not been studied extensively.

The aim of this retrospective study was to clarify the clinicopathological characteristics of small and large EI-CRCs and their implications for endoscopic treatment.

MATERIALS AND METHODS

Subjects

Five hundred and eighty-three patients (374 male and 209 female) with EI-CRC that had been resected surgically or endoscopically at the National Cancer Center Hospital, between January 1980 and January 2004, were examined retrospectively. In all of these patients, cancer cells invaded through the muscularis mucosa into the submucosal layer but did not extend deeply into the muscularis propria. Eligibility also required the lesions to be macroscopically non-pedunculated (sessile, flat and depressed). Patients with synchronous advanced CRC, multiple EI-CRCs, inflammatory bowel disease, hereditary non-polyposis colorectal cancer and familial adenomatous polyposis were excluded from the study.

Methods

All lesions were classified into two groups according to their endoscopic image size: small (≤ 10 mm) and large (> 10 mm). Furthermore, lesions were classified into three categories (sessile, 0- Ⅰs, Ⅰs+Ⅱa; flat, 0-Ⅱa; and depressed, 0-Ⅱc, Ⅱa+Ⅱc, Ⅰs+Ⅱc) according to the Paris classification[7]. Clinicopathological features, incidence of LNM and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

Histopathology

Resected specimens were fixed in 10% formalin and examined histopathologically following hematoxylin and eosin staining. Histopathological diagnosis was based on the World Health Organization (WHO) criteria[8]. Submucosal invasion was measured from the muscularis mucosa to the deepest portion. When the muscularis mucosa could not be identified because of cancer invasion, the vertical length was measured from the surface of the lesion to the deepest portion according to Kitajima's classification[9]. Tumors with a vertical length of < 1000 μm in the submucosal layer were classified as submucosal superficial invasive cancers (sm-superficial), and lesions with a length ≥ 1000 μm were classified as submucosal deep invasive cancers (sm-deep). The tumor growth patterns were histopathologically divided into polypoid growth (PG) and non-polypoid growth (NPG) types. Shimoda *et al*[10] have reported polyp cancers with protrusions caused by intramucosal proliferation of the carcinoma or coexistent adenoma that behaved as PG type carcinoma, while flat/depressed type carcinoma without polypoid proliferation of intramucosal tumor behaved as NPG type carcinoma.

Statistical analysis

The significance of differences in proportions was assessed by the χ^2 test, Fisher's exact test and the Wilcoxon matched-pairs signed-ranks test using SPSS statistical software (SPSS for Windows , version 16.0J, Tokyo, Japan). Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 583 EI-CRCs were retrospectively evaluated, with 120 (21%) small and 463 (79%) large lesions identified (Table 1). The gender ratio (male/female) was 2.4 and 1.7, and the mean age was 61.5 and 62.4 years in the small and large lesion groups, respectively. Mean size of the small and large lesions was 8.3 and 22.1 mm, respectively.

Macroscopic type, growth type and location

Macroscopic assessment of small lesions identified 51 cases as sessile (42%), 14 as flat (12%), and 55 as depressed (46%). Similarly, large lesion groups comprised 233 sessile (50%), 64 flat (14%), and 166 depressed (36%) type. PG types were identified in 32% (38/120) and 54% (250/463) of small and large lesions, respectively. In contrast, the prevalence of NPG type in the small lesion group was significantly higher than in the large lesion group (68% *vs* 46%, $P < 0.0001$). Regarding tumor location, there were 33 (27%) rectal, 56 (47%) distal colon and 31 (26%) proximal colon cancers in the small lesion group. In contrast, there were 213 (46%) rectal, 139 (30%) distal colon and 111 (24%) proximal cancers in the large lesion group. The incidence of rectal cancer in the large lesion group was significantly higher than in the small lesion group ($P = 0.02$).

LNM

Among the lesions treated surgically, the incidence of LNM was 11.2% (10/89) and 12.1% (46/381) in small and large lesion groups, respectively ($P = 0.85$) (Table 2).

Depth of invasion/LVI/PDA

Histopathological analysis of the small lesion group revealed sm-deep cancer in 90 (75%) cases, LVI in 26 (22%) and PDA in 12 (10%). Similarly, the large lesion group exhibited sm-deep cancer in 380 (82%) cases, LVI in 125 (27%), and PDA in 79 (17%). Therefore, in relation to depth of invasion, LVI and PDA, there were no significant differences between the groups.

Treatment strategy

Among the small lesion group, 62 (52%) cases were initially treated with endoscopic mucosal resection (EMR), while 58 (48%) cases were surgically resected. In contrast, among the large lesion group, 133 (29%) cases were initially treated with EMR, while 330 (71%) cases were surgically resected. Among all lesions treated by EMR, there were no differences in the rate of positive and unknown vertical and/or lateral cut margins in the small (18%, 11/62) and large lesion groups (20%, 26/133). Furthermore, among all positive cut margin cases in the small and large lesion groups, there were 11 (100%) and 18 (69%) positive vertical margin cases (Table 3, Figures 1 and 2).

Table 1 Comparison of clinicopathological and endoscopic characteristics for 583 study cases

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
No. of lesions, *n* (%)	120 (21)	463 (79)	
Gender (M/F)	85/35	289/174	0.09
Age (yr), mean (range)	61.5 (39-84)	62.4 (30-90)	0.86
Macroscopic type, *n* (%)			
Sessile (0-Is, Is+IIa)	51 (42)	233 (50)	0.13
Flat (0-IIa)	14 (12)	64 (14)	
Depressed (0-IIc, IIa+IIc, Is+IIc)	55 (46)	166 (36)	
Size (mm), mean ± SD	8.3 ± 1.6	22.1 ± 9.6	
Growth pattern (PG/NPG)	38/82	250/213	< 0.0001
Location, *n* (%)			
Rectum	33 (27)	213 (46)	0.02
Distal colon[1]	56 (47)	139 (30)	
Proximal colon[2]	31 (26)	111 (24)	

[1]Descending-sigmoid colon; [2]Cecum-transverse colon.

Table 3 Comparison of treatment, surgical and positive rate between groups *n* (%)

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
Initial treatment			
EMR	62 (52)	133 (29)	< 0.0001
Surgery	58 (48)	330 (71)	
Positive rate of cut margin[1]	11 (18)	26 (20)	0.81
In EMR cases			
Lateral	0 (0)	8 (31)	0.08
Vertical	11 (100)	18 (69)	

[1]Positive and unknown cut margin. EMR: Endoscopic mucosal resection.

According to the initial treatment, there were 134 (69%) and 336 (87%) sm-deep cancers in the EMR and surgery groups, respectively. Furthermore, there were 33 (17%) and 118 (30%) LVI-positive, and 18 (9%) and 73 (19%) PDA-positive cases in the EMR and surgery groups, respectively. There were 37 (19%) positive cut margin cases, including 29 (78%) positive vertical margins in the EMR group. In contrast, there were no positive cut margin cases in the surgery group. In the EMR group, 82 (42%) patients underwent additional surgery with LN dissection after EMR within 6 mo. The incidence of LNM was 11.0% (9/82) and 12.1% (47/388) in the EMR and surgery groups, respectively ($P = 0.79$) (Table 4).

DISCUSSION

Several authors have reported a strong association between lesion size and submucosal invasion or risk of LNM when referring to the grade of malignancy of early CRC. Large lesion size has been considered an indicator of deep submucosal invasion and presence of LNM. However, in this large retrospective study, small EI-CRC demonstrated a similar aggressive behavior and malignant potential to those of large lesions, with a similar risk of LNM , LVI and PDA among both groups.

Intramucosal CRC is thought generally to have no potential for LNM. In contrast, it has been reported that

Table 2 Incidence of LNM and clinicopathological characteristics based on tumor size *n* (%)

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
LNM	10/89 (11.2)	46/381 (12.1)	0.85
Depth of invasion			
sm-superficial (< 1000 μm)	30 (25)	83 (18)	0.08
sm-deep (≥ 1000 μm)	90 (75)	380 (82)	
LVI	26 (22)	125 (27)	0.23
PDA	12 (10)	79 (17)	0.06

LVI: Lymphovascular invasion; PDA: Poorly differentiated adenocarcinoma; LNM: Lymph node metastasis.

Table 4 Comparison of clinicopathological characteristics and incidence of LNM based on the treatment strategy *n* (%)

	EMR (*n* = 195)	Surgery (*n* = 388)	*P* value
Depth of invasion			
sm-superficial (< 1000 μm)	61 (32)	52 (13)	< 0.0001
sm-deep (≥ 1000 μm)	134 (69)	336 (87)	
LVI	33 (17)	118 (30)	0.0006
PDA	18 (9)	73 (19)	0.0006
Positive rate of cut margin[1]	37 (19)	0 (0)	< 0.0001
Lateral	8 (22)	0 (0)	
Vertical	29 (78)	0 (0)	
Additional surgical operation	82 (42)	-	
LNM	9/82 (11.0)	47/388 (12.1)	0.79

[1]Positive and unknown cut margin.

LNM occurs in 6%-13% of patients with submucosal invasive CRC[11-15]. Therefore, radical surgery with LN dissection is recommended strongly in these cases. At present, EMR provides an endoscopic cure of early stage CRC when there is no risk of LNM. Advances in endoscopic instruments and techniques have increased the detection rates of early stage CRC and have expanded the indications for EMR[16].

In the past 20 years, many investigators have proposed the following histopathological criteria when considering additional surgery after EMR of submucosal cancers: massive submucosal invasion (≥ 1000 μm), and/or LVI, and/or PDA[17-22]. Among these factors, LVI and PDA are impossible to predict before resection. At this point, it is crucial to predict the vertical depth of invasion of submucosal cancers prior to EMR. In our center, we use routinely a magnifying colonoscope to decide on the adequate treatment of early stage CRC. Magnifying chromoendoscopy (MCE) is a standardized validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern), in a simple and rapid manner. We have reported previously the efficacy of MCE to diagnose an invasive pattern as a typical finding of sm-deep cancers, and have demonstrated that it provides a good correlation between pit pattern and tumor depth in flat and depressed CRC[23-27].

Many authors have reported that depressed and/or NPG type lesions are considered to have a high malignant potential, compared to the polypoid type lesions of similar

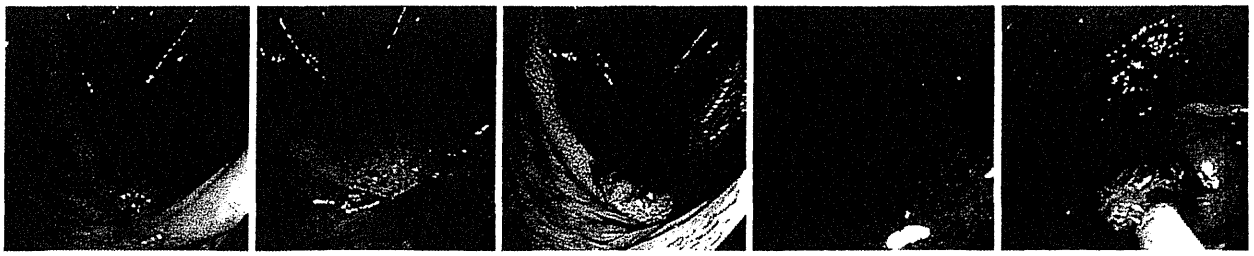

Figure 1 The lesion was located in the transverse colon. Endoscopic examination revealed a flat, elevated lesion with a central depression, which was macroscopically diagnosed as 0- II a+ II c. The high-magnification view revealed a typical type VI pit (invasive) pattern on the depressed margin. The final endoscopic diagnosis was a 0- II a+ II c type early colon cancer with submucosal deep invasion. However, patient strongly hoped EMR as an initial treatment. We performed EMR after injecting normal saline into the submucosa.

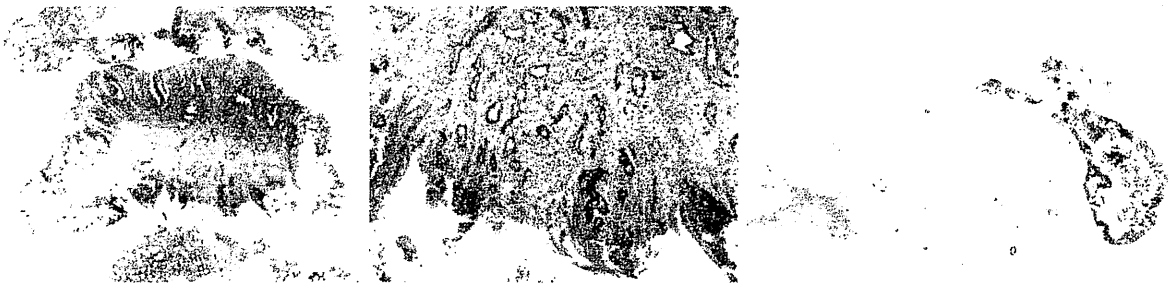

Figure 2 The final histopathological diagnosis was early invasive colon cancer, well-differentiated adenocarcinoma, sm-deep, NPG type, ly (-), v (-), cut end (+) (vertical margin positive). Since cancer was exposed in the vertical cut margin, additional surgical resection was performed and LNM was detected.

size[4,26-31]. Kurisu *et al*[20] have investigated the development and progression of EI-CRC. In that study, NPG lesions were significantly smaller in size (14.2 mm *vs* 24.2 mm) but showed deeper infiltration than PG types. They concluded that tumor development and the degree of invasion differed significantly between the two types of carcinoma. On the other hand, non-polypoid colorectal neoplasms (NP-CRNs) have been reported recently in the United States. Soetikno *et al*[31] have reported the prevalence of NP-CRNs in a veterans' hospital population. The overall prevalence of NP-CRNs and NP-CRNs with in situ or submucosal invasive carcinoma was 9.35% and 0.82%, respectively. They also concluded that NP-CRNs were more likely to contain carcinoma (OR: 9.78) than polypoid lesions, regardless of size. In the present study, small EI-CRCs $\leq$ 10 mm in diameter showed a significantly higher incidence of NPG type lesions than in the large lesion group ($P < 0.0001$). However, there was no significant difference in proportion of the macroscopic type between the groups ($P = 0.13$). Among the lesions diagnosed as Is type (sessile) in the small lesions group, 47% (14/30) were classified as NPG type histopathologically. From these results, we conclude that further investigation is required to confirm the growth pattern, especially for small sessile lesions diagnosed during colonoscopy.

In contrast, the rate of EMR as an initial treatment was 33% (195/583) in our study. In particular, it was significantly higher in the small lesion than the large lesion group (52% *vs* 29%, $P < 0.0001$). Among the 195 lesions removed by EMR as an initial treatment in both groups, 61 cases (32%) were sm-superficial cancers. On the other hand, there was no significant difference in the positive rate of cut margins between the small and large lesion groups (18% *vs* 20%). This result implies that EMR should not be performed readily for EI-CRC, from the viewpoint of no-touch isolation[32] and EMR complications. Intramucosal lesions (adenoma or intramucosal cancer) are usually well lifted by submucosal injection. In contrast, invasive cancer, especially sm-deep cancer, cannot be lifted because of the presence of submucosal fibrosis or desmoplastic reaction. Uno *et al*[33] have reported this phenomenon as the "non-lifting sign". Kobayashi *et al*[34] have reported, among 271 colorectal neoplastic lesions, that the non-lifting sign of deeper infiltration had a sensitivity of 61.5%, specificity of 98.4%, and accuracy of 94.8%. In contrast, endoscopic diagnosis had a sensitivity of 84.6%, specificity of 98.8%, and accuracy of 97.4%, with statistically significant differences in terms of sensitivity and accuracy. Furthermore, since submucosal injection varies depending on the expertise of the endoscopist, we consider that an endoscopic diagnosis is much more important and accurate when endoscopic resection is considered as the therapeutic option.

There are some limitations to this study. Firstly, this was a single-center study, and although the number of examined EI-CRCs was adequate, a multicenter analysis should be performed to clarify the clinical importance of small EI-CRCs. In addition, this study was carried out retrospectively between 1980 and 2004. In relation to endoscopic treatment for early CRC, endoscopic submucosal dissection (ESD) technique and Glycerol/Sodium hyaluronate as an injected solution during EMR has made progress recently[35,36]. In particular, ESD provides not only an *en bloc* large specimen but also

negative lateral and vertical cut margins.

In conclusion, with regard to the risk of LNM, small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions. Moreover, from the perspective of the concept of no-touch isolation, therapeutic cost, and complications during EMR, special attention must be paid when treating even small early stage lesions, especially NPG type lesions.

COMMENTS

Background

In general, small colorectal lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size.

Research frontiers

The aim of this retrospective study was to clarify the clinicopathological characteristics of small (≤ 10 mm) and large (> 10 mm) EI-CRCs.

Innovations and breakthroughs

A total of 583 EI-CRCs were evaluated retrospectively, with 120 (21%) small and 463 (79%) large lesions identified. With regard to the risk of lymph-node metastasis (LNM), small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions.

Peer review

The authors examined retrospectively a large group of patients with EI-CRCs gathered over 20 years in a national cancer hospital, and demonstrated that small EI-CRCs (≤ 10 mm) had the same aggressiveness and malignant potential as large cancers. Special attention must be paid when treating even small lesions.

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GASTROENTEROLOGY

Treatment strategy for laterally spreading tumors in Japan: Before and after the introduction of endoscopic submucosal dissection

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Key words
colonoscopy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), laterally spreading tumor.

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Abstract

Background and Aims: Laterally spreading tumors (LST) in the colorectum are considered good candidates for endoscopic resection (ER). Because LST-non-granular (NG) tumors show multifocal invasion into the submucosal layer, en bloc resection is necessary for adequate histopathological evaluation. Therefore, surgical resection has been recommended when a lesion is suspected to be an invasive cancer and too large to resect en bloc. The aim of the present study was to evaluate whether the introduction of colorectal ESD, which was developed for en bloc resection of early gastric cancers, could improve the en bloc resection rate of large LST-NG-type tumors and reduce the surgical resection rate.

Methods: Between January 1999 and December 2005, a total of 166 LST-NG-type tumors measuring ≥ 20 mm in 161 patients were included in this study. The en bloc resection rate and the surgical resection rate were historically compared between two periods, before and after the introduction of ESD.

Results: The en bloc resection rate for ER lesions was significantly higher in the latter period (35.0% [14/40] *vs* 76.5% [75/98]; $P < 0.001$), and the rate of surgery for adenomas and intramucosal or sm minute cancers was significantly lower in the latter period (20.0% [10/50] *vs* 1.1% [1/89]; $P < 0.001$).

Conclusions: The introduction of colonic ESD was able to change our treatment strategy for LST, improving the en bloc resection rate and reducing the surgical resection rate.

Introduction

Flat and depressed colorectal lesions have been well described in both Eastern and Western countries, and the importance of early detection and definitive endoscopic resection (ER) has been emphasized.[1–7] Laterally spreading tumors (LST) are typical flat lesions that extend laterally and circumferentially rather than vertically along the colonic wall, and are considered to be good candidates for ER.[8–10] LST have been subdivided into the granular type (LST-G type) and the non-granular type (LST-NG type).[5] It has been reported that the LST-G-type tumors show a low incidence of submucosal invasion and, when present, that submucosal invasion occurs under the largest nodule in the majority of such tumors. Therefore, piecemeal resection is acceptable for accurate histological assessment if the largest nodule can be included in one piece. However, LST-NG-type tumors have a higher incidence of submucosal invasion, which is often multifocal and, therefore, it is difficult to estimate the deepest point of invasion endoscopically. This means that piecemeal resection has a possibility to miss the deepest point of invasion or lymphovascular involvement if the lesion is divided at these significant points. Hence, en bloc resection is necessary for LST-NG-type tumors to evaluate the resected specimen adequately.[11,12] However, because of their larger size, en bloc resection of LST-NG-type tumors is sometimes difficult by conventional endoscopic mucosal resection (EMR), especially for lesions ≥ 20 mm in size, and such lesions are resected surgically even if they are adenoma or intramucosal cancer. Therefore, we have introduced the endoscopic submucosal dissection (ESD) technique to overcome such size limitations and to allow resection of large LST-NG-type tumors en bloc. ESD was originally developed to achieve en bloc resection of large early gastric cancers in 1995,[13] and its use as a standard therapy for gastric cancer is becoming widespread in Japan.[14–17] Although ESD has made it possible to achieve a high en bloc resection rate and has reduced the rate of recurrence of gastric cancer, it can only be used for colorectal or esophageal cancer in the hands of experienced endoscopists because of its technical difficulty and high complication rate.[14,18–21]

The aim of the present study was to evaluate whether the introduction of colorectal ESD could improve the en bloc resection rate of LST-NG-type tumors and increase LST-NG-type tumors cured by ER.

Methods

Patients

Between January 1999 and December 2005, a total of 526 colorectal LST measuring ≥ 20 mm in 507 patients were resected endoscopically or surgically at the National Cancer Center Hospital. The study period was divided into two periods, before and after the introduction of ESD in October 2003. The medical charts were collected and analyzed retrospectively. We defined LST as lesions with a low vertical axis extending laterally along the interior luminal wall, and subdivided them into two subtypes based on endoscopic findings. The granular type (LST-G type) was defined as a lesion with even or uneven nodules on the surface, and the non-granular type (LST-NG type) as a lesion with a smooth surface (Fig. 1).

Patients who had advanced colorectal cancer, familial adenomatous polyposis or inflammatory bowel disease were excluded from this study. Finally, 166 LST-NG-type tumors measuring ≥ 20 mm in 161 patients were included, and the rate of LST-NG-type tumors which were resected en bloc or cured by ER were historically compared between the two periods before and after the introduction of ESD.

Endoscopic assessment for diagnosis of invasion depth

When a LST lesion was identified, its surface was washed with water, and 0.4% indigo carmine was sprayed directly through the accessory channel of the scope. Lesions with fold convergence, an expansive appearance, an irregular surface contour, a demarcated depressed area or a large nodule (≥ 1 cm) were regarded as deeply infiltrated submucosal cancer.[12,22] Pit pattern analysis using high-magnification colonoscopy (CF-200Z, CF-240ZI, PCF-240ZI and CF-H260AZI; Olympus Optical Co., Tokyo, Japan) was added to determine the invasion depth in all cases.[23–25]

Therapeutic strategy for LST-NG-type tumors

Colorectal ESD was officially introduced to the National Cancer Center Hospital in October 2003, and it changed our therapeutic strategy for LST-NG-type tumors ≥ 20 mm in diameter.

In the period before the introduction of colorectal ESD, EMR using a snare with submucosal injection was the first choice. Because LST-NG-type tumors sometimes invade the submucosal layer multifocally, we tried to resect the lesions en bloc for accurate histological assessment.[11,12] Therefore, we recommended surgical resection when a lesion was considered a possible invasive cancer and was too large, especially exceeding 30 mm in size, or showing non-lifting sign positivity, defined as a case in which the surrounding mucosa, but not the lesion, was elevated by submucosal injection.[22]

In the latter period, we started to carried out ESD for lesions ≥ 20 mm in size or lesions not lifted by submucosal injection to obtain specimens suitable for histological assessment. However, we also carried out conventional EMR and endoscopic piecemeal mucosal resection (EPMR) for selected lesions which were relatively small and well lifted by submucosal injection.

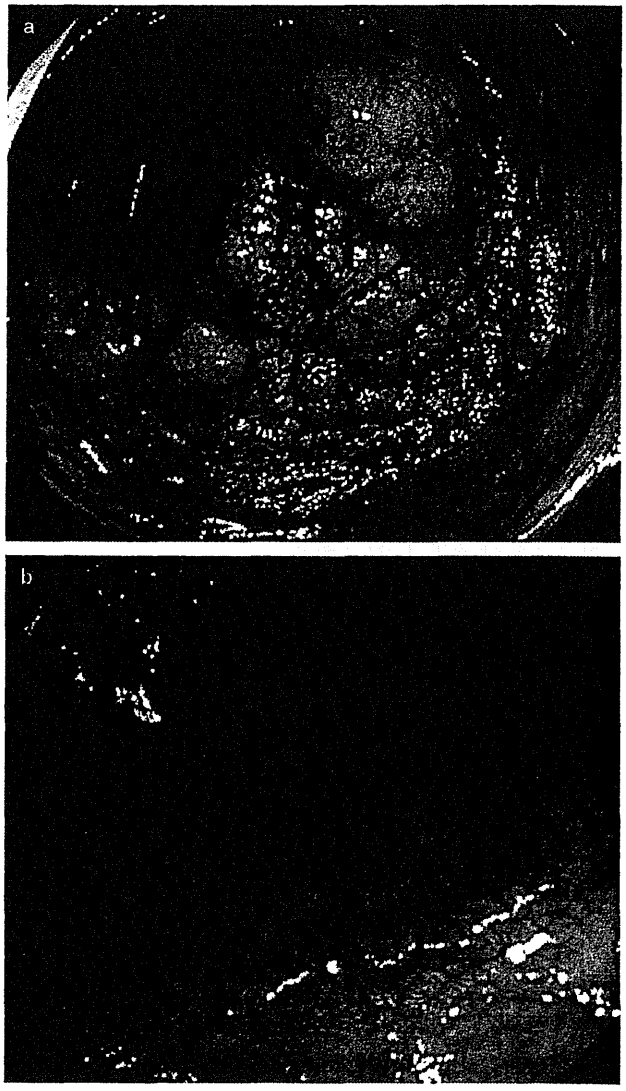

Figure 1 (a) Laterally spreading tumors granular type (LST-G): a lesion with even or uneven nodules on the surface. (b) LST-non-granular type (LST-NG): a lesion with a smooth surface.

Adenomas, intramucosal cancers and submucosal minute invasion cancers (submucosal invasion but less than 1 mm below the muscularis mucosae[26,27]) without lymphovascular involvement or a poorly differentiated component are considered to rarely have lymph node metastasis, and therefore we judged such cases to have been curatively resected and did not recommend additional therapy.[28] Lateral cut-end-positive status was not considered to assess the curability; therefore, some cases were judged as curative even in the EPMR cases.

EMR and ESD procedures

Endoscopic mucosal resection was carried out using the inject and cut technique. Normal saline or glycerol (Glyceol [10% glycerol and 5% fructose in normal saline solution]; Chugai Pharmaceutical Co., Tokyo, Japan) was injected into the submucosa of the lesion with a 23-gauge needle,[29] and then the lifted lesion was resected using an oval snare (SD-210L-25; Olympus). In this study, we distinguished EMR from EPMR according to the number of resected specimens: single or multiple.

ESD was carried out using a monopolar needle knife, a flex knife (Olympus) and a bipolar needle knife (B-knife) (XEMEX Co, Tokyo, Japan) with submucosal injection of sodium hyaluronate solution.[14] Other devices, such as an insulation-tipped knife (IT knife; Olympus), were used to cut the submucosal layer if necessary.[18] Although several lesions were finally resected using a snare after circumferential incision, they were regarded as ESD. Sedation using midazolam and carbon dioxide insufflation was routinely used during ESD.[30]

Both procedures were basically carried out in the inpatient setting, and length of stay was 3 or 4 days for E(P)MR and 5 days for ESD, if the complication did not occur.

Histopathological analysis

All resected specimens were fixed in 10% buffered formalin solution and stained with hematoxylin and eosin. Histopathological diagnosis was based on the Japanese classification of cancer of the colon and rectum, and submucosal cancers are subclassified into minute and deep (≥ 1 mm from the muscularis mucosae to the deepest point of invasion).[27]

Statistical analysis

All values are reported as mean ± standard deviation when applicable. Comparisons were made with the χ^2, Fisher's exact and *t*-tests. Differences at $P < 0.05$ were considered to be statistically significant. All calculations were conducted using the SPSS statistical software package (SPSS, Chicago, IL, USA).

Results

Clinicopathological characteristics of LST in each period are shown in Table 1. There were no significant differences between the initial and latter periods except for the incidence of LST-NG-type tumors (25.7% [63/245] *vs* 36.7% [103/281]; $P = 0.007$).

Initial treatment for LST-NG-type tumors in the initial period

In the initial period, 63 LST-NG-type tumors measuring ≥ 20 mm were resected endoscopically or surgically in our hospital. Forty of these lesions were carried out ER, and 14 (35.0%) lesions were resected en bloc (Table 2). All of the 40 lesions resected endoscopically were judged curative on the basis of histopathology, and no additional treatment such as surgery or radiation therapy was carried out.

Although 50 of all 63 LST-NG-type tumors were adenomas and intramucosal or sm minute cancers which were regarded as the curable candidates for ER, 10 (20.0%) were resected surgically. The reasons for selecting surgical resection were the presence of non-lifting sign and difficulty with endoscopic resection in three lesions, a size excessive for ER in four lesions, and possible presence of invasive cancer and likely indication for definitive en bloc resection in three lesions.

Initial treatment for LST-NG-type tumors in the latter period in comparison with the initial period

In the latter period, 103 LST-NG-type tumors ≥ 20 mm were resected endoscopically or surgically. Ninety-eight of these lesions were carried out ER, and 75 (76.5%) lesions were resected en bloc (Table 3). Ten of 98 (10.2%) lesions resected endoscopically were

Table 1 Clinicopathological characteristics of the lesions

	Initial period	Latter period
No. LST ≥ 20 mm	245	281
No. LST-NG type ≥ 20 mm	63 (25.7%)	103 (36.7%)
Size of LST-NG type ≥ 20 mm (mean[SD])	25.3 (6.2)	25.4 (7.5)
Location		
Proximal colon	46 (73.0%)	67 (65.0%)
Distal colon	10 (15.9%)	24 (23.3%)
Rectum	7 (11.1%)	12 (11.7%)
Histopathology		
Adenoma or m-Ca	40 (63.5%)	76 (73.8%)
sm-minute-Ca	10 (15.9%)	13 (12.6%)
sm-deep-Ca	13 (20.6%)	14 (13.6%)

m-Ca, intramucosal cancer; sm-deep-Ca, submucosal deep invasion cancer; sm-minute-Ca, cancer with submucosal invasion but less than 1 mm below the muscularis mucosae.

Table 2 Initial treatment for LST-NG type ≥ 20 mm in the initial period

	EMR		ESD		Surgery
	En bloc	Piecemeal	En bloc	Piecemeal	
Group A ($n = 50$)	14 (28%)	26 (52%)	–	–	10 (20%)
Group B ($n = 13$)	0	0	–	–	13 (100%)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Group A, adenomas, m-Ca and sm-minute-Ca; Group B, sm-deep-Ca.

Table 3 Initial treatment for LST-NG type ≥ 20 mm in the latter period

	EMR		ESD		Surgery
	En bloc	Piecemeal	En bloc	Piecemeal	
Group A ($n = 89$)	18 (20%)	17 (19%)	47 (53%)	6 (7%)	1 (1%)
Group B ($n = 14$)	1 (7%)	0	9 (64%)	0	4 (29%)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Group A, adenomas, m-Ca and sm-minute-Ca; Group B, sm-deep-Ca.

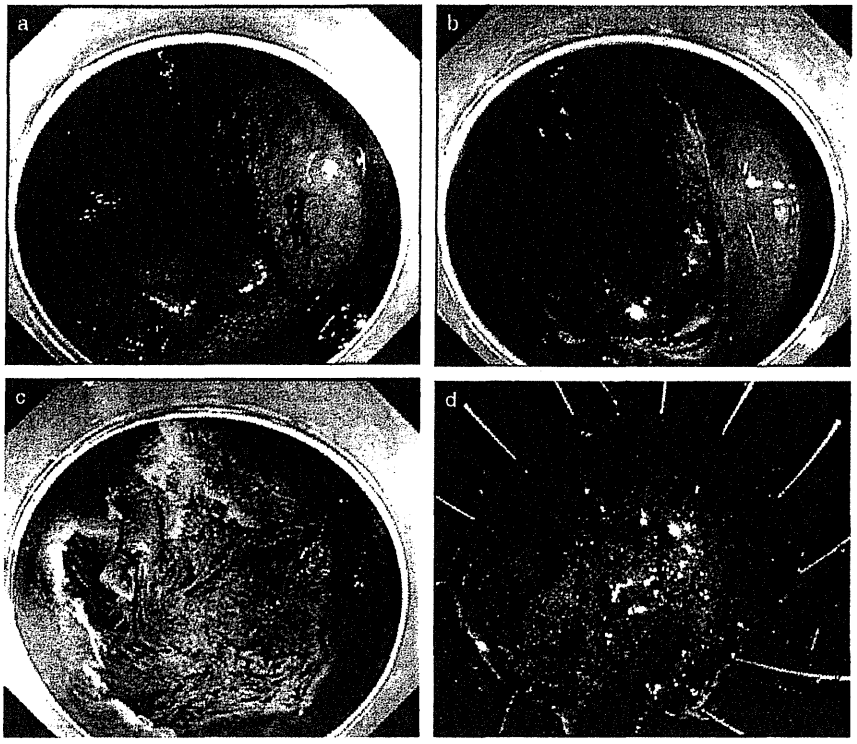

Figure 2 Endoscopic submucosal dissection (ESD) case treated in the latter period: (a) Laterally spreading tumors non-granular type (LST-NG) lesion, approximately 30 mm in size, was located in the transverse colon. Although the lesion showed non-lifting sign positivity, it was diagnosed as intramucosal cancer. (b,c) Circumferential incision in the mucosa was made by a needle knife, and the sm layer was cut by an IT knife. (d) Resected specimen revealed sm1 cancer, and the resected margin was histopathologically free of tumor.

diagnosed pathologically as sm deep invasion, and additional surgery was recommended.

ESD was carried out for 62 lesions, and 56 lesions were resected en bloc (Fig. 2). The en bloc resection rate of ESD was 90.3%.

Only one of 89 (1.1%) curable candidates for ER was resected surgically, because ESD for this large lesion was judged difficult at the time immediately after introduction of this technique.

The en bloc resection rate of the ER lesion in the latter period was significantly higher than that in the initial period (76.5% *vs* 35.0%; $P < 0.001$), and the rate of surgery for the curable candidates for ER (adenoma and intramucosal or sm minute cancers) was significantly lower in the latter period (1.1% *vs* 20.0%; $P < 0.001$) (Table 4). In contrast, the rate of non-curative ER that was detected histopathologically as sm deep invasion was significantly higher in the latter period (10.2% *vs* 0%; $P = 0.036$).

Complications of ER

In the initial period, no perforation and late bleeding occurred during or immediately after ER. However, three cases of perforation during the ER procedure occurred in the latter period. All three of these were ESD cases (4.8% of 62 ESD cases), and were manageable conservatively with antibiotic therapy and fasting after endoscopic closure using endoclips.

Discussion

We have shown that, in our institution, the introduction of colorectal ESD has dramatically improved the en bloc resection rate of LST-NG-type tumors and increased LST-NG-type tumors cured by ER. It has overcome two difficulties with endoscopic therapy for such tumors. One is the size limitation of en bloc resection, and the other is positivity for the non-lifting sign after submucosal injection. Generally, lesions ≥ 20 mm in size are difficult to resect en bloc by conventional EMR, whereas ESD has no size limitation if the operator is sufficiently experienced. In the initial period before the introduction of ESD, 52% of adenomas and intramucosal or sm minute cancers were treated by EPMR, and this could lead to insufficient histological assessment and a high likelihood of local recurrence.[10,23] Since its introduction, ESD has provided specimens that are suitable for accurate histological assessment, and it is also predicted to lead to the reduction of local recurrence.

Table 4 Comparison between the initial and latter periods

	Initial period	Latter period	*P*
En bloc resection for EMR/ESD lesions	35.0% (14/40)	76.5% (75/98)	< 0.001[†]
Surgical resection for Group A	20.0% (10/50)	1.1% (1/89)	< 0.001[†]
Non-curative EMR/ESD for Group B	0% (0/40)	10.2 (10/98)	0.036[‡]

[†]χ^2-test.
[‡]Fisher's exact test.
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Group A, adenomas, m-Ca and sm-minute-Ca; Group B, sm-deep-Ca.

In contrast, en bloc resection using the ESD technique is sometimes difficult even for the experienced endoscopist. We previously reported that perforation occurred in 10 of 200 patients and median operation time of colorectal ESD was 90 min.[31] In this series, the en bloc resection rate of ESD was 90.3%, in line with other reports by Japanese experts,[19–21] although the range of those reported rates was not narrow (80.0–98.4%). In addition, the perforation rate of ESD was higher than that for conventional EMR. The rate of perforation in our series was 4.8%, and thus compatible with other reports (1.4–14.3%).[19–21,32] Although all patients with perforation were manageable conservatively,[33] the potential for severe complications, such as peritonitis and pneumoscrotum,[32,34] exists. In order to establish colorectal ESD as a standard therapy, a number of negative factors need to be overcome, such as the risk of perforation, the long procedure time and technical difficulty.

Recently, the first series of colorectal ESD from Western countries was published by Repici *et al.*[35] Their ESD method differed from ours in some respects; they did not use sodium hyaluronate solution for submucosal injection and routinely performed snaring, and their en bloc resection rate (55.1%) was considerably lower than that in some series reported from Japan.

The rate of non-curative ER followed by additional surgery in the latter period was significantly higher than that in the initial period. This may have been due to the fact that we tended to underestimate the invasion depth of LST after the introduction of ESD, because we intended to carry out EMR or ESD for all curable candidates for ER. When we were unable to judge the invasion depth of the lesion with confidence, we recommended ESD not only for treatment but to obtain an adequate specimen for histopathological diagnosis. After ESD, we were able to decide whether additional surgery was necessary. An additional explanation is that more accurate histopathological evaluation using en bloc specimens revealed the 'true' invasion depth of the lesions. Histopathological diagnosis using a multi-fragment specimen may result in underestimation of the invasion depth. The introduction of ESD overcame the limitation of lesion size and changed not only our treatment strategy but also the efficiency of our endoscopic and histopathological diagnosis.

Our study had two limitations. One is that the comparison was a historical one between two different periods. Therefore, some factors, such as the development of devices and improvement of the operator's technique, might have influenced our results. For example, when considering lesion characteristics, the incidence of LST-NG-type tumors was significantly higher in the latter period. One possible reason may have been the increase in the number of patients referred from private physicians who knew that ESD had been introduced at our hospital. In Japan, colorectal ESD is not as widespread as gastric ESD, and is available at only a few academic centers.[14,19–21,31] Another limitation of our study is that follow up was not evaluated. Although high en bloc resection rate correlates to low local recurrence rate,[36] long-term outcome date, including not only local recurrence but additional treatment, is necessary to prove the superiority of ESD. Moreover, comparison between ESD and laparoscopic colectomy would help to clarify the effectiveness of ESD in terms of outcome, complication and cost.

In conclusion, we have shown that the introduction of colorectal ESD has changed our treatment strategy for LST, achieving an improvement of the en bloc resection rate and a reduction of the surgical resection rate. In order to establish colorectal ESD as a standard therapy for LST-NG-type tumors ≥ 20 mm in size, efforts should be made to overcome its technical difficulty and high complication rate.

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GASTROENTEROLOGY

Evaluation of visualization of squamous cell carcinoma of esophagus and pharynx using an autofluorescence imaging videoendoscope system

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Key words
autofluorescence imaging, esophagus, pharynx, squamous cell carcinoma, white light endoscopy.

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Abstract

Background and Aim: An autofluorescence imaging (AFI) videoendoscope system produces pseudo-color images combining autofluorescence and green reflectance, with the utility of this system previously confirmed for the diagnosis of bronchial squamous cell carcinoma (SCC). Our aim was to evaluate visualization of esophageal and pharyngeal SCC comparing AFI with white light endoscopy (WLE).

Methods: Thirty-two patients with superficial esophageal SCC and 11 patients with superficial pharyngeal SCC diagnosed in other hospitals were enrolled in this prospective study. We observed the esophagus and pharynx with WLE followed by AFI and took both WLE and AFI images of the esophageal and pharyngeal SCC. Three experienced endoscopists subsequently evaluated the visualization quality of images from both systems on a three-tier scale: visible, illegible and invisible.

Results: A total of 39 superficial esophageal SCC were diagnosed with 20, 11 and eight lesions classified as visible, illegible and invisible, respectively, by WLE compared to 31, three and five lesions, respectively, using AFI. Using AFI, 79% of superficial esophageal SCC lesions were visible, compared to only 51% with WLE ($P < 0.05$). In addition, 12 superficial pharyngeal SCC were diagnosed with four, five and three lesions considered as visible, illegible and invisible, respectively, using WLE in contrast to nine, three and 0 lesions, respectively, by AFI. Thus, using AFI, 75% of superficial pharyngeal SCC lesions were visible compared with only 33% with WLE ($P = 0.13$).

Conclusion: The AFI system appears to be more useful than WLE for early diagnosis of SCC of the esophagus and pharynx.

Introduction

Esophageal squamous cell carcinoma (SCC) is devastating because of its aggressive clinical course and high mortality rate. However, the prognosis of esophageal SCC has been improving recently because of earlier detection, which increases the possibility of curative treatments such as esophagectomy with three-field lymph-node dissection[1,2] and endoscopic resection (ER).[3,4] In particular, the prognosis of patients treated for carcinomas confined within the intraepithelium or proper mucosal layer has been excellent with reported 5-year survival rates ranging from 85% to 100%.[5,6]

In order to detect esophageal SCC at an early stage, Lugol chromoendoscopy (LC) has been widely used in high-risk populations, resulting in a dramatic increase in the number of superficial SCC detected.[7–9] Adverse effects such as retrosternal pain and discomfort, however, often occur because of the mucosal irritation caused by Lugol staining.[10–14]

It is well known that patients with esophageal SCC often have synchronous and metachronous pharyngeal SCC.[15] The long-term outcome of patients after ER for esophageal SCC has been influenced to a greater extent by the existence of a second malignancy, particularly pharyngeal cancer, in addition to the initial esophageal cancer.[15,16] Few effective screening and follow-up strategies have been developed, however, and pharyngeal cancer is usually diagnosed at an advanced stage with a resultant poor prognosis.[17–22] In addition, we cannot carry out LC for pharyngeal SCC because it causes severe mucosal irritation leading to patient pain and discomfort and can even result in airway aspiration.

Therefore, in order to detect not only esophageal SCC, but also pharyngeal SCC at an earlier stage without Lugol staining, a new effective endoscopic technique needs to be developed. The autofluorescence imaging (AFI) videoendoscope system (Olympus Medical Systems Corp., Tokyo, Japan) is one of the most recently developed, non-invasive optical techniques.[23–27] It produces real-time, pseudo-color images that combine autofluorescence and

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.

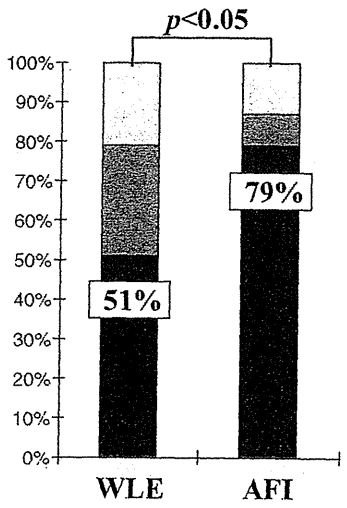

Figure 1 Visualization of superficial esophageal squamous cell carcinoma (SCC) by autofluorescence imaging (AFI) and white light endoscopy (WLE). Percentage of visible lesions was 79% with AFI and 51% with WLE ($P < 0.05$). P value was calculated using McNemar's test. ☐ Invisible; ▨ Illegible; ■ Visible.

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

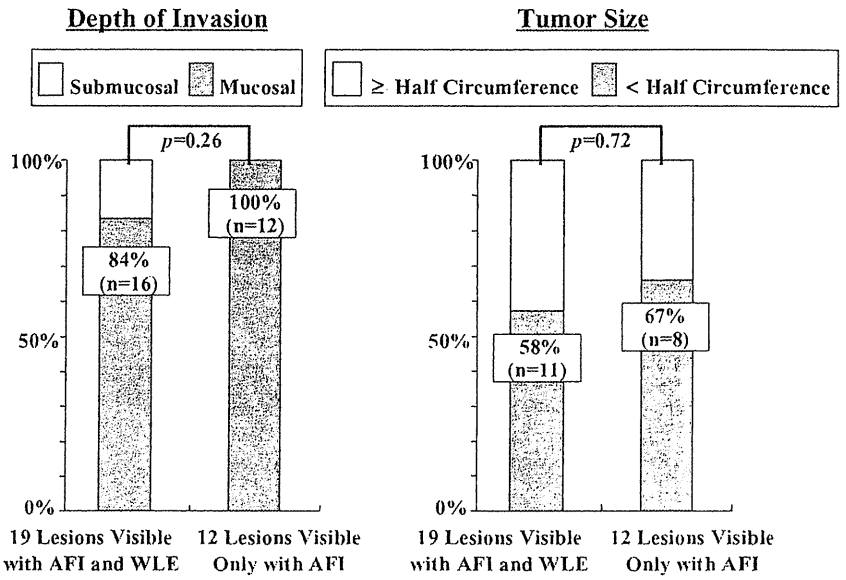

Figure 2 Clinicopathological features of lesions visible by autofluorescence imaging (AFI) only compared with lesions visible by both white light endoscopy (WLE) and AFI. *P* values were calculated using Fisher's test.

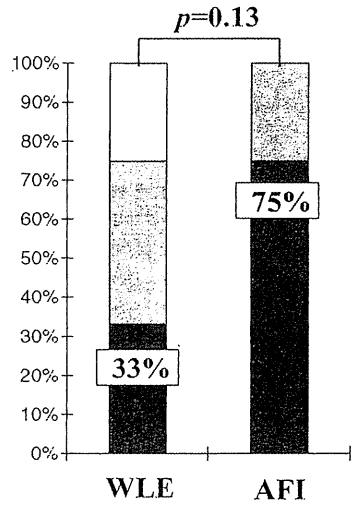

Figure 3 Visualization of superficial pharyngeal squamous cell carcinoma (SCC) by autofluorescence imaging (AFI) and white light endoscopy (WLE). Percentage of visible lesions was 75% with AFI and 33% with WLE ($P = 0.13$). *P* value was calculated using McNemar's test. ☐ Invisible; ☐ Illegible; ■ Visible.

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

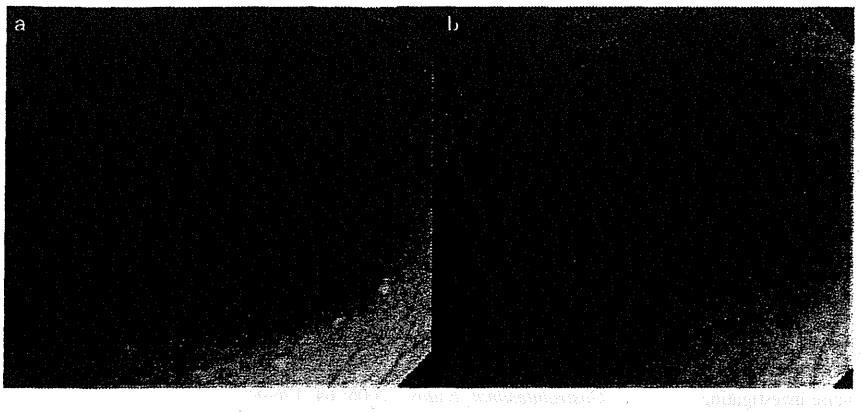

Figure 4 Squamous cell carcinoma (SCC) in the middle thoracic esophagus (mucosal invasion: Category 4.2. of the Vienna classification; flat type; less than half circumference). (a) Conventional white light endoscopy (WLE) showed a slightly reddish area that was evaluated as being illegible. (b) Autofluorescence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

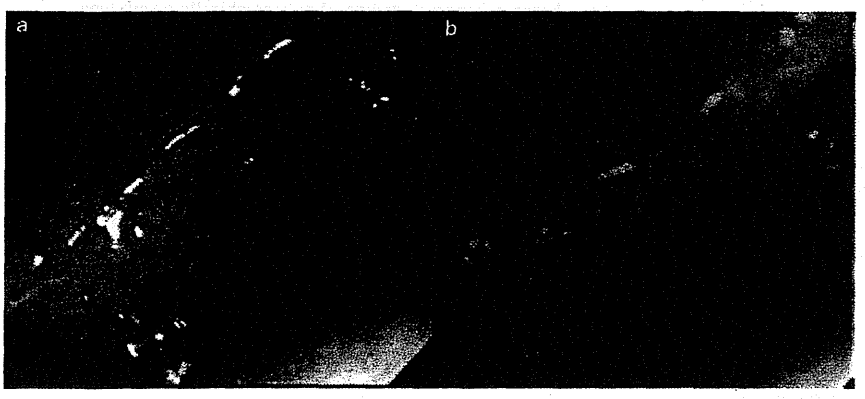

Figure 5 Squamous cell carcinoma (SCC) in situ of the right hypopharynx. (a) Conventional white light endoscopy (WLE) showed a slightly elevated area that was evaluated as being illegible. (b) Autofluorescence imaging (AFI) endoscopy showed a clearly demarcated area magenta in color that was evaluated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

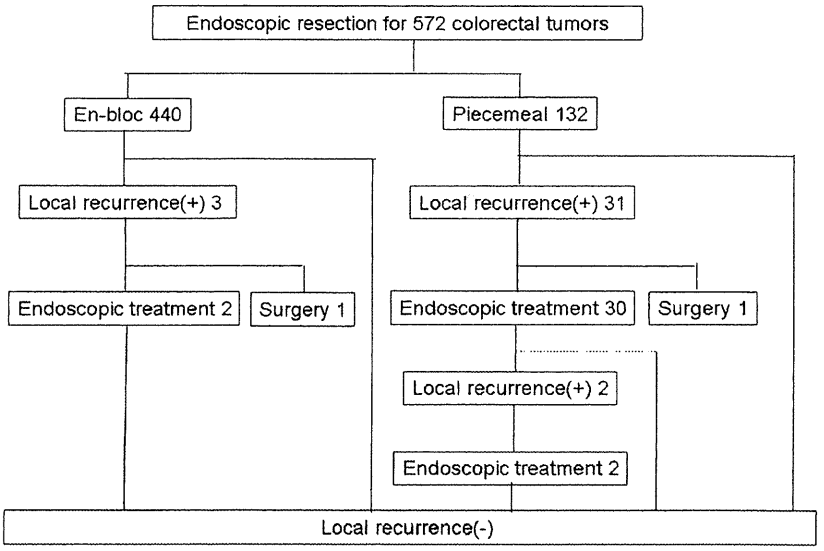

Fig. 1 A chart of 572 colorectal tumors followed up after endoscopic resection

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.

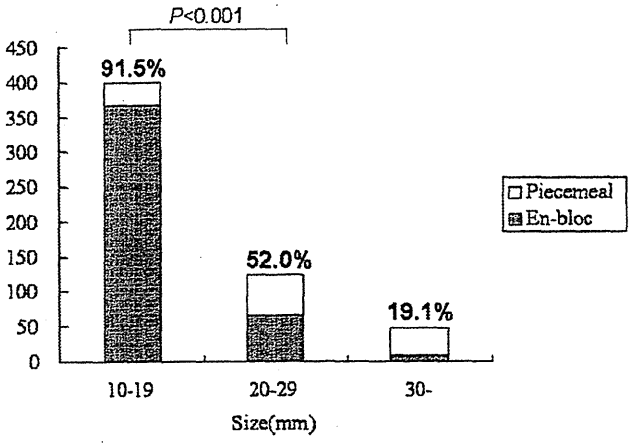

Fig. 2 En-bloc resection rates by lesion size

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)

*$P<0.001$