal dissection for large colorectal tumors (with videos). *Gastrointest. Endosc.* 2007; **66**: 836–9.
17. Taku K, Sano Y, Fu KI *et al.* Iatrogenic perforation associated with therapeutic colonoscopy: A multicenter study in Japan. *J. Gastroenterol. Hepatol.* 2007; **22**: 1409–14.
18. Hotta K, Oyama T, Miyata Y *et al.* Techniques for and challenges with endoscopic submucosal dissection methods employing Hook knife for colorectal neoplasms. *Early Colorectal Cancer* 2006; **10**: 501–5. (in Japanese with English abstract.)
19. Tsuda S. Complications related to endoscopic submucosal dissection (ESD) of colon and rectum and risk management procedures. *Early Colorectal Cancer* 2006; **10**: 539–50. (in Japanese with English abstract.)
20. Saito Y, Matsuda T, Kikuchi T *et al.* Successful endoscopic closures of colorectal perforations requiring abdominal decompression after endoscopic mucosal resection and submucosal dissection for early colorectal cancer. *Dig. Endosc.* 2007; **19**: S34–39.
21. Sano Y, Saitoh Y. Risk management of therapeutic colonoscopy (hot biopsy, polypectomy, endoscopic mucosal resection and endoscopic submucosal dissection). *Dig. Endosc.* 2007; **19**: S19–25.