学位論文

「Diagnostic performance of EUS for evaluating the invasion depth of early colorectal cancers.」

（超音波内視鏡による早期大腸癌の深達度診断についての研究）

指導教授名　小泉　和三郎

申請者氏名　迎　美幸

著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

Abstract

Background: Endoscopic ultrasonography (EUS) is one technique used to estimate the invasion depth of early colorectal cancer (CRC), but its diagnostic accuracy remains a matter of debate. **Objective:** To assess the accuracy of EUS for estimating the invasion depth of early CRCs. **Patients:** The invasion depth of early CRCs was estimated by EUS from 1989 through 2012. **Main outcome measures**: Accuracy of EUS diagnosis, risk factors for misdiagnosis, and characteristics of lesions that were difficult to image. **Results**: We estimated the invasion depth of 714 early CRCs on EUS. Among lesions able to be visualized on EUS, the overall diagnostic accuracy of EUS for differentiating between lesions that could be resected endoscopically (Tis and T1a cancers) and those that required colectomy (T1b cancers) was 89%. Submucosal cancer and a macroscopic classification of superficial type were independent risk factors for misdiagnosis. Ninety lesions (13%) were difficult to image. Risk factors for difficulty in imaging were protruding-type morphology and tumor location in the sigmoid colon or from the descending colon to the cecum. **Conclusions**: Although some lesions were difficult to visualize, EUS is considered a useful technique for the diagnosis of invasion depth and the selection of treatment in patients with early CRC.

An accurate preoperative evaluation of invasion depth as well as tumor size and macroscopic characteristics on imaging studies or endoscopic examination is essential for deciding the treatment policy for colorectal cancer (CRC). Early CRC with mucosal to submucosal invasion is a borderline lesion for the selection of either endoscopic resection or colectomy. Mucosal cancer (Tis cancer) can be resected endoscopically because there is no risk of metastasis. In contrast, the treatment of choice for cancer with submucosal invasion differs according to the depth of tumor invasion. Tumors with slight submucosal invasion of less than 1000 μm in depth (T1a cancer) are very rarely associated with metastasis; endoscopic resection is thus indicated for such lesions. In contrast, tumors with massive submucosal invasion of 1000 μm or deeper (T1b cancer) have a 10% to 15% risk of metastasis and must therefore be surgically treated by colectomy with lymph-node dissection (1).

At present, the invasion depth of early CRC is basically estimated on colonoscopic examination with chromoendoscopy. However, if the depth of tumor invasion is difficult to estimate, additional techniques such as magnifying endoscopy to assess pit patterns and endoscopic ultrasonography (EUS) are performed. Although many studies have reported that EUS is useful for estimating the invasion depth of early CRC (2-14), clear ultrasonographic images are occasionally difficult to obtain (15,16). However, the diagnostic accuracy of EUS

for estimating the depth of invasion and factors causing difficulty in imaging remain to be fully assessed. In this study, we retrospectively evaluated the diagnostic usefulness and limitations of EUS in a series of patients with early CRC.

METHODS

Classification of the invasion depth of early CRC

The invasion depth of early-stage colorectal cancer was classified according to the Japanese Classification of Colorectal Carcinoma (17). Cancer confined to the mucosal layer was defined as Tis cancer, and cancer invading the submucosa was defined as T1 cancer, similar to the tumor-node-metastasis classification in Western countries (18). T1 cancer was subclassified into T1a cancer and T1b cancer according to the vertical depth of submucosal invasion. The vertical invasion distance of submucosal layer was measured with the use of a digital micrometer (Mitutoyo Corporation, Kawasaki, Japan).

Methods for EUS

After the completion of conventional endoscopy, EUS was performed. As premedication, scopolamine butylbromide (20 mg) or glucagon (1 mg) was given intramuscularly to suppress intestinal peristalsis. Before EUS was performed to evaluate the depth of invasion, the portion of the intestine near the tumor was filled with deaerated water that had been warmed to about body temperature.

The EUS device used was a radial-type echo-colonoscope (Olympus) for 107 lesions and a ultrasonic probe (Olympus) for 607 lesions. The following models of echo-colonoscopes were used: CF-UM3 and CF-UM20 (7.5 MHz) for 40 lesions, and CF-UMQ230 (7.5 MHz switchable to 12 MHZ) for 67 lesions. Frequencies of ultrasonic probes were 12 MHz (UM-2R and UM-DP12-25R) for 13 lesions, and 20 MHz (UM-3R and UM-DP20-25R) for 594 lesions. As imaging processors, models EU-M20 and EU-M2000 (Olympus) were used. All EUS examinations to evaluate the CRCs were performed by endoscopists who had at least 5 years' experience in colonoscopy. Before colonoscopy, informed consent for colonoscopic examination was obtained in writing from all patients.

On EUS, the normal colorectal wall was basically visualized as a 5-layer structure. From the luminal side, the hyperechoic first layer and hypoechoic second layer correspond to

the mucosa, the hyperechoic third layer to the submucosa, the hypoechoic fourth layer to the muscularis propria, and the hyperechoic fifth layer to the subserosa or serosa (adventitia) (19). The invasion depth of the CRCs on EUS was evaluated to be the deepest layer that showed narrowing or rupture of the wall structure due to tumor. The resolution of currently available EUS devices precludes adequate visualization of the muscularis mucosae of the colorectal wall and accurate measurement of the depth of submucosal invasion by carcinomas (20). Submucosal carcinomas were thus classified into two groups on the basis of the degree of submucosal invasion on EUS. Tumors with invasion limited to the first to second layers of the colorectal wall were diagnosed to be Tis cancer. If the superior margin of the third layer was slightly narrowed by tumor, T1a cancer was diagnosed. If the third layer was severely narrowed or ruptured, but the fourth layer remained intact, T1b cancer was diagnosed (10).

Study Variables

The depth of invasion as evaluated on EUS by the endoscopist was compared with the histopathologically determined depth of invasion for early CRCs for which the layered structure of the colorectal wall adjacent to the tumor was clearly depicted on EUS (for lesions able to be visualized). On the basis of the depth of invasion of the early CRCs as evaluated on

EUS, the lesions were classified as to whether endoscopic resection (Tis and T1a cancers) or colectomy (T1b cancers) was indicated. The lesions were similarly classified on the basis of the histopathological findings, and the results were compared with those obtained on EUS. The diagnostic accuracy of EUS were calculated only for lesions able to be visualized on EUS. The sensitivity of EUS was defined as the percentage of Tis or T1a cancers correctly diagnosed as Tis or T1a cancers on EUS, and specificity was defined as the percentage of T1b cancers correctly diagnosed as T1b cancer or as cancer with deeper invasion on EUS. The percentage of lesions that were accurately diagnosed among all lesions was defined as the overall diagnostic accuracy.

To investigate factors affecting the overall diagnostic accuracy of EUS, the effects of tumor location, size, macroscopic type, invasion depth, instruments used, selected treatment, and examination time were examined by univariate and multivariate analyses. For lesions for which the invasion depth was overestimated on EUS, the EUS findings were contrasted with the histopathological findings to examine the reasons for misdiagnosis.

The features and frequencies of lesions that were difficult to image were also examined. Difficult-to-image lesions were defined as lesions for which the layered structure of the adjacent colorectum could not be clearly visualized. The effects of tumor location, tumor

size, macroscopic type, invasion depth, instruments used, and the examination time were evaluated by univariate and multivariate analyses to delineate the reasons for difficult-to-image lesions. Our institutional review board approved the study protocol.

Statistical analysis

Numerical data are expressed as means ± standard deviation. Mann-Whitney U tests and logistic regression analysis were used to analyze the results. P values of less than 0.05 were considered to indicate statistical significance. Results were evaluated statistically using the SPSS statistical software package, version 17.0.

RESULTS

General data

From January 1989 through August 2012, we examined 714 early CRC by conventional endoscopy followed by EUS to estimate the depth of tumor invasion. After endoscopic resection or colectomy, the invasion depth of all lesions was confirmed histopathologically. Sixty-four percent of the lesions were located in the rectum or sigmoid colon (Table 1). The macroscopic type of the tumors was classified according to the Paris endoscopic classification (21) and the system reported by Kudo et al (22). Protruding lesions

(41%) and superficial tumors (39%) were most common, followed by laterally spreading tumors (LSTs, 20%). Nongranular-type LSTs were classified as superficial tumors. The mean tumor diameter was 2.4 ± 1.6 cm. The invasion depths of the lesions were as follows: 401 Tis cancers, 75 T1a cancers, and 238 T1b cancers. As for treatment, over half of the lesions were resected surgically, and 37% were resected endoscopically (Table 1).

Depth of tumor invasion on EUS

The depth of invasion was assessable on EUS for 624 (87%) of the 714 lesions. There were 347 Tis cancers, 67 T1a cancers, and 210 T1b cancers. Among lesions able to be imaged on EUS, sensitivity of EUS was 90% and specificity was 87%. The overall diagnostic accuracy was 89% (Table 2).

The overall diagnostic accuracy of EUS was compared according to tumor location, macroscopic appearance, tumor size, invasion depth, instrument used, selected treatment, and examination time (Table 3). As for tumor location, the diagnostic accuracy was significantly higher for rectal tumors than for tumors located from the descending colon to the cecum. As for tumor type, the diagnostic accuracy of EUS was significantly higher for protruding tumors and LSTs than for superficial lesions. Tumor size, instruments used, selected treatment, and examination time were unrelated to diagnostic accuracy. As for the depth of invasion, the diagnostic accuracy was significantly higher for Tis cancer, which had the highest rate of correct diagnosis (94%), than for T1a cancer (69%) and T1b cancer (87%). The diagnostic accuracy of EUS was lowest for T1a cancer, and the difference compared with the diagnostic accuracy for T1b cancer was also significant. On multivariate analysis, T1a

cancer, T1b cancer, and a macroscopic classification of superficial type were independent risk factors for the misdiagnosis of invasion depth (Table 4).

EUS findings could be closely contrasted with histopathological findings of resected specimens for 25 of the 41 lesions of Tis cancer or T1a cancer for which the depth of invasion was overestimated on EUS. With the exception of 4 lesions for which the cause was unclear, the reasons for overestimating the depth of invasion were lymphoid hyperplasia (11 lesions) or fibrosis (9 lesions) in the submucosa beneath the tumor and high-grade inflammatory-cell infiltration (6 lesions), with some overlap. Such histopathological changes were depicted as hypoechoic lesions on EUS, similar to tumors, leading to the overestimation of the depth of invasion. The macroscopic type of the 21 lesions associated with such changes was superficial in 18 lesions and protruded in 3. None of these lesions were LSTs.

Analysis of difficult-to-image lesions

Ninety (13%) of the 714 lesions were difficult to image on EUS. The reasons for the difficulty in imaging were examined by reviewing the findings of conventional endoscopy and EUS. The reasons were deep-echo attenuation in 44 lesions (49%), difficulty in vertical scanning of the tumor on EUS in 35 (39%), and inadequate filling of the colon with deaerated water because of intestinal peristalsis in 12 (13%).

The proportions of difficult-to-image lesions were compared according to tumor location, macroscopic type, tumor size, invasion depth, instrument used, and examination time (Table 5). As for tumor location, the proportions of difficult-to-image lesions were significantly higher among tumors located in the sigmoid colon and the descending colon to the cecum than among tumors located in the rectum. With respect to macroscopic type, the proportion of difficult-to-image lesions was significantly higher for protruding tumors than for superficial tumors or LSTs. As for the instrument used, the proportion of difficult-to-image lesions was significantly higher for an ultrasonic probe than for an echo-colonoscope. Tumor size, invasion depth, and examination time were unrelated to the proportion of difficult-to-image lesions. On multivariate analysis, lesion location in the sigmoid colon and from the descending colon to the cecum and a protruding macroscopic type were independent risk factors for difficulty in imaging (Table 6).

DISCUSSION

Histopathological characteristics such as tumor location, tumor size, macroscopic type, and depth of invasion should be taken into account when selecting treatment for early CRC. As for the depth of invasion, Tis and T1a cancers are rarely associated with metastasis

and can therefore be curatively treated by endoscopic resection. However, surgical resection with lymph-node dissection is indicated for T1b cancer. Therefore, estimation of the invasion depth of Tis and T1 cancers on the basis of preoperative endoscopic findings plays an important role in the selection of treatment.

The invasion depth of early CRC is basically estimated on the basis of conventional endoscopic findings. However, apart from tumor diameter, endoscopic findings used to estimate the depth of invasion are difficult to evaluate objectively (23). Therefore, the diagnostic accuracy largely depends on the experience and skill of the endoscopist. Experienced endoscopists can accurately estimate the depth of invasion of more than 80% of lesions on only conventional endoscopy (14). However, diagnostic accuracy on conventional endoscopy has been reported to be lower for less experienced endoscopists (24).

EUS and magnifying endoscopy is used to examine the fine details of lesions for which it is difficult to evaluate the depth of invasion on conventional endoscopy. Evaluation of pit patterns on the tumor surface by magnifying endoscopy has been reported to be useful for estimation of the invasion depth of early CRC, as well as for the selection of treatment (25-27). EUS can produce vertical images of gastrointestinal lesions, allowing the depth of invasion to be objectively evaluated on the basis of changes in the normal layered structure of the

colorectal wall. When clear EUS images were obtained, the rate of correctly differentiating Tis and T1a cancer from T1b cancer has been reported to be as high as about 90% (5-14). In our study, the rate of correct differential diagnosis was 89%, indicating good diagnostic results. One study did not support the diagnostic accuracy of EUS for evaluating whether endoscopic resection was indicated for colorectal tumors (28), but that study was small and used an early-model echo-colonoscope with a low frequency. In the present study, we evaluated a large series of lesions, most of which were scanned by high-frequency ultrasonic probes. This may account for why our results differed from those in the previous study.

Among the 400 lesions diagnosed as Tis cancer or T1a cancer on EUS in our study, 203 (51%) were resected endoscopically, and 197 (49%) were treated by colectomy. The main reason for performing surgical resection in many patients was that many of the lesions were relatively large, diagnosed before ESD became a routine procedure and were therefore resected surgically. In fact, the mean diameter of surgically resected lesions (3.2 ± 2.0 cm) was significantly greater that that of endoscopically resected lesions (2.2 ± 1.4 cm, $p<0.001$).

A previous study comparing the diagnostic accuracy of EUS with that of the evaluation of pit patterns on magnifying endoscopy in patients with early CRC reported that EUS is superior (13), whereas another study found that diagnostic accuracy is generally

similar (27). EUS can provide a more objective assessment of the depth of tumor invasion than conventional endoscopy, and pit patterns can be evaluated on magnifying endoscopy. We previously reported the results of a study comparing the diagnostic accuracy of various endoscopic techniques for evaluating the invasion depth of early CRCs (14). Endoscopists with at least 10 years of experience in colonoscopy assessed the endoscopic images. If good-quality images were obtained on EUS, the rate of accurately diagnosing the depth of invasion tended to be higher for EUS than for conventional endoscopy. The diagnostic accuracy of EUS is thus less likely to be affected by the experience and ability of endoscopists. Therefore, the concurrent use of EUS can enhance diagnostic accuracy of lesions for which it is difficult to estimate the depth of invasion on conventional endoscopy. This applies not only for inexperienced endoscopists, but also for even skilled endoscopists. In particular, the use of an ultrasonic probe allows EUS to be easily performed in the same session as conventional endoscopy.

In the present study, we performed multivariate analysis to investigate factors influencing the diagnostic accuracy of EUS for estimating the invasion depth of early CRC. A submucosal depth of invasion and superficial macroscopic type were shown to be independent risk factors for misdiagnosis of the depth of invasion. The submucosa of the colorectal wall is

thinner than that of the gastric wall, making it more difficult to estimate the degree of submucosal invasion on EUS. Furthermore, invasion of the submucosa by carcinoma is sometimes accompanied by fibrosis or high-grade inflammatory cell infiltration immediately below and around the tumor, as well as by lymphoid hyperplasia. These histologic changes are depicted as hypoechoic lesions, similar to carcinomas with high cellular density, leading to misdiagnosis of invasion depth. It is difficult to distinguish cancer from fibrosis with the currently available resolution power of EUS (20). Further enhancement of the resolution power of EUS is thus needed to solve this problem.

Diagnostic accuracy was lower for superficial tumors than for protruding tumors and LSTs. This is attributed to the fact that the frequency of T1a cancer, which is more likely to be misdiagnosed than Tis cancer and T1b cancer, was higher among superficial tumors (18%, 46 of 255 lesions) than among protruding tumors (7%, 17 of 238 lesions) and LSTs (3%, 4 of 131 lesions). In addition, as compared with protruding tumors and LSTs, superficial tumors had higher frequencies of submucosal lymphoid hyperplasia, fibrosis, and high-grade inflammatory-cell infiltration below the tumor, findings that are likely to be misinterpreted as tumor invasion on EUS (Fig. 1a-c). These histopathological features of superficial tumors were considered responsible for the lower diagnostic accuracy as compared with other

macroscopic types of tumors.

When the diagnostic accuracy was compared according to type of EUS device used, an echo-colonoscope tended to have a higher accuracy rate than an ultrasonic probe (Table 3). In Japan, echo-colonoscopes were initially used for the diagnosis of colorectal disease on EUS. However, the thick outer diameter and long hard tip of echo-colonoscopes caused problems in insertability and maneuverability. This was one reason why most lesions scanned by an echo-colonoscope were located from the rectum to the sigmoid colon. In addition, the relatively high accuracy of an echo-colonoscope was most likely attributed in part to the low number of lesions located from the descending colon to the cecum, for which the diagnostic accuracy is generally low (Table 3). In Japan, echo-colonoscopes are currently not commercially available, and EUS is performed with the use of an ultrasonic probe after conventional endoscopy. Because echo-colonoscopes that are easy to insert and maneuver have yet to be developed, we believe that ultrasonic probes should be used to diagnose colorectal disease on EUS.

Another problem associated with the diagnosis of early CRC on EUS was the presence of difficult-to-image lesions. In our study, 13% of all lesions were difficult to image on EUS. Other studies have reported that 10% to 17% of early CRCs were difficult to visualize on EUS (15,16). Our study showed that lesions location in the sigmoid colon or from the

descending colon to the cecum and a protruding macroscopic type were independent risk factors for difficult-to-image lesions. As compared with the rectum, the region from the sigmoid colon to the cecum has thicker haustra and more flexures. These anatomic features often make it difficult to vertically scan lesions arising in this region on EUS. In addition, intestinal peristalsis is more common in the proximal colon than in the rectum, which may have also contributed to the higher frequency of difficult-to-image lesions in the former. The high rate of difficult-to-image lesions among protruding tumors was attributed to a higher rate of deep echo attenuation as compared with superficial tumors and to greater difficulty in vertically scanning semipedunculated and other types of protruding lesions. Studies performed at other centers have reported that colorectal tumors arising on folds or in the colonic flexure, as well as tall lesions are often difficult to visualize (28,29).

Our study had several important limitations. First, this was a retrospective study performed in a single center. Second, because EUS was performed after the completion of conventional endoscopy, the evaluation of the depth of tumor invasion on conventional endoscopy might have biased the diagnosis on EUS. Another factor was that all sessions of EUS in our study were performed by endoscopists who had at least 5 years of experience. If less-experienced endoscopists had performed EUS, the same results might not have been

obtained.

To our knowledge, this is the first study in which multivariate analysis was used to identify factors related to difficult-to-image lesions and the diagnostic accuracy of EUS for estimating the depth of tumor invasion in patients with early CRC. Although our study was performed at a single center, we evaluated the diagnostic accuracy of EUS for 714 early CRCs. Our results are therefore considered to reflect the diagnostic accuracy of currently available EUS devices.

Our results suggest that EUS is useful for estimating the depth of tumor invasion and deciding the treatment policy in patients with early CRC. However, an appreciable number of lesions arising in the proximal colon as well as protruding tumors were difficult to image. Our results will hopefully contribute to a better understanding of the advantages and limitations of EUS for the diagnosis of early CRC. Because EUS-based diagnosis requires high-cost equipment and can be stressful even for experienced endoscopists, the characteristics of lesions that can be effectively diagnosed on EUS should be confirmed by evidence-based studies.

Further prospective studies are needed to compare the diagnostic accuracy of EUS with that of other endoscopic techniques such as magnifying endoscopy, with the ultimate goal of

establishing a strategy for evaluating the depth of invasion on the basis of lesion characteristics in patients with early CRC.

References

1) Kitajima K, Fujimori T, Fuji S, Takeda J, Ohkura Y, Kawamata H,et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol. 2004; 39:534-543

2) Saitoh Y, Obara T, Einami K, Nomura M, Taruishi M, Ayabe T, et al. Efficacy of high-frequency ultrasound probes for the preoperative staging of invasion depth in flat and depressed colorectal tumors. Gastrointest Endosc. 1996;44:34-39

3) Hamda S, Akahoshi K, Chijiiwa Y, Sasaki I , Nawata H. Preoperative staging of colorectal cancer by a 15 MHz ultrasound miniprobe.Surgery.1997;123:264-9

4) Hunerbein M, Totkas S, Ghadimi BM, Schlag PM. Preoperative evaluation of colorectal neoplasms by colonoscopic miniprobe ultrasonography. Ann Surg. 2000; 232 (1): 46–50

5) Akasu T, Kondo H, Moriya Y , Sugihara K, Gotoda T, Fujita S, et al .Endorectal ultrasonography and treatment of early stage rectal cancer. World j. surg.2000; 24: 1061–68

6) Saitoh Y, Watari J, Fujiya M , Kohgo Y. High-frequency ultrasound probes in the evaluation of colorectal neoplasia. Dig. Endosc.2001;13(Suppl.): S14–18

7) Akahoshi K, Yoshinaga S, Soejima A et al. Transit endoscopic ultrasound of colorectal cancer using a 12 MHz catheter probe. Br J Radiol .2001; 74:1017–22

8) Tseng LJ, Jao YTFN, Mo LR. Preoperative staging of colorectal cancer with a balloon-sheathed miniprobe. Endoscopy .2002; 34 (7): 564–68

9) Matsumoto T, Hizawa K, Esaki M, Kurahara K, Mizuno M, Hirakawa K,et al. Comparison of US and magnifying colonoscopy for assessment of small colorectal cancers. Gastrointest Endosc.2002; 56: 354–60

10) Kobayashi K, Kida M, Katsumata T, Yoshizawa S, Yokoyama K, Sada M, et al. Clinical role of endoscopic ultrasonography for the diagnosis of early colorectal cancer and selecting the treatment procedure. Dig Endosc. 2003; 15:298-305

11) Hunerbein M, Handke T, Ulmer C, Schlag PM. Impact of miniprobe ultrasonography on planning of minimally invasive surgery for gastric and colonic tumours. Surg Endosc.2004; 18: 601–05

12) Hurlstone DP, Brown S, Cross SS, Shorthouse AJ, Sanders DS. Endoscopic ultrasound miniprobe staging of colorectal cancer: Can management be modified? Endoscopy. 2005; 37: 710–14

13) Hurlstone DP, Brown S, Cross SS, Shorthouse AJ, Sanders DS. High magnification chromoscopic colonoscopy or high frequency 20 MHz mini probe endoscopic ultrasound staging for early colorectal neoplasia: a comparative prospective analysis.Gut.2005;54:1585-89

14) Haruki S, Kobayashi K, Yokoyama K, Sada M , Koizumi W. Comparison of diagnostic accuracies of various endoscopic examination techniques for evaluating the invasion depth of colorectal tumors. Gastroenterology Research and Practice. 2012,Article ID 621512,7 pages

15) Matsunaga A, Mochizuki F, Fujita N, Ando M, Tominaga G, Nomura M, et al. Diagnosis of early colorectal cancer by endoscopic ultrasonography(EUS). Gastroenterol Endosc. 1996;38:279-87(in Japanese with English abstract)

16) Yoshimoto K, Sakai Y. Golden standard of colorectal endoscopic ultrasonography for the definitive diagnosis of colorectal cancer. Dig. Endosc. 2001; 13 (Suppl.): S22–6.

17) Japanese Society for Cancer of the Colon Rectum, Japanese Classification of Colorectal Carcinoma, Kanehara ＆Co., Tokyo Japan,2nd edition,2009

18) Obrocea FL, Sajin M, Marinescu EC, et al. Colorectal cancer and the 7th revision of the TNM staging system: review of changes and suggestions for uniform pathologic reporting. Rom J Morphol Embryol 2011;52:537-44.

19) Yamashita Y, Machi J, Shirouzu K, Morotomi T, Isomoto H , Kakegawa T. Evaluation of endorectal ultrasound for the assessment of wall invasion of rectal cancer. Dis Colon Rectum.1988;31:617-23.

20) Kikuchi Y, Tsuda S, Yurioka M, Sakurai T, Matsui T, Yao T,et al. Diagnosis of the depth of infiltration in colorectal cancer-diagnosis and issues of the depth of infiltration investigated by endoscopic ultrasonography(EUS), Stomach and Intestine.1997;32:1651-62 (in Japanese with English abstract).

21) Paris Workshop Participants. The Paris endoscopic classification of superficial neoplastic lesions: Esophagus, stomach and colon. Gastrointest Endosc. 2002; 58:S3-S43

22) Kudo S, Lambert R, Allen JI, Fujii H, Fujii T, Kashida H et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008; 68 (Suppl.):S3-S47

23) Saitoh Y, Obara T, Watari J ,Nomura M, Taruishi M, Orii Y, Taniguchi M, Ayabe T, Ashida T, Kohgo Y. Invasion depth diagnosis of depressed type early colorectal cancers by combined use of videoendoscopy and chromoendoscopy. Gastrointest Endosc. 1998;48:362-370

24) Matsunaga A, Nomura M, Uchimi K, Hirasawa D, Fujita N. Diagnosis of early colorectal cancer by colonoscopy, endoscopic ultrasound using a microscanner and magnifying endoscopy. J. Jpn. Soc. Colo-proctol 2002;55:841-845 (in Japanese with English abstract).

25) Hurlstone DP, Cross SS, Adam I, Shorthouse AJ, Brown S, Sanders DS, et al. Efficacy of high magnification chromoscopic colonoscopy for the diagnosis of neoplasia in flat and depressed lesions of the colorectum: a prospective analysis. Gut. 2004; 53:284-290

26) Matsuda T, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N, et al. Efficacy of the Invasive/Non-invasive Pattern by Magnifying Chromoendoscopy to Estimate the Depth of Invasion of Early Colorectal Neoplasms. Am J Gastroenterol. 2008; 103:2700-2706

27) Fu KI, Kato S, Sano Y, Onuma E, Saito Y, Matsuda T, Koba I, et al. Staging of early colorectal cancers: Magnifying colonoscopy versus endoscopic ultrasonography for estimation of depth of invasion. Dig Dis Sci.2008;53:1886-1892

28) Hizawa K, Suekane H, Aoyagi K, Matsumoto T, Nakamura S , Fujishima M. Use of endosonographic evaluation of colorectal tumor depth in determining the appropriateness of endoscopic mucosal resection. Am J Gastroenterol 1996;91:768-71.

29) Watanabe H, Miwa H, Terai T, Imai Y, Ogihara T, Sato N. Endoscopic ultrasonography for colorectal cancer using submucosal saline solution injection. Gastrointest Endosc.1997;45:508-11

TABLE 1. Characteristics of 714 lesions of early CRC examined by EUS

Patients	705 patients (446 males, 259 females)
Age Mean(SD)	64.0 (10.2)
Tumor location	
Rectum	285 lesions (40%)
Sigmoid colon	172 lesions (24%)
Descending colon to cecum	257 lesions (36%)
Macroscopic appearance	
Protruding type	290 lesions (41%)
Superficial type	277 lesions (39%)
LST	147 lesions (20%)
Tumor size	
<2.0cm	312 lesions (44%)
≥2.0cm	402 lesions (56%)
Mean (SD)	2.4 (1.6) cm
Invasion depth	
Tis cancer	401 lesions (56%)
T1 cancer	313 lesions (44%)
T1a cancer	75 lesions
T1b cancer	238 lesions
Trestment method	
Endoscopic resection	262 lesions (37%) [12]
Local resection	88 lesions (12%) [4]
Radical operation	364 lesions (51%)

SD, Standard deviation

LST denotes laterally spreading tumor; pTis cancer, pathological mucosal cancer;
pT1 cancer, pathological submucosal cancer;
pT1a cancer, pathological submucosal cancer with slight invasion;
and pT1b cancer, pathological submucosal cancer with massive invasion.
[ ],additional radical operation

TABLE 2. Diagnostic accuracy of EUS for differentiating mucosal cancer or submucosal cancer with slight invasion from submucosal cancer with massive invasion

		EUS diagnosis		
		cTis or cT1a cancer	cT1b cancer or cancers with deeper invasion	
Histological diagnosis	pTis cancer or pT1a cancer (414)	373	41	90% † (373/414)
	pT1b cancer (210)	27	183	87% ‡ (183/210)
	Total (624)			89% ¶ (556/624)

†:Sensitivity ‡:Specificity ¶:Overall accuracy

TABLE 3. Comparison of diagnostic accuracy on EUS

	Sensitivity(%)	Specificity(%)	Accuracy(%)	p value
Tumor location				
Rectum	94	86	91 [A]	p=0.720 (A versus B)
Sigmoid colon	90	94	91 [B]	p=0.117 (B versus C)
Descending colon to cecum	86	81	75 [C]	p=0.024*(A versus C)
Macroscopic appearance				
Protruding type	94	88	92 [A]	p=0.007*(A versus B)
Superficial type	81	92	85 [B]	p=0.003* (B versus C)
LST	99	47	93 [C]	p=0.296 (A versus C)
Tumor size				
<2.0cm	86	91	88 [A]	p=0.466
≥2.0cm	93	82	90 [B]	(A versus B)
Invasion depth				
Tis cancer	94	NA	94 [A]	p<0.001* (A versus B)
T1a cancer	69	NA	69 [B]	p<0.001*(B versus C)
T1b cancer	NA	87	87 [C]	p=0.023* (A versus C)
Instrument used				
Echo-colonoscope	98	89	95 [A]	p=0.057
Ultrasonic probe	88	87	88 [B]	(A versus B)
Selected treatment				
Endoscopic resection	97	52	92[A]	p=0.123(A versus B) p=0.870 (B versus C)
Local resection	94	69	87[B]	p=0.076 (A versus C)
Radical operation	79	96	88[C]	
Examination time				
1989-2000	94	83	90[A]	p=0.365
2001-2012	87	89	88[B]	(A versus B)

* Statistically significant NA; not available

TABLE 4. Risk factors for misdiagnosis of the depth of invasion on multivariate analysis

	p value	Odds ratio	95%CI
pT1a cancer	p<0.001	6.127	3.068-12.237
pT1b cancer	p=0.037	1.925	1.039-3.564
Superficial type	p=0.023	1.894	1.094-3.277

CI, Confidence interval

TABLE 5. Characteristics of difficult-to-image lesions

	Inadequate imaging			
	Yes	No	Frequency of inadequate imaging lesions(%)	p value
Tumor location				
Rectum	19	266	7[A]	p=0.027* (A versus B)
Sigmoid colon	22	150	13[B]	p=0.087 (B versus C)
Descending colon to cecum	49	208	19[C]	p<0.001* (A versus C)
Macroscopic appearance				
Protruding type	52	238	18[A]	p=0.001* (A versus B)
Superficial type	22	255	8[B]	p=0.950 (B versus C)
LST	16	131	11[C]	p=0.019* (A versus C)
Tumor size				
<2.0cm	37	275	12[A]	p=0.820 (A versus B)
≥2.0cm	53	349	13[B]	
Invasion depth				
Tis cancer	54	347	13[A]	p=0.485 (A versus B)
T1a cancer	8	67	11[B]	p=0.760 (B versus C)
T1b cancer	28	210	12[C]	p=0.547 (A versus C)
Instrument used				
Echo-colonoscope	7	100	7[A]	p=0.040* (A versus B)
Ultrasonic probe	83	524	14[B]	
Examination time				
1989-2000	36	252	13[A]	p=0.945 (A versus B)
2001-2012	54	372	13[B]	

* Statistically significant

TABLE 6. Risk factors for difficult-to-image lesions on multivariate analysis

	p value	Odds ratio	95%CI
Sigmoid colon	p=0.045	1.947	1.014-3.740
Descending colon to cecum	p<0.001	4.221	2.358-7.555
Protruding type	p<0.001	2.898	1.796-4.678

CI, Confidence interval

Fig. 1.

A case of submucosal with massive invasion in which lymphoid hyperplasia was difficult to differentiate from submucosal tumor invasion on EUS.

Fig1-a. Colonoscopic picture, showing a superficial-type tumor accompanied by a depressed area.

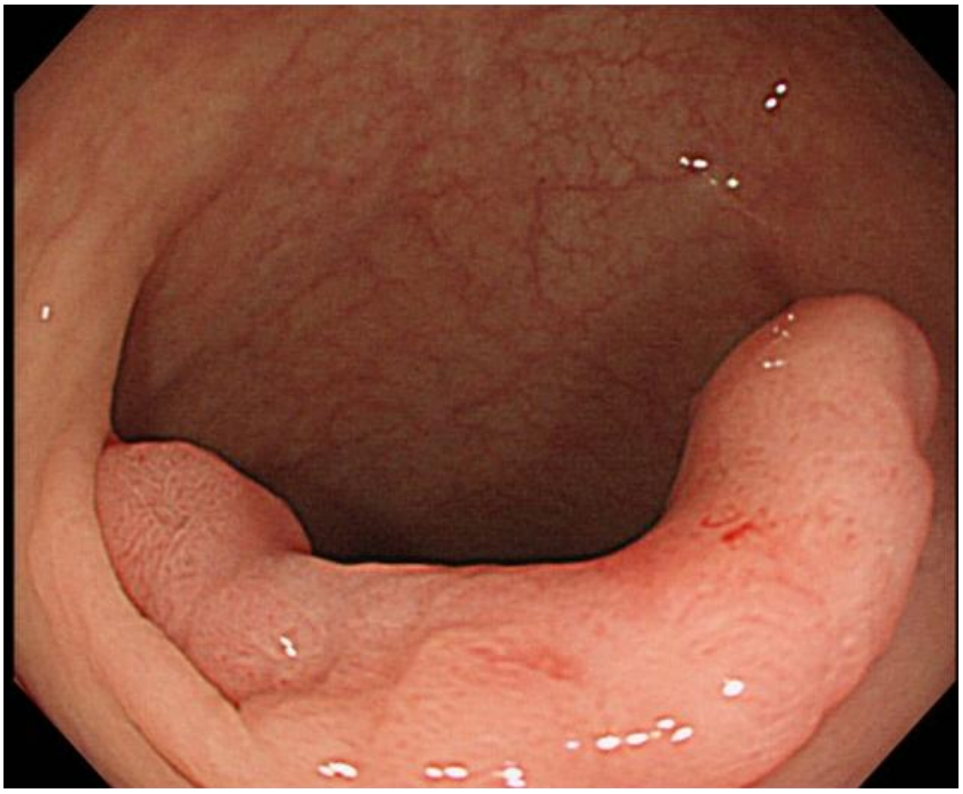

Fig1-b. EUS image clearly shows the tumor with distinct narrowing of the third layer, suggesting the presence of deeper submucosal invasion.

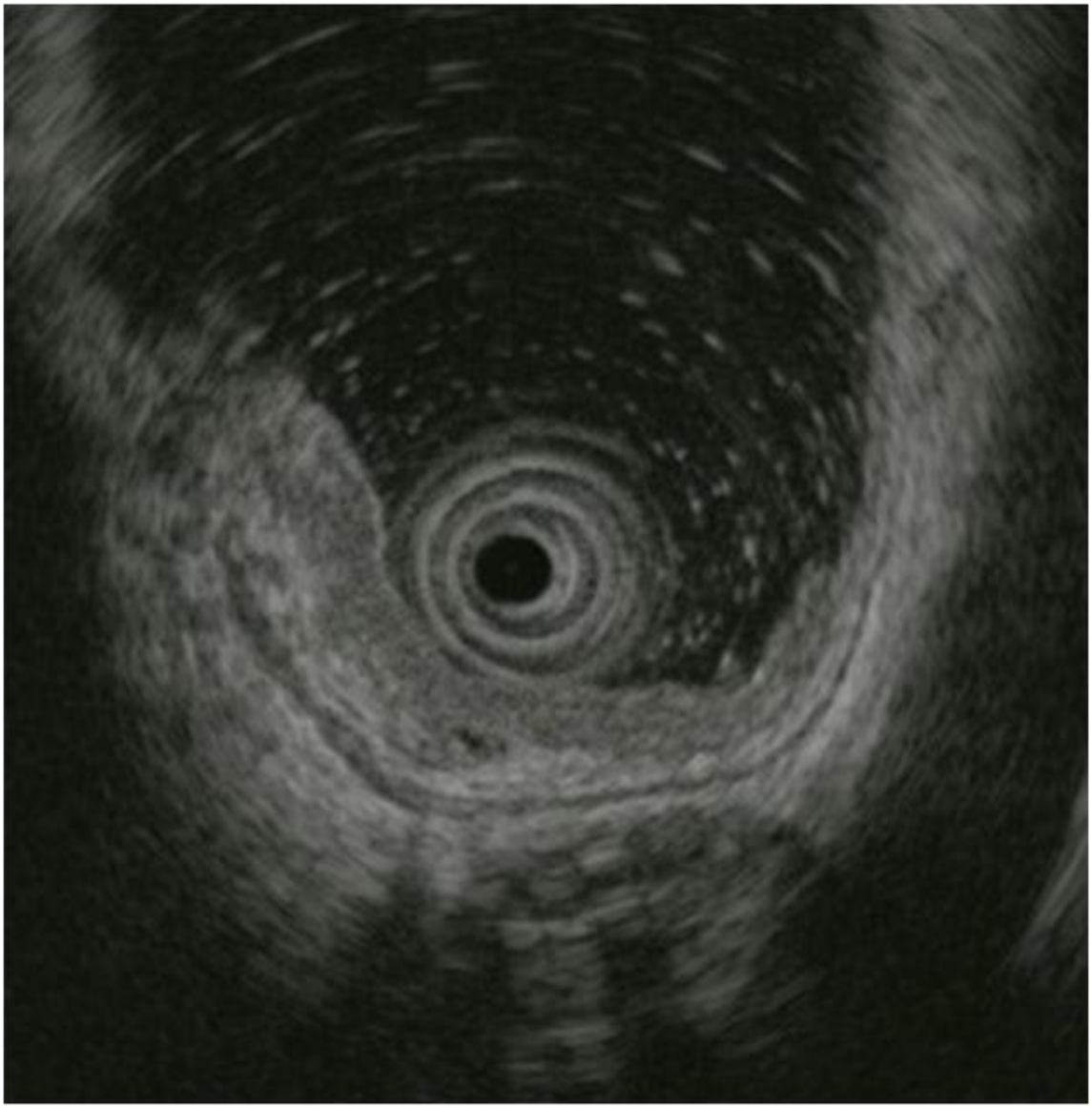

Fig1-c. Histological findings of the surgically resected specimen, showing that the tumor has invaded the deep submucosa in association with lymphoid hyperplasia. It was difficult to differentiate cancer from lymphoid hyperplasia on preoperative EUS (hematoxylin and eosin staining).