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ORIGINAL ARTICLE

Validation of Fujinon intelligent chromoendoscopy with high definition endoscopes in colonoscopy

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Abstract

AIM: To validate high definition endoscopes with Fujinon intelligent chromoendoscopy (FICE) in colonoscopy.

METHODS: The image quality of normal white light endoscopy (WLE), that of the 10 available FICE filters and that of a gold standard (0.2% indigo carmine dye) were compared.

RESULTS: FICE-filter 4 [red, green, and blue (RGB) wavelengths of 520, 500, and 405 nm, respectively] provided the best images for evaluating the vascular pattern compared to white light. The mucosal surface was best assessed using filter 4. However, the views obtained were not rated significantly better than those observed with white light. The "gold standard", indigo carmine (IC) dye, was found to be superior to both white light and filter 4. Filter 6 (RGB wavelengths of 580, 520, and 460 nm, respectively) allowed for exploration of the IC-stained mucosa. When assessing mucosal polyps, both FICE with magnification, and magnification following dye spraying were superior to the same techniques without magnification and to white light imaging. In the presence of suboptimal bowel preparation, observation with the FICE mode was possible, and endoscopists considered it to be superior to observation with white light.

CONCLUSION: FICE-filter 4 with magnification improves the image quality of the colonic vascular patterns obtained with WLE.

Key words: Colonoscopy; Computed virtual chromoendoscopy; Fujinon intelligent chromoendoscopy; Magnifying colonoscopy; Polyp diagnosis

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INTRODUCTION

Chromoendoscopy has been proven to be a valuable tool for the study of colorectal neoplasia. Indigo carmine (IC) can be used with conventional endoscopy[1] or with magnifying colonoscopy[2-5].

Endoscopy manufacturers have developed artificial image enhancements, including "virtual chromoendoscopy", as a quicker and less messy alternative to dye spraying.

The Olympus narrow band imaging (NBI) system employs a narrow band light to increase the contrast. This has been shown to enhance the views, and it provides similar diagnostic accuracy to chromoendoscopy[4-6]. Computed virtual chromoendoscopy (Fujinon intelligent chromoendoscopy, FICE) was subsequently developed[7]; with this technique, the wavelength does not change. Instead, the endoscopy processor reconstructs the image and displays what the mucosa would look like if illuminated using a certain wavelength. FICE has 10 pre-programmed settings, some of which have been tested in the upper gastrointestinal tract[7] and in Barrett's mucosa[8]. In a third preliminary study, we used one of the FICE settings to compare detection of colonic polyps with white light endoscopy (WLE)[9]. However, this study did not compare the views obtained using different FICE settings and did not comment on the capabilities in the presence of suboptimal bowel cleansing or after the application of indigo carmine dye. Our study aimed to: (1) systematically compare the 10 pre-set FICE settings with normal white light and indigo carmine dye in terms of their ability to enhance views of normal mucosa and polyps, (2) assess FICE in the presence of suboptimal bowel preparation, (3) determine whether poor bowel preparation markedly degrades the capabilities of "virtual chromoendoscopy" systems[10].

MATERIALS AND METHODS

High definition magnification colonoscopes (EC-590ZW/M), and the Fujinon EPX-4400 medical video endoscope system were used in the study.

The quality of mucosal and vascular pattern views

In study one, 560 areas of normal colonic mucosa in 10 patients were observed in real time by two experienced endoscopists (Parra-Blanco A and González N), who assessed the quality of mucosal and vascular pattern views. The views were obtained with white light, 0.5% indigo carmine dye, and the different FICE settings (Table 1) both with and without magnification (× 100). The quality of the mucosal views was scored according to the following scale: 0 (poor), 1 (fair), 2 (good), and 3 (excellent). Each endoscopist was blinded to the other endoscopist's assessments.

Diagnostic accuracy

In study two, 114 pictures were taken of 19 mucosal polyps (14 tubular adenomas, 4 hyperplastic polyps, and 1 normal mucosa). The pictures were obtained with white light, 0.5% indigo carmine (IC) dye, and the highest rated FICE settings according to study one (FICE setting 4), both with and without magnification (× 100). Polyp size and shape were estimated by comparison with closed biopsy forceps (Radial Jaw 3, Boston Scientific Corporation). The mean size of the polyps was 2.8 mm (range 1-5 mm). Figure 1 illustrates the sequence of images corresponding to one of the cases.

A panel of 5 fully trained endoscopists was asked to classify each lesion into one of the following categories: benign (for types I and II crypt patterns), neoplastic (types III and IV crypts), and invasive (type V pattern)[11]. For the assessment of the capillary pattern, Sano's classification was used[10]. The panel members were asked to grade the degree of certainty in the prediction according to the following scale: (1) very uncertain, (2) uncertain, (3) reasonably certain, (4) absolutely certain.

Table 1 Spectral specification of each FICE filter estimation set with assignments to the color channels

	Blue (B) channel	Green (G) channel	Red (R) channel
0	500	445	415
1	500	470	420
2	550	500	470
3	540	490	420
4	520	500	405
5	500	480	420
6	580	520	460
7	520	450	400
8	540	415	415
9	550	500	400

FICE: Fujinon intelligent chromoendoscopy.

The feasibility of FICE colonoscopy in the presence of suboptimal bowel preparation

In study three, the feasibility of FICE colonoscopy in the presence of suboptimal bowel preparation was evaluated. Images from 17 colonic areas with small or moderate amounts of liquid or solid stools were recorded, both with the conventional view and with FICE setting 4. The panel of endoscopists rated: (a) the image quality of FICE setting 4 as superior, equal, or inferior to that of WLE; (b) the ability of FICE-4 to trace the fecal contents as compared to WLE (superior, equal, or inferior).

The ability of FICE to trace the polyp margin and recognize the irregularities of the polyp surface

In study four, the ability to trace the polyp margin and recognize the irregularities of the polyp surface was compared between FICE setting 4, conventional endoscopy, and IC. Ninety images corresponding to 15 polyps were obtained and presented to the panel. The panel rated the ability of FICE to trace the margin and surface as superior, equal, or inferior to that of the other techniques.

The feasibility of FICE colonoscopy in IC-stained mucosa

In study five, the feasibility of FICE colonoscopy in IC-stained mucosa was tested. In a preliminary phase, both endoscopists participating in study one had determined that colonoscopy with FICE setting 6 was the most adequate to observe the IC-stained mucosa, with a global image quality that was at least as good as with WLE. Then, 48 images corresponding to 12 polyps were taken, including views with IC and with IC plus FICE setting 6. The members of the panel were asked to rate the ability of FICE-6 plus IC to trace the margin and surface of the polyps as superior, equal, or inferior to the performance of IC.

The study was approved by the Research Ethics Committee of Hospital Universitario de Canarias, and a signed informed consent document was obtained from all participating patients.

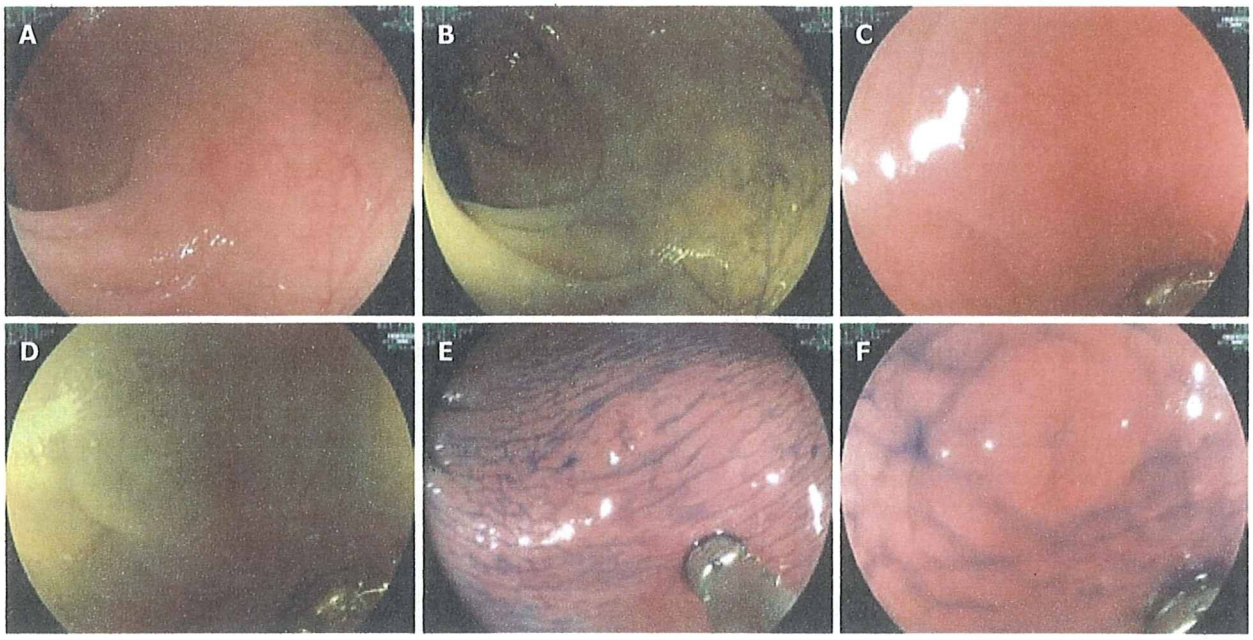

Figure 1 Presentation of a sequence of images for the different diagnostic modalities corresponding to a case included in study two (histopathological diagnosis: tubular adenoma with mild dysplasia). A: Circumscribed erythema with loss of vascular pattern, which can be difficult to detect; B: Observation with Fujinon intelligent chromoendoscopy (FICE) 4. Note that the innominate grooves can be seen in the normal surrounding mucosa; C: Observation under 0.5% indigo carmine (IC), which reveals a 0-IIc depressed lesion 3 mm in size; D: High magnification view, showing vascular pattern type Sano II; E: Same magnification image observed under FICE 4, which provides enhanced vascular contrast; F: Under 0.5% IC plus magnification, the depression and the vascular patterns are evident.

Statistical analysis

No sample sizes were calculated, as this was a pilot study, and no data were available when the study was performed regarding colonoscopy with FICE.

Categorical variables are expressed with frequencies and percentages. Proportions were compared using the χ^2 test or Fisher's exact test whenever required. Means were compared with the unpaired Student's t test, and means and standard deviations (SD) are reported.

For the same endoscopist, comparisons between techniques on quality of the images were carried out using the Wilcoxon test.

Calculated $P < 0.05$ values were considered to indicate statistical significance.

RESULTS

Normal mucosa and vascular pattern

The assessment of FICE settings is shown in Figure 2. In evaluating the normal mucosa, only filter 4 was scored by both assessors as superior to conventional WLE (Table 2). The gold standard for mucosal observation, indigo carmine, was regarded as far superior to any FICE setting according to all assessors. In fact, the normal colonic innominate grooves could only be seen with the aid of dye spraying.

In evaluating the vascular pattern, FICE setting 4 (corresponding to RGB wavelengths 520, 500, and 405 nm, respectively) and FICE setting 2 were found to provide the best image quality. When mucosal and vascular pattern ratings were taken together, FICE setting 4 was considered the best by both assessors.

Endoscopic diagnosis

Study two (Figure 1): The histological predictions for the five participants are indicated in Table 3. In general, the diagnostic accuracy was related to the level of experience of the endoscopists in the panel. IC plus magnification, FICE setting 4 plus magnification, and IC without magnification were the most accurate techniques. The following differences among the techniques were statistically significant (Table 3): Conventional *vs* IC-Magnification: $P = 0.002$; Conventional-Magnification *vs* FICE-Magnification: $P = 0.02$; Conventional *vs* IC: $P = 0.02$; Conventional *vs* IC-M: $P = 0.001$; FICE *vs* FICE-Magnification: $P = 0.048$; FICE *vs* IC: $P = 0.048$; FICE *vs* IC-Magnification: $P = 0.004$.

The following differences among endoscopists were statistically significant (Table 3): Endoscopist 2 *vs* 4: $P = 0.003$; Endoscopist 2 *vs* 5: $P = 0.006$; Endoscopist 3 *vs* 4: $P < 0.001$; Endoscopist 3 *vs* 5: $P = 0.002$.

The endoscopists' level of confidence in the endoscopic diagnosis was increased with these techniques compared to making the diagnosis with white light only (Figure 3).

FICE and mucosa, polyps

In study three, FICE was particularly useful in evaluating the mucosa in the presence of suboptimal bowel preparation, and the panel found that in that situation, the view was generally better with FICE setting 4 than with WLE (Table 4). Small solid feces showed up as a vivid yellow color and transparent liquid as a darker yellow color; its distinction from colonic mucosa could be clearly seen (Figure 4).

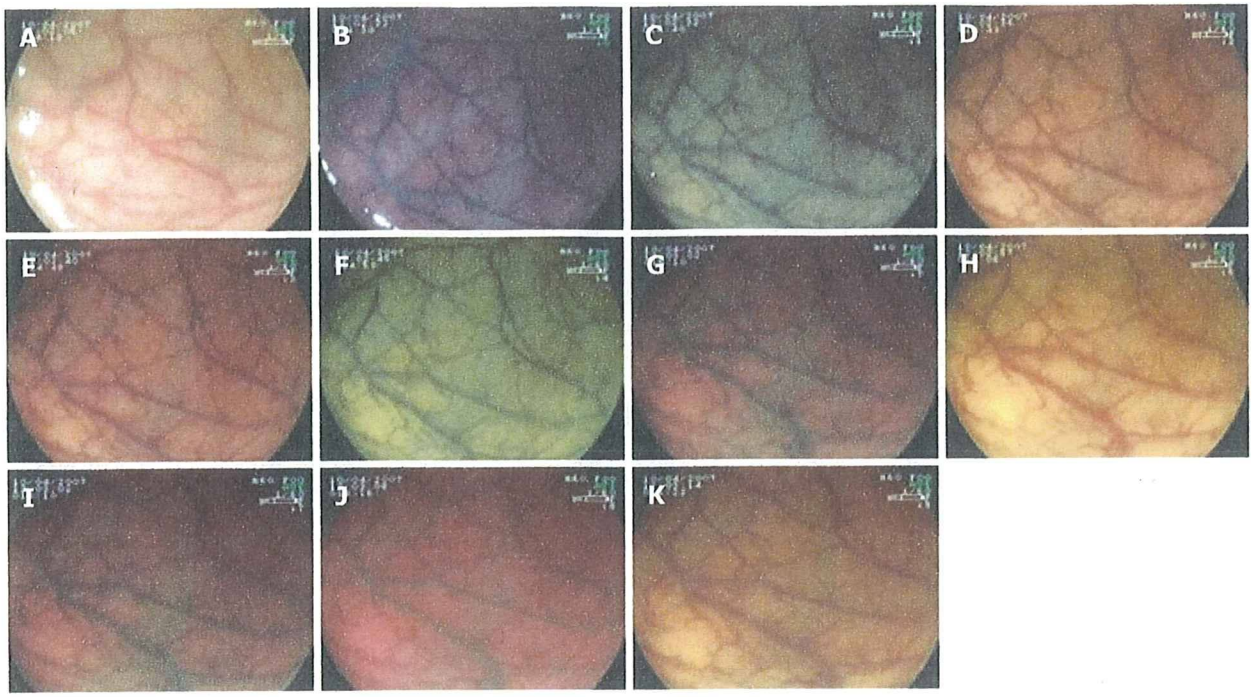

Figure 2 Images corresponding to the first study examining the evaluation of the vascular pattern without magnification. A: Plain endoscopy; B: Filter 0; C: Filter 1; D: Filter 2; E: Filter 3; F: Filter 4; G: Filter 5; H: Filter 6; I: Filter 7; J: Filter 8; K: Filter 9.

Table 2 Individual scores for mucosal and vascular patterns with conventional imaging, indigo carmine, and FICE with each of the 10 filters

Type of endoscopy	Endoscopist 1				Endoscopist 2			
	Mucosal pattern	Vascular pattern	Sum score	*n*	Mucosal pattern	Vascular pattern	Sum score	*n*
Without FICE								
Conv	12	35	44	38	21	40	61	38
Indigo	59	-	59	20	59	-	59	20
FICE								
0	6	20	26	38	8	23	31	38
1	8	32	40	38	15	33	48	38
2	13	42	55	38	20	50	70	38
3	14	43	57	38	17	48	65	38
4	15	45	60	38	25	49	74	38
5	11	32	43	38	19	38	57	38
6	11	38	49	37	19	52	71	37
7	10	28	38	38	14	34	48	38
8	11	30	41	38	15	30	45	38
9	14	44	58	38	18	48	66	38

Table 3 Accuracy of prediction of histopathological diagnosis among the five endoscopists with the different techniques applied *n* (%)

Endoscopists	1 (*n* = 19)	2 (*n* = 19)	3 (*n* = 19)	4 (*n* = 19)	5 (*n* = 19)	Global (*n* = 95)
Conv	9 (47.4)	13 (68.4)	12 (63.1)	10 (52.6)	10 (52.6)	54 (56.8)
Conv-M	12 (63.1)	12 (63.1)	14 (73.7)	6 (31.6)	9 (47.4)	53 (55.8)
FICE	10 (52.6)	11 (57.9)	12 (63.1)	13 (68.4)	10 (52.6)	56 (58.9)
FICE-M	15 (78.9)	14 (73.7)	15 (78.9)	11 (57.9)	12 (63.1)	67 (70.5)
Indigo	15 (78.9)	15 (78.9)	15 (78.9)	10 (52.6)	12 (63.1)	67 (70.5)
Indigo-M	17 (89.4)	16 (84.2)	15 (78.9)	13 (68.4)	12 (63.1)	73 (76.8)
Mean percentage	77.9	85.3	87.3	66.3	68.4	

Conv: Conventional; Conv-M: Conventional + magnification; FICE-M: FICE + magnification; Indigo-M: Indigo + magnification.

In study four, FICE setting 4 was found to be better than conventional endoscopy for tracing the margin of the polyps and observing the surface irregularities, and IC was found to be better than FICE setting 4 (Tables 5 and 6, Figure 5).

In study five, when the polyps were observed under IC plus FICE setting 6, the view was not considered inferior

Table 4 Evaluation of image quality of FICE-4 as compared to conventional WLE in the presence of remaining liquid or solid fecal content

Endoscopists	Quality				Fecal content			
	FICE better (%)	FICE equal (%)	FICE worse (%)	P^1	FICE better (%)	FICE equal (%)	FICE worse (%)	P^1
1	87.5	12.5	0		87.5	12.5	0	
2	93.8	6.2	0		100	0	0	
3	28.6	71.4	0		57.1	42.9	0	
4	87.5	12.5	0		100	0	0	
5	87.5	12.5	0	< 0.001	93.8	6.2	0	
Global mean	77.0			< 0.001	87.7			< 0.001

[1]*P* values are comparing the observed proportion of better with respect to 50%; WLE: White light endoscopy.

Table 5 Comparison of the observation quality of the margins and surfaces of the polyps with FICE *vs* conventional WLE

Endoscopists	Margin				Surface			
	FICE better (%)	FICE equal (%)	FICE worse (%)	P^1	FICE better (%)	FICE equal (%)	FICE worse (%)	P^1
1	73.3	26.7	0		73.3	26.7	0	
2	75.0	25.0	0		43.8	56.3	0	
3	13.3	80.0	6.7		68.8	25.0	6.2	
4	68.8	25.0	6.2		31.3	68.8	0	
5	81.3	18.8	0		87.5	12.5	0	
Global mean	62.3			0.02	60.9			0.013

[1]*P* values are comparing the observed proportion of better with respect to 50%.

to that of IC alone (Table 7, Figure 6). Therefore, it can be concluded that colonoscopy with FICE setting 6 in the IC-stained mucosa is feasible.

DISCUSSION

Virtual chromoendoscopy has been developed by endoscope manufacturers to reduce the need for dye spraying. FICE comes with 10 pre-installed settings, which have not previously been evaluated and compared to normal dye spraying techniques and WLE.

In our study, setting 4 was found to be best when assessing mucosal and vascular architecture. Teixeira *et al*[12] have reported on the effectiveness of FICE with magnification endoscopes in the differential diagnosis of neoplastic and non-neoplastic lesions. The FICE setting employed was R 500 nm, G 520 nm, and B 405 nm, as we felt that it provided the best imaging of the capillary vessels, after having compared multiple filter settings. However, those comparisons were not probably performed in a structured fashion, as no specific data about the comparisons is available in the study.

We described the settings as provided by the manufacturer. Because it is possible to personalize the filter settings and rename them, care should be taken not to misinterpret the filters used in different studies. Paradoxically, we found that the FICE settings that most closely correlated with the Olympus NBI mode provided the worst mucosal views. NBI and FICE are indeed different technologies, and the results obtained with one of them cannot be extrapolated to the other.

FICE was generally better at assessing vascular architecture than the mucosal surface. Moreover, indigo carmine dye spraying was significantly superior to any FICE setting. In particular, the innominate grooves, important features when recognizing flat lesions, were perfectly outlined by indigo carmine dye.

Magnification appears to be as effective with FICE as with IC, whereas IC would be superior to FICE in the absence of magnification. Because this is a pilot study, these results should be confirmed in larger studies. The endoscopists participating in image interpretation were far more familiar with IC than with FICE. A learning curve in diagnostic interpretation of FICE may exist. Another possible explanation for the superiority of IC over FICE in our study could be that the former seems to provide a better mucosal contrast, and in the absence of magnification, this might lead to significant differences. In the only study available regarding FICE for the diagnosis of colonic polyps, Pohl *et al*[9] also found that IC and FICE were superior to WLE both with and without magnification. However, no difference was found when IC and FICE were compared. Because the mean size of polyps in their study was 7 mm, and lesions up to 20 mm in size were included, their results cannot be directly compared to those from our study, as our polyps were significantly smaller. Although they performed a sub-analysis on the subgroup of lesions ≤ 5 mm in size, no information was provided about possible differences between IC and FICE. Moreover, images were evaluated for diagnostic performance by one single endoscopist, whereas five endoscopists were involved in our study.

The diagnostic accuracy with the different techniques in our study was lower than in some other series[2,5,13-16]. Possible explanations for such differences are that some series included larger polyps, which are probably easier to diagnose[5,13-15], or that diagnosis was estimated with a live video-endoscopy image and not with stored

Table 6 Comparison of the observation quality of the margins and surfaces of the polyps with FICE *vs* IC

Endoscopists	Margin				Surface			
	FICE better (%)	FICE equal (%)	FICE worse (%)	P^1	FICE better (%)	FICE equal (%)	FICE worse (%)	P^1
1	0	20.0	80.0		6.7	13.3	80.0	
2	0	50	50.0		0	25.0	75.0	
3	0	31.3	68.8		0	25.0	75.0	
4	50.0	25.0	25.0		0	68.8	31.3	
5	0	50.0	50.0		0	18.8	81.3	
Global mean		35.3		< 0.001		30.2		< 0.001

[1]*P* values are comparing the observed proportion of equal with respect to 50%. IC: Indigo carmine.

Table 7 Comparison of the observation quality of the polyps with FICE-6 + IC *vs* IC

Endoscopists	Quality			
	FICE-6 + IC better (%)	FICE-6 + IC equal (%)	FICE-6 + IC worse (%)	P^1
1	53.8	46.2	0	
2	61.5	30.8	7.7	
3	30.8	69.2	0	
4	30.8	69.2	0	
5	69.2	30.8	0	
Global mean	49.2			0.37

[1]*P* values are comparing the observed proportion of better with respect to 50%.

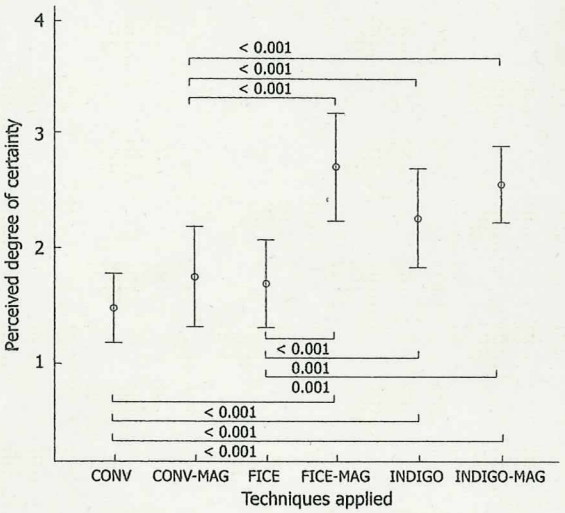

Figure 3 Degree of certainty in the endoscopic diagnosis for all participating endoscopists with the six diagnostic modalities employed, when endoscopic images were sequentially shown for each case (mean ± SD). INDIGO-MAG: Indigo carmine plus magnification; FICE-MAG: FICE plus magnification; CONV-MAG: Conventional imaging plus magnification; CONV: Conventional.

pictures[2,13], which could enable a more exact diagnosis. Some series used absorptive stains, which can be more accurate[13,14]. Moreover, endoscopists with varying degrees of experience in magnifying colonoscopy participated in our study, and there were significant differences in diagnostic accuracy among them. In a recent study, East *et al*[16] reported a diagnostic accuracy of 69%-72% for magnification with methylene blue and 72%-84% for magnification plus NBI, which is similar to our findings. Further larger studies should compare FICE with IC without magnification in order to ascertain possible differences between the techniques.

The perceived degree of certainty in the diagnosis given with the different techniques applied was also evaluated. We believe that this issue deserves consideration when test performance is evaluated, as it could have an influence on the therapeutic strategy chosen by the endoscopist. We found that IC (with and without magnification) and FICE plus magnification - the techniques with a higher diagnostic accuracy - were associated with a greater perception of accurate diagnosis, and in fact they were more accurate.

Virtual chromoendoscopy techniques are expected to increase mucosal contrast. In fact, they should probably do so if they are to replace endoscopic stains. In our study, FICE was superior in highlighting the contour of lesions compared with WLE. However, IC remains the gold standard as it was found to be superior to FICE. Machida *et al*[4] came to a similar conclusion when comparing NBI with dye staining. One very important issue that will have to be explored in future studies is whether FICE or NBI can aid in the recognition of depressed lesions (Paris type 0-IIc). These lesions are frequently small but frequently harbour high grade dysplasia or early invasive cancer[11,17].

Adequate bowel cleansing is a prerequisite for the application of chromoendoscopy, as the mixture of stains and remaining fecal content worsens endoscopic observation[18]. It appears important to determine whether FICE can be applied when there is some fecal content remaining, because in most colonoscopies, at least some liquid material persists. when the NBI technology is used, suboptimal bowel preparation appears to negatively affect the endoscopic view. According to our initial impression and the endoscopists' subjective opinion measured in the study, FICE setting 4 was better than WLE for adequately observing the colonic mucosa when bowel content was present and for localizing and individualizing small fecal particles. Liquid and especially small fecal particles showed up as a vivid yellow color. This property of FICE might be useful to differentiate more accurately between small polyps and feces, allowing for targeted washing when small particles are detected.

Finally, it is important to know the effect of IC on FICE observation. It is possible that both techniques could be applied in combination for certain indications, as FICE allows for better observation of the vascular

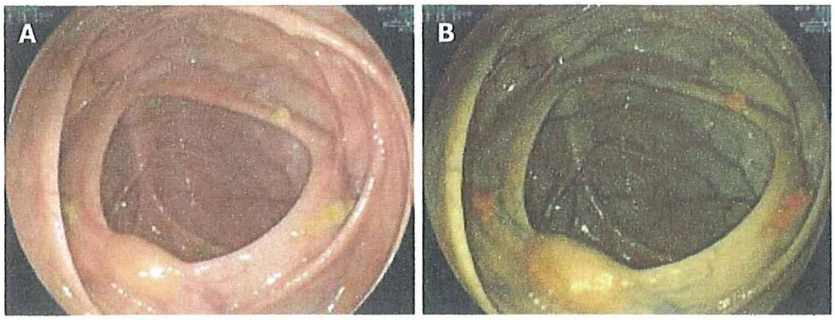

Figure 4 Observation of the colonic mucosa in the presence of remaining stool particles. A: Plain endoscopy; B: FICE 4.

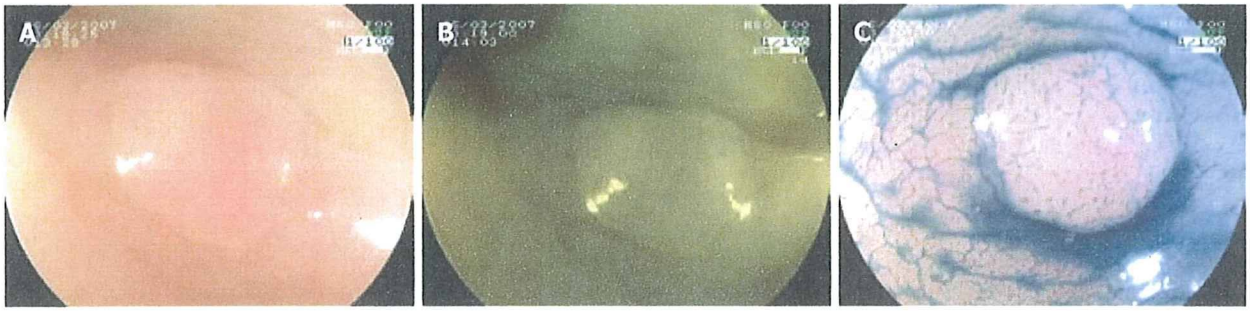

Figure 5 Sequence of images shown for the evaluation of mucosal contrast, in a 0-IIa flat elevated lesion, 3 mm in maximum diameter (histopathological diagnosis: tubular adenoma with mild dysplasia). A: Plain endoscopy plus magnification; B: FICE 4 plus magnification; C: 0.5% IC plus magnification.

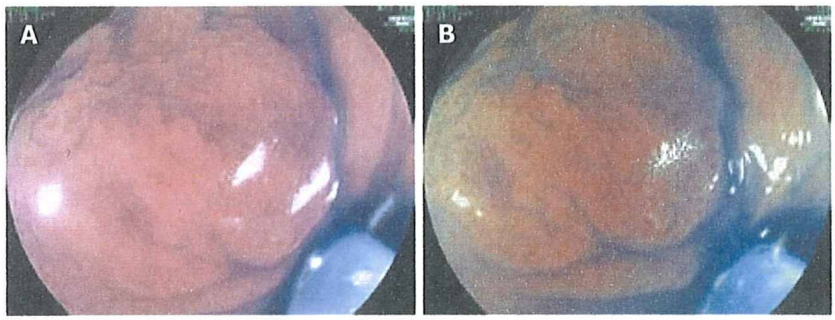

Figure 6 A flat elevated tubular adenoma, shown for the evaluation of FICE 6 plus IC. A: 0.5% IC plus magnification; B: 0.5% IC plus magnification plus FICE 6.

pattern and IC more clearly highlights the lesion edge and surface shape. FICE 6 did not interfere with endoscopic observation. The effect of IC on NBI observation has not been described, but in our experience, the endoscopic view is worsened, resulting in a greenish color.

It is noteworthy that in all cases, FICE was applied with magnifying high definition endoscopes (1 300 000 pixels). When we tried conventional endoscopes (resolution 410 000 pixels), we felt that the image quality was greatly worsened when any FICE filter was applied. Therefore, the results of our study apply only to high resolution endoscopes.

Our study has several limitations: first, the determination of the image quality provided by the different filters is unavoidably a subjective issue. However, we used a scale, a method similar to that used in previous studies[4], and each endoscopist was blinded to the assessments of the other endoscopists. Moreover, although filter 4 had the highest scores, other filters also seemed to provide clear endoscopic images, but they were not evaluated in the current study. The effect of these filters in the colon could represent a field of future research. A second limitation is that our pilot study on polyps only included small lesions, and none of the lesions was invasive; therefore, the usefulness of FICE for the prediction of invasiveness was not assessed. Finally, one investigator selected the endoscopic images and also participated in the prediction of histopathological diagnosis. However, he was unaware of the diagnosis, and in fact, he did not review any of the histopathological reports for any endoscopic procedure during the study period. When this investigator's assessments were excluded, there were no changes in the statistical results for the diagnostic accuracy of the techniques.

In conclusion, FICE setting 4 seems to be the most suitable for the observation of the colonic mucosa with high definition endoscopes. Its performance in the diagnosis of small polyps appears similar to IC when magnification is applied; however, in our pilot study, IC was superior to FICE in the absence of magnification. FICE seems to depict the polyp shape better than WLE but less clearly than IC. The presence of small amounts of liquid or solid feces or IC does not appear to interfere with endoscopic observation when FICE is applied. This is an initial description, and future studies should clarify the role of FICE in colonoscopic diagnosis.

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COMMENTS

Background

Fujinon intelligent chromoendoscopy (FICE) provides virtual chromoendoscopy, without the need for endoscopic stains. However, knowledge about the most adequate FICE settings in colonoscopy, and how it compares with conventional chromoendoscopy is still limited.

Research frontiers

Many issues regarding colonoscopic imaging with FICE have to be explored, including comparison with other virtual chromoendoscopy technologies, traditional chromoendoscopy with stains, and even the influence of the quality of colonic cleansing.

Innovations and breakthroughs

In this study a structured methodology was applied in order to determine which one among the multiple FICE-filters available provides a better observation of the vascular and mucosal patterns. After the most adequate filter was selected, it was applied for the examination of colonic polyps. In previous studies such a methodology to choose the best FICE-filter was not applied or described in detail. Additionally, in this study certain features of FICE imaging are explored, such as the possibility of applying it to observe indigo carmine-stained mucosa, or whether the existence of fecal contents has an influence on FICE imaging.

Applications

Our results suggest that FICE is adequate for the observation of the vascular pattern, that indigo carmine is better for examining the fine mucosal surface and the margin and shape of the lesion, and that endoscopic stains (like indigo carmine) can be applied in combination with FICE-6. As opposed to narrow band imaging, indigo carmine or colonic fecal contents do not seem to interfere with FICE imaging. In fact, FICE-4 could clarify whether small mucosal irregularities are really mucosal lesions or adherent particles, and this could have an application in screening colonoscopy.

Terminology

Virtual chromoendoscopy: The contrast of mucosal and vascular patterns is enhanced without the need of any endoscopic stain, by just pressing a button in the endoscope. FICE: Virtual chromoendoscopy is obtained by means of spectral estimation technology, i.e. computerized image reconstruction by the endoscopic processor. FICE filters or settings: there are 10 pre-programmed filters which are switched on the keyboard, each of which has different settings for estimated R, G, and B wavelengths.

Peer review

This is a prospective study to validate high definition endoscopes with FICE in colonoscopy. This paper is quite interesting.

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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.

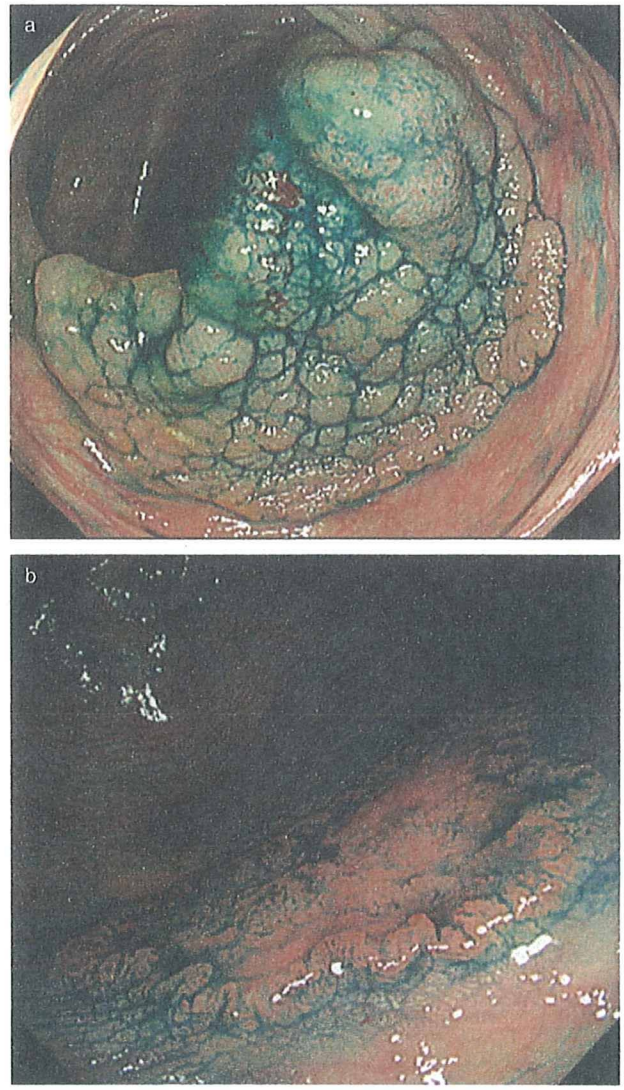

Figure 1 (a) Laterally spreading tumors granular type (LST-G): a lesion with even or uneven nodules on the surface. (b) LST-non-granular type (LST-NG): a lesion with a smooth surface.

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.

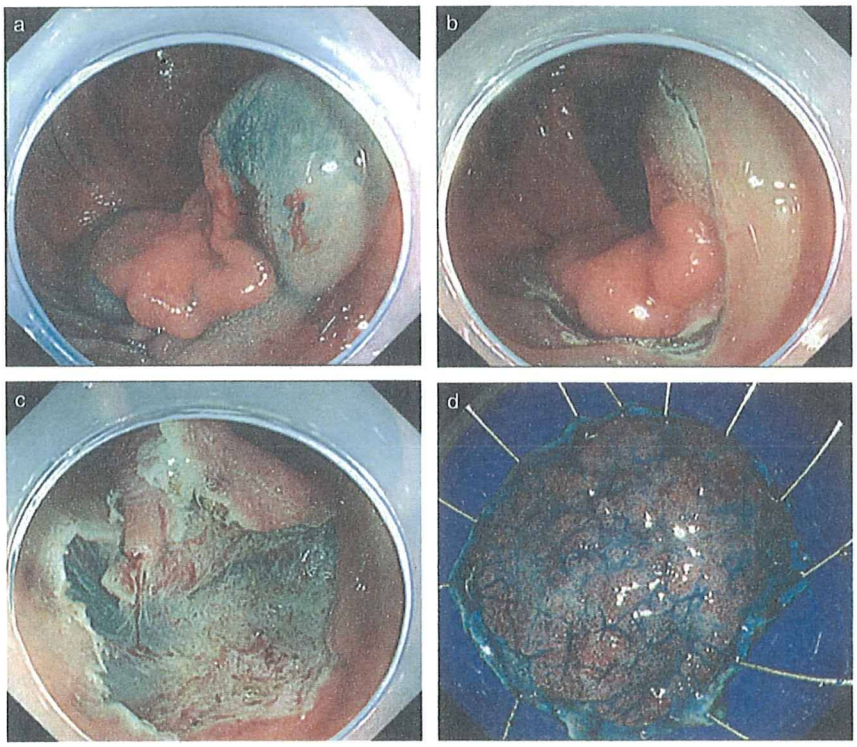

Figure 2 Endoscopic submucosal dissection (ESD) case treated in the latter period: (a) Laterally spreading tumors non-granular type (LST-NG) lesion, approximately 30 mm in size, was located in the transverse colon. Although the lesion showed non-lifting sign positivity, it was diagnosed as intramucosal 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

Lymph node staging in esophageal squamous cell carcinoma: A comparative study of endoscopic ultrasonography versus computed tomography

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computed tomography, endosonography, esophageal neoplasms, lymph nodes, squamous cell.

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Abstract

Background and Aim: Endoscopic ultrasonography (EUS) is established as a standard approach for locoregional staging of esophageal cancer. However, only a few published studies have attempted to correlate the station of the abnormal lymph nodes detected by EUS with the definitive histology. We compared EUS and computed tomography (CT) in the initial staging of esophageal squamous cell carcinoma.

Methods: Consecutive patients with esophageal cancer undergoing EUS were evaluated. EUS findings and patient data including histopatology were collected prospectively and analyzed retrospectively. Lymph node locations were divided into three groups; abdominal (A), paraesophageal (B), and thoracic paratracheal (C).

Results: A total of 365 consecutive patients underwent EUS and 159 patients underwent esophagectomy without neoadjuvant chemotherapy. Thirty-eight patients were excluded (insufficient EUS, etc.), and 121 patients were enrolled. The overall accuracy of EUS was 64% (sensitivity 68%, specificity 58%, positive predictive value [PPV] 68%), CT was 51% (sensitivity 33%, specificity 75%, PPV 64%), and CT + EUS was 64% (sensitivity 74%, specificity 50%, PPV 66%). The accuracy of EUS was higher than CT in Groups A and C. Sensitivity of CT was lower than that of EUS alone and CT + EUS.

Conclusions: This study has demonstrated that EUS is a more accurate technique than contrast-enhanced CT for detecting abnormal lymph nodes. Sensitivity of CT was lower than that of EUS alone and CT + EUS. But some metastatic lymph nodes in neck and abdominal fields are only detectable by CT. Therefore, both EUS and CT should be undertaken for routine examination prior to treatment of esophageal cancer.

Introduction

The initial staging of esophageal cancer is important because it influences the choice of treatment, and predicts outcome.[1] Factors that influence surgical decision-making include the relationship of the tumor to the trachea or bronchus (site), the depth of tumor invasion (T-stage), the presence of regional lymph node metastases (N-stage), and the presence of distant metastases (M-stage). In the past, computed tomography (CT) scanning was the major staging method, whereas more recently, endoscopic ultrasonography (EUS) and 18-fluorodeoxyglucose-positron emission tomography (PET) scanning have become more widely available.[1–4] It is currently believed that EUS is the most accurate method of staging esophageal cancer for T- and N-stage.[4–8] For this reason, once distant metastases have been excluded, EUS plays a key role in tumor evaluation. The reported EUS accuracy rates range from 61% to 92% for T-stage and from 70% to 90% for N-stage. The overall TNM classification is assessed accurately in approximately 70% of cases.[9–13] However, the findings of EUS are not necessarily definitive for identification of individual lymph nodes containing metastases. Most published studies have referred only to N-staging and not to individual lymph nodes. Moreover, in spite of the differences in growth patterns between squamous cell carcinoma (SCC) and adenocarcinoma, only a few published studies have focused on SCC. In the present study, we evaluated a large number of esophageal SCCs treated at a single institution in a short period, and divided metastatic lymph nodes detected at the initial staging into several groups according to their location.

Methods

Patients

From January 2004 to December 2005, consecutive patients with esophageal cancer presenting at the National Cancer Center Hospital, Tokyo, Japan, and subsequently undergoing EUS for initial

staging, were evaluated. Exclusion criteria were (i) previous esophagectomy (including preoperative neo-adjuvant chemotherapy); (ii) multiple esophageal cancers (except m1 [cancer *in situ*] and m2 [lamina propria]); (iii) synchronous gastric cancer; (iv) cancers other than SCC (adenocarcinoma, basaloid cell carcinoma, etc.); and (v) inability to carry out EUS (due to the scope being unable to pass through due to malignant stricture, etc.). EUS findings and details of histopathology along with other relevant patient data were collected prospectively and analyzed retrospectively for this study. These data were then evaluated to determine the accuracy of EUS examination, and to compare the outcome with that of helical CT.

EUS imaging

We used a commercially available US endoscope with GF-UMQ200 (switchable to frequencies of 7.5 and 20.0 MHz) and GF-UM2000 (switchable to 5.0, 7.5, 12.0, and 20.0 MHz) radial sector scanners (Olympus Optical Co. Ltd, Tokyo, Japan). The radial EUS scope was advanced to the pylorus and then slowly withdrawn under continuous imaging with a low frequency (5.0 or 7.5 MHz). A balloon with a radius of 1.5 cm, which could be filled with water for better acoustic contact, was placed over the transducer head. Information about the presence or absence of either enlarged lymph nodes or lymph nodes with abnormal echogenicity was determined. Regional lymph nodes that were round, measured ≥5 mm, and had hypoechoic areas with a distinct margin were considered to be metastasis-positive (Fig. 1).

CT imaging

Computed tomography scanning was carried out on supine subjects using a 16-row multidetector CT apparatus (Aquilion16, Toshiba Medical, Tokyo, Japan). The CT protocol did not vary depending on the location of the known esophageal tumor. Slices 5–10 mm thick were used. Helical CT was used for all patients to determine information about the presence or absence of lymph node metastases.

Data analysis

Endoscopic ultrasonography and CT examinations were carried out to determine metastases in local lymph nodes before surgery. Due to the real-time nature of the EUS technique, only one expert gave the final diagnosis. On the other hand, CT was interpreted by a team of radiologists and surgeons. Pathologic staging was determined by examining the resected esophageal specimen.

Lymph nodes detected by EUS were divided into three groups (Fig. 2): abdominal lymph nodes (Group A; right and left cardial, along the lesser curvature of the stomach), paraesophageal lymph nodes (Group B; upper, middle and lower thoracic paraesophageal), and thoracic paratracheal lymph nodes (Group C; recurrent nerve, left tracheobronchial). Lymph nodes in other locations (Group D) that could not be detected by EUS were not compared with CT in this study. The accuracy, sensitivity, specificity, and PPV (positive predictive value) of each technique were calculated for each anatomic group of nodes.

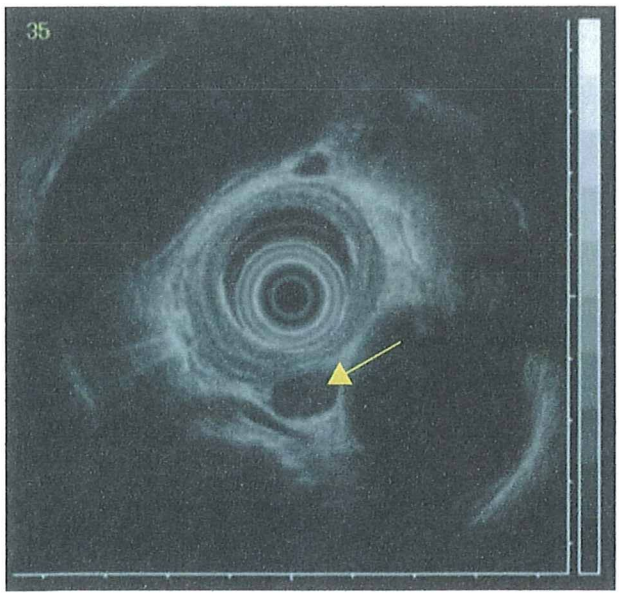

Figure 1 Endoscopic ultrasonography (EUS) findings of metastatic lymph node (middle thoracic paraesophageal lymph node, 7.6 mm).

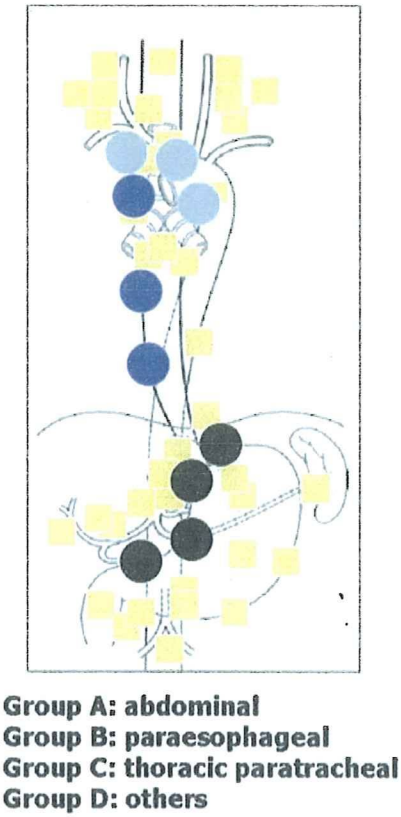

Figure 2 Lymph node subgroups.

Results

Eligible patients

A total of 365 consecutive patients (372 lesions) underwent EUS for initial staging of esophageal cancer. One hundred and fifty-nine of these patients (162 lesions) underwent esophagectomy without preoperative neo-adjuvant chemotherapy. Three patients with multiple esophageal cancers, three patients who underwent esophagectomy with gastrectomy for advanced gastric cancer, nine with adenocarcinomas, nine with basaloid cell carcinomas, and 14 who could not be evaluated by EUS (including 13 in whom the EUS scope could not be passed through due to malignant stricture) were excluded. Finally, 121 patients (121 lesions) were enrolled in this study.

Patient characteristics

Patient characteristics are listed in Table 1. The study group comprised 104 male and 17 female patients with a mean age of 63.1 years (median age: 63 years, range 41–80 years). In terms of location, 19 tumors were in the upper third of the esophagus, 61 in the middle third and 41 in the lower third of the gastro-esophageal junction. Histopathologically the tumors were divided into five groups according to depth as follows: T1a (mucosa) 17, T1b (submucosa) 38, T2 (muscularis propria) 17, T3 (adventitia) 47, T4 (adjacent to other organs) 2. The overall rate of lymph node metastasis (overall/group A/B/C/D) was 64%/38%/25%/31%/36%, respectively.

Relationship between lymph node metastasis and other factors

The relationship between lymph node metastasis and other factors (gender, age, tumor location and histopathological depth) is shown in Table 2. The incidence of LN metastasis was 74% (Group A/B/C/D: 0%/26%/58%/21%) in the upper third of the esophagus, 62% (41%/30%/39%/38%) in the middle third, and 61% (51%/17%/7%/34%) in the lower third to the gasto-esophageal junction. The respective incidence rates of LN metastasis were 12% in T1a (mucosa), 53% in T1b (submucosa), 71% in T2 (muscularis propria), 87% in T3 (adventitia), and 100% in T4 (adjacent organs).

Diagnostic accuracy

Comparison of the accuracy, sensitivity, specificity, and PPV (positive predictive value) of the selected lymph nodes (Groups A, B, C) evaluated by EUS, CT, and EUS + CT is shown in Table 3. The overall accuracy of EUS for lymph node staging was 64%, that of CT was 51%, and that of CT + EUS was 64%. In Group A (abdominal lymph nodes), the accuracy of EUS was 77%, that of CT was 68%, and that of CT + EUS was 77%. In Group B (paraesophageal lymph nodes), the accuracy of EUS was 74%, that of CT was 76%, and that of CT + EUS was 74%. There was no significant difference in accuracy, sensitivity, or specificity between

Table 1 Patient characteristics

Eligible		121	
Gender	Male	104	(86%)
	Female	17	(14%)
Age	Mean	63.1 years	
	Median (range)	63 years	(41–80 years)
Location	Upper esophagus	19	(16%)
	Middle esophagus	61	(50%)
	Lower esophagus-GEJ	41	(34%)
pT	T1aM (mucosa)	17	(14%)
	T1bSM (submucosa)	38	(31%)
	T2MP (muscularis propria)	17	(14%)
	T3Ad (adventitia)	47	(39%)
	T4Adj (adjacent organ)	2	(2%)
LN metastasis	All	77	(64%)
	Group A	46	(38%)
	Group B	30	(25%)
	Group C	38	(31%)
	Group D	43	(36%)

GEJ, gastroesophageal junction; LN, lymph node.

Table 2 Lymph node metastasis of each subgroup

		n	All		Group A		Group B		Group C		Group D	
Gender	Male	104	69	(66%)	41	(39%)	29	(28%)	35	(34%)	39	(38%)
	Female	17	8	(47%)	5	(29%)	1	(6%)	3	(18%)	4	(24%)
Age (years)	41–50	8	7	(88%)	3	(38%)	3	(38%)	5	(63%)	5	(63%)
	51–70	91	59	(65%)	37	(41%)	24	(26%)	27	(30%)	34	(37%)
	71–80	22	11	(50%)	6	(27%)	3	(14%)	6	(27%)	4	(18%)
Location	Upper esophagus	19	14	(74%)	0	(0%)	5	(26%)	11	(58%)	4	(21%)
	Middle esophagus	61	38	(62%)	25	(41%)	18	(30%)	24	(39%)	23	(38%)
	Lower esophagus-GEJ	41	25	(61%)	21	(51%)	7	(17%)	3	(7%)	14	(34%)
Depth	T1aM (mucosa)	17	2	(12%)	2	(12%)	0	(0%)	0	(0%)	2	(12%)
	T1bSM (submucosa)	38	20	(53%)	9	(24%)	3	(8%)	9	(24%)	7	(18%)
	T2MP (muscularis propria)	17	12	(71%)	9	(53%)	4	(24%)	6	(35%)	4	(24%)
	T3Ad (adventitia)	47	41	(87%)	24	(51%)	21	(45%)	21	(45%)	28	(60%)
	T4Adj (adjacent organ)	2	2	(100%)	2	(100%)	2	(100%)	2	(100%)	2	(100%)

GEJ, gastroesophageal junction.

Table 3 Diagnostic accuracy

		Accuracy	Sensitivity	Specificity	PPV
All	EUS	0.64	0.68	0.58	0.68
	CT	0.51	0.33	0.75	0.64
	EUS + CT	0.64	0.74	0.5	0.66
Group A	EUS	0.77	0.54	0.91	0.78
	CT	0.68	0.22	0.96	0.77
	EUS + CT	0.77	0.59	0.88	0.75
Group B	EUS	0.74	0.47	0.82	0.47
	CT	0.76	0.07	0.99	0.67
	EUS + CT	0.74	0.47	0.82	0.47
Group C	EUS	0.7	0.47	0.81	0.53
	CT	0.64	0.34	0.78	0.42
	EUS + CT	0.64	0.55	0.67	0.44

Group A (abdominal lymph nodes).
Group B (paraesophageal lymph nodes).
Group C (thoracic paratracheal lymph nodes).
CT, computed tomography; EUS, endoscopic ultrasonography; PPV, positive predictive value.

CT + EUS and EUS alone. In Group C (thoracic paratracheal lymph nodes), the accuracy of EUS was 70%, that of CT was 64%, and that of CT + EUS was 64%. Sensitivity of CT was lower than that of EUS alone and CT + EUS in all three groups.

Discussion

Despite advances in operative and non-operative strategies over the last few decades, as well as the development of new diagnostic methods, esophageal cancer is still a disease with a poor prognosis. The most important parameters for predicting the outcome of patients without distant metastases who undergo surgery for esophageal cancer are the depth of tumor penetration through the esophageal wall and the presence or absence of local lymph node metastases.[14] Patients diagnosed as having esophageal cancer should be first evaluated for the presence of comorbidity (mainly cardiac or pulmonary disease), which may preclude surgery and chemoradiotherapy. Patients who are deemed fit for surgery and chemoradiotherapy should undergo preoperative tumor staging, and the first consideration is to exclude the presence of distant metastasis or unresectable disease. For this purpose, helical CT scanning, and more recently 18-fluorodeoxyglucose-PET scanning, is typically used (diagnostic accuracy 70–80%).[15] Patients with apparently resectable disease, as judged from these imaging techniques, should undergo more detailed locoregional staging (T and N stage). Although CT scanning can provide information about likely lymph node metastases, its ability to stage accurately the depth of primary tumor invasion is more limited to local staging of the extent of tumor invasion, and lymph node involvement requires a different strategy.[2,3] In a meta-analysis by Kelly *et al.*,[16] the accuracy of conventional EUS for N staging was 79%. Studies comparing EUS with CT for evaluation of regional lymph node involvement have consistently demonstrated that endoscopic ultrasound is more accurate for N staging.[16–18] For this reason, EUS has taken a central role in the initial staging of esophageal cancer, most notably because of its accuracy in determining depth of tumor invasion and regional lymph node metastases.[5,18–20] However, the findings of EUS are not necessarily definitive for identification of individual lymph nodes containing metastases. Most published studies have referred only to N-staging, and not to individual lymph nodes. In the present study, we divided lymph nodes with metastases from esophageal cancer into four groups according to their location. Lymph nodes evaluated by EUS were divided into three groups (Fig. 2): abdominal lymph nodes (Group A; right and left cardial, along the lesser curvature of the stomach), paraesophageal lymph nodes (Group B; upper, middle and lower thoracic paraesophageal), and thoracic paratracheal lymph nodes (Group C; recurrent nerve, left tracheobronchial). Lymph nodes in other locations (Group D) that could not be detected by EUS were not compared with CT in this study. We compared the performance of EUS with CT, and also CT + EUS, for detection of metastatic lymph nodes in each subgroup. The accuracy of EUS was higher than that of CT in Groups A and C. In Group B, the accuracy of EUS and CT was nearly equal. The sensitivity of EUS + CT was highest among the three groups.

The criterion for identifying lymph node metastasis on CT scans is the presence of enlarged lymph nodes exceeding 10 mm in diameter.[21] However, the diagnostic accuracy of this criterion is poor because small metastatic lymph nodes cannot be detected, and because large thoracic lymph nodes can be reactive rather than enlarged because of metastasis.[21] For these reasons, the accuracy for CT diagnosis for mediastinal node metastasis varies between 38% and 70%, and if lymph nodes larger than 8 mm in diameter around the celiac axis are considered to be abnormal, then a sensitivity of 48% and a specificity of 93% for lymph node metastasis is achieved.[22] As EUS becomes increasing available, the role of CT scanning in local staging is becoming less important. However, it will continue to play an important role for the detection of distant metastases, particularly in the liver and lungs. Recently, thin-slice (1-mm) CT and PET-CT scanning have also become available for staging. Our next area of investigation would be to compare these modalities with EUS for locoregional staging in esophageal cancer. However, there are some differences in esophageal cancer between Japan and other developed countries. In relation to tumor location, in one USA series of esophageal tumors treated between 1976 and 1998, adenocarcinomas of the distal esophagus accounted for 73.5% of the total, whereas tumors of the upper thoracic esophagus accounted for only 4.5%.[23] On the other hand, in Japan, the middle thoracic esophagus is the most common site (about 70%), whereas upper esophageal cancer accounts for about 15%.[24] In the present series, SCC was located in the upper, middle, and lower esophagus in 15.7%, 50.4%, and 33.9% of cases, respectively, and it was shown that the location of metastatic lymph nodes differed according to the location of the primary tumor. Metastasis to abdominal lymph nodes (Group A; right and left cardial, along the lesser curvature of the stomach) was found in 0% of upper esophageal cancers, but in 51.2% of lower esophageal cancers. Also, metastasis to thoracic paratracheal lymph nodes (Group C; recurrent nerve, left tracheobronchial) was more frequent in upper esophageal cancer than in lower esophageal cancer. Therefore, it appears to be important to make a thorough and detailed survey of lymph nodes before surgery and chemoradiotherapy. The other difference between Japan and other developed countries is histopathological type. In Japan, the majority of esophageal cancers are SCC, whereas adenocarcinoma pre-