発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Fujimori S, Takahashi Y, Gudis K, Seo T, Ehara A, Kobayashi T, Mitsui K, Yonezawa M, Tanaka S, Tatsuguchi A, Sakamoto C	Rebamipide has the potential to reduce the intensity of NSAID-induced small intestinal injury: a double-blind, randomized, controlled trial evaluated by capsule endoscopy	J Gastroenterol.	46	57-64	2011
Ohmiya N, Nakamura M, Goto H	Venous varicosities in the jejunum	Gastroenterology	140	406, 738	2011
Takenaka H, Ohmiya N, Hirooka Y, Nakamura M, Ohno E, Miyahara R, Kawashima H, Itoh A, Watanabe O, Ando T, Goto H	Endoscopic and Imaging Findings in Protein-losing Enteropathy.	J Clin Gastroenterol		in press	2011
Higurashi T, Endo H, Sakai E, Nakajima A, et al.	Capsule-endoscopic findings of ulcerative colitis patients	Digestion	84	306-14	2011
Endo H, Higurashi T, Sakai E, Nakajima A, et al.	Efficacy of *lactobacillus casei* treatment on small bowel injury in chronic low-dose aspirin users: a pilot randomized controlled study.	J Gastroenterol.	47	894-905	2011
Hosono K, Endo H, Sakai E, Nakajima A, et al.	Optimal approach for small bowel endoscopy using polyethylene glycol and metoclopramide with the assistant of a real-time viewer	Digestion	84	119-25	2011
Endo H, Sakai E, Nakajima A, et al.	Leptin acts as a growth factor for colorectal tumors at stages subsequent to tumour initiation in murine colon carcinogenesis.	Gut	60	1363-71	2011

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Endo H, Sakai E, Nakajima A, et al.	Quantitative analysis of low-dose aspirin-associated small bowel injury using a capsule endoscopy scoring index.	Dig Endosc.	23	56-61	2011
Maehata Y, Esaki M, Morishita T, Kochi S, Endo S, Shikata K, Kobayashi H, Matsumoto T.	Small bowel injury induced by selective cyclooxygenase-2 inhibitors: a prospective, double-blind, randomized clinical trial comparing celecoxib and meloxicam	J Gastroenterol		[Epub ahead of print]	2011
Matsumoto T, Kubokura N, Matsui T, Iida M, Yao T	Chronic nonspecific multiple ulcer of the small intestine segregates in offspring from consanguinity	J Crohns Colitis	5	559-65	2011
Matsumoto T, Esaki M, Kurahara K, Hirai F, Fuchigami T, Matsui T, Iida M	Double-contrast barium enteroclysis as a patency tool for nonsteroidal anti-inflammatory drug-induced enteropathy	Dig Dis Sci.	56	3247-53	2011
Yamada A, Watabe H, Yamaji Y, Yoshida H, Omata M, Koike K	Incidence of small intestinal lesions in patients with iron deficiency anemia.	Hepatogastro-enterology	58	1240-3	2011
Yamada A, Watabe H, Obi S, Sugimoto T, Kondo S, Ohta M, Togo G, Ogura K, Yamaji Y, Okamoto M, Yoshida H, Kawabe T, Koike K, Omata M	Surveillance of small intestinal abnormalities in patients with hepatocellular carcinoma: a prospective capsule endoscopy study	Dig Endosc.	23	124-9	2011

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Takano N, Yamada A, Watabe H, Togo G, Yamaji Y, Yoshida H, Kawabe T, Omata M, Koike K	Single-balloon versus double-balloon endoscopy for achieving total enteroscopy: a randomized, controlled trial	Gastrointest Endosc.	73	734-9	2011
Tsuji Y, Ohata K, Sekiguchi M, Ito T, Chiba H, Gunji T, Yamamichi N, Fujishiro M, Matsuhashi N, Koike K	An effective training system for endoscopic submucosal dissection of gastric neoplasm	Endoscopy	43	1033-8	2011
Kobayashi Y, Watabe H, Yamada A, Hirata Y, Yamaji Y, Yoshida H, Koike K.	Diagnostic yield of capsule endoscopy for gastric diseases	Abdom Imaging	37	29-34	2012

Ⅳ. 研究成果の刊行物・別刷

The incidence of deep vein thrombosis in Japanese patients undergoing endoscopic submucosal dissection

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Background: Endoscopic submucosal dissection (ESD) is more invasive than other common endoscopic procedures and may increase the risk for deep vein thrombosis (DVT)/pulmonary embolism. The incidence of DVT/pulmonary embolism after ESD has not been adequately studied.

Objective: To evaluate DVT incidence and disease-specific features of D-dimer levels in ESD patients.

Design: Prospective cohort study.

Setting: Single academic center.

Patients: This study involved 60 patients with superficial gastric neoplasms indicated for ESD.

Intervention: For all patients who underwent ESD, ultrasonography of the lower limbs was performed to detect DVT the day after ESD. D-dimer levels were measured 3 times: before ESD, immediately after ESD, and the day after ESD.

Main Outcome Measurements: DVT incidence after ESD.

Results: The DVT incidence was 10.0% (6/60). At all 3 time points, D-dimer measurements were higher in patients with DVT than in patients without DVT. According to receiver operating characteristic curve analysis, the resulting cut-off value of the D-dimer level the day after ESD was 1.9 μg/mL (sensitivity 83.3%; specificity 79.6%) for ESD patients, with superior association to pre-ESD or immediately after ESD. In univariate analyses, high D-dimer levels the day after ESD and the presence of comorbidities were significantly associated with DVT development.

Limitations: Single center and small number of patients.

Conclusion: ESD procedures have a moderate risk for venous thromboembolism. In patients undergoing ESD, D-dimer levels, especially on the day after ESD, may have specific features associated with DVT development. (Gastrointest Endosc 2011;74:798-804.)

Pulmonary thromboembolism (PTE) is a clinically serious condition in which a thrombus or other embolic process causes embolism in the pulmonary circuit. Overall, 90% of PTE results from deep vein thrombosis (DVT) involving veins of the lower limbs. Recently, PTE and DVT have been regarded as sequential conditions, and the general term venous thromboembolism (VTE) has been applied. VTE is both a social and a health care problem. Advanced age, malignant disease, inflammation, protracted bed rest, obesity, ischemic heart disease, and preg-

Abbreviations: AUC, area under the ROC curve; BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; ESD, endoscopic submucosal dissection; PTE, pulmonary thromboembolism; ROC, receiver operating characteristic; VTE, venous thromboembolism.

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nancy are among the known risk factors contributing to VTE.[1]

Endoscopic submucosal dissection (ESD) was developed to overcome the technical limitations of EMR.[2-4] ESD permits en bloc resection for larger lesions and has a higher rate of histologically complete resection (>80%) than conventional EMR.[5] However, ESD often necessitates that patients assume the same position for a prolonged period during and after the procedure, because of technical difficulties and frequent complications such as bleeding or perforation.[3,6] Therefore, the ESD procedure may be associated with a risk for VTE. It is thus important to confirm that the risk of thromboembolism is significant when ESD is performed and to predict the occurrence of DVT in order to prevent this clinically serious condition. However, the incidence of DVT among patients undergoing ESD has not previously been investigated.

The D-dimer is a marker of endogenous fibrinolysis and should therefore be detectable in patients with DVT. On the other hand, D-dimer levels vary depending on disease characteristics, sampling time points after surgery, and the amount of bleeding. Several studies have shown the D-dimer assay to be a sensitive but nonspecific marker of DVT.[7-9] However, disease-specific screening for DVT has received little attention.[10]

The present study aimed to evaluate DVT incidence and investigate the disease-specific features of D-dimer levels in patients undergoing ESD as a potential accurate marker of DVT.

Take-home Message

- This is the first prospective study to assess the incidence of deep vein thrombosis (DVT) after endoscopic submucosal dissection (ESD) for gastric neoplasia.
- ESD procedures have a moderate risk for thromboembolism. D-dimer levels, especially on the day after ESD, may have specific features in association with DVT development in ESD patients.

METHODS

Study design and patient population

This prospective, cohort study was conducted from June 2007 to February 2009 at Nippon Medical School. We included consecutive patients aged at least 20 years with gastric neoplasms indicated for ESD. The lesions were judged by using magnified chromoendoscopy and pathology evaluation of biopsy specimens. The judgment was based on the expanded criteria for ESD. These criteria indicate an extremely low risk of lymph node metastasis, as reported by Gotoda et al.[11] The exclusion criteria were age >90 years; the presence of congenital and secondary coagulopathy, thrombophilia, malignancy other than gastric neoplasm, recent surgical procedures (within the preceding 12 months); pregnancy; use of estrogens; acute inflammatory disease, and body mass index (BMI) exceeding 30. Patients with preexisting coagulation disorders, as evidenced by DVT on ultrasonography of the lower limbs in the preoperative state, were also excluded. The following demographic characteristics were collected at screening before ESD: age, sex, BMI (18.5 kg/m^2 ≦ normal value range < 25.0 kg/m^2), comorbidities (chronic heart failure, chronic obstructive pulmonary disease, chronic renal disease, stroke), and use of anti-thrombotic drugs (warfarin, aspirin, ticlopidine, ethyl icosapentate, clopidogrel, and dipyridamole). When patients had taken anti-thrombotic drugs, therapy with these drugs was stopped from 5, 10, 14, 5, and 7 days before the ESD procedure, respectively, until at least the day after ESD. Patients who had been treated with warfarin were routinely treated with heparin when warfarin was discontinued, and heparin treatment was stopped 3 hours before and restarted 3 hours after ESD, as indicated in the guidelines.[12]

The protocol was approved by institutional review boards. Written, informed consent was obtained from all participants.

ESD

Gastric neoplasms were first identified and demarcated by using white-light endoscopy and chromoendoscopy with indigo carmine solution. ESD procedures were performed by using a flex-knife (KD-630L; Olympus, Tokyo, Japan), an insulation-tipped diathermy knife (IT knife; Olympus), and electrosurgical generators (VIO 300D; ERBE, Tubingen, Germany). Four operators (M.K., K.M., T.S., N.U.) carried out all ESD procedures in the present study. Patients were placed in the left lateral decubitus position on a pressure dispersion mattress and were sedated by intravenous injection of midazolam, flunitrazepam, and pentazocine. All patients were ordered to be at bed rest overnight after ESD, except for use of the lavatory, and none were given DVT prophylaxis.

Measurement of plasma D-dimer levels

Venous blood samples were collected at 3 time points: before ESD, immediately after ESD, and the day after ESD (18-24 hours after ESD). D-dimer levels were measured by the latex turbidimetric method (Nanopia D-dimer; Sekisui Medical, Tokyo, Japan: measurement range 0.5-60 μg/mL).

Diagnosis of DVT by ultrasonography of the lower limbs

We performed ultrasonography of the lower limbs for DVT detection at 2 time points: preoperatively and the day after ESD (24 hours after ESD). All examinations were performed by an experienced vascular technologist who used either an ATL Ultramark 9 or an ATL HDL 3000

computed sonography/color flow Doppler scanner (Advanced Technologies Laboratories, Bothell, Wash).

Statistical analysis

Depending on the type of baseline data, the results of comparisons between groups were analyzed by using a paired or unpaired *t* test for continuous variables. Continuous variables are expressed as mean ± SE. Crude associations for categorical data were evaluated by using a Fisher exact test or a chi-square test. One-way repeated-measures analysis of variance was performed on the plasma D-dimer data to identify interactions between time and groups or time-specific effects for each group. All *P* values were 2-tailed, and differences with values of $P < .05$ were regarded as statistically significant.

Preoperative factors (age, sex, BMI, comorbidities, and use of anti-thrombotic drugs), and postoperative factors (operative time and D-dimer level) were included as potential risk factors for DVT in the univariate analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for risk factors. Statistical analysis was performed with StatView version 5.0 (SAS Institute, Cary, NC) or SPSS 11.0 for Windows (SPSS Inc, Chicago, Ill).

To identify the time of plasma D-dimer measurement indicating the highest diagnostic performance in terms of DVT development among 3 time points (before ESD, immediately after ESD, and the day after ESD), we used receiver operating characteristic (ROC) curve analysis. ROC curves for D-dimer levels were plotted by using Medcalc version 9 (Medcalc software, Mariakerke, Belgium). The area under the ROC curve (AUC) was calculated and then compared among the 3 time points. The time point with the largest AUC was defined as the most associated with DVT. Optimal cut-off points were determined on the basis of maximum values of the Youden index, calculated as [sensitivity + specificity − 1] and the minimum values of the square root of $[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$, which indicates minimum distance from the upper left corner to the point on the ROC curve.[13]

RESULTS

Patient characteristics

From June 2007 to February 2009, 71 patients with gastric neoplasms were enrolled in the study. Of these, 11 were excluded because of age exceeding 90 years (n = 1), incomplete follow-up (n = 5), detection of DVT on preoperative ultrasonography (n = 1), malignancy other than gastric neoplasms (n = 2), or recent surgical procedures (n = 2). Thus, 60 patients were studied and underwent ultrasonography postoperatively. The mean age of the patients was 71.2 years (range 49-88 years). Women accounted for 26.7% of patients. The mean BMI was 22.4 (range 16.5-28.8 kg/m^2). The mean operative time was 136.6 minutes (range 50-380 minutes).

Incidence of DVT after ESD

DVT was detected in 6 (10.0%; 95% CI, 2.3%-17.7%) of the 60 cases by ultrasonography the day after ESD. However, these patients with DVT were clinically asymptomatic.

Influence of ESD on plasma D-dimer levels in venous blood samples

After time-specific effects of D-dimer levels had been confirmed by 1-way repeated-measures analysis of variance in all patients ($P = .0009$), D-dimer levels were compared among time points.

In all patients, D-dimer levels in venous blood samples increased significantly from 0.988 ± 0.123 μg/mL before ESD to 1.383 ± 0.257 μg/mL immediately after ESD and 1.997 ± 0.410 μg/mL the day after ESD ($P = .0411$ or $P = .0026$, respectively). Additionally, the D-dimer level the day after ESD was significantly higher than that immediately after ESD ($P = .0239$ by paired *t* test). In patients with DVT, D-dimer levels immediately after ESD or the day after ESD tended to be elevated as compared with the before-ESD levels, although the difference in D-dimer levels between each time point was not statistically significant. In patients without DVT, there were no significant changes in D-dimer levels among any time points examined.

As shown in Figure 1, after interactions for times and groups of D-dimer levels had been statistically confirmed ($P = .001$ by 1-way repeated-measures analysis of variance), the D-dimer levels were compared between patients with versus without DVT at each time point. The D-dimer levels were higher in patients with DVT than in those without DVT at all time points examined: before ESD (1.88 ± 0.746 μg/mL vs 0.89 ± 0.105 μg/mL; $P = .0147$, unpaired *t* test), immediately after ESD (2.97 ± 1.722 μg/mL vs 1.2 ± 0.209 μg/mL; $P = .0368$, unpaired *t* test), and the day after ESD (6.47 ± 3.44 μg/mL vs 1.5 ± 0.193 μg/mL; $P = .0002$, unpaired *t* test) (Fig. 1).

Association with D-dimer levels and DVT development

The association with D-dimer levels and DVT development was assessed by using ROC curve analysis at 3 time points. As shown in Figures 2, 3, and 4, AUCs before ESD, immediately after ESD, and the day after ESD were 0.748 (95% CI, 0.620-0.852), 0.713 (95% CI, 0.582-0.822), and 0.843 (95% CI, 0.726-0.924), respectively.

Judging from the AUC values, the association with DVT development and D-dimer levels on the day after ESD was stronger than that before ESD or immediately after ESD. Thus, cut-off points showing optimal performance were

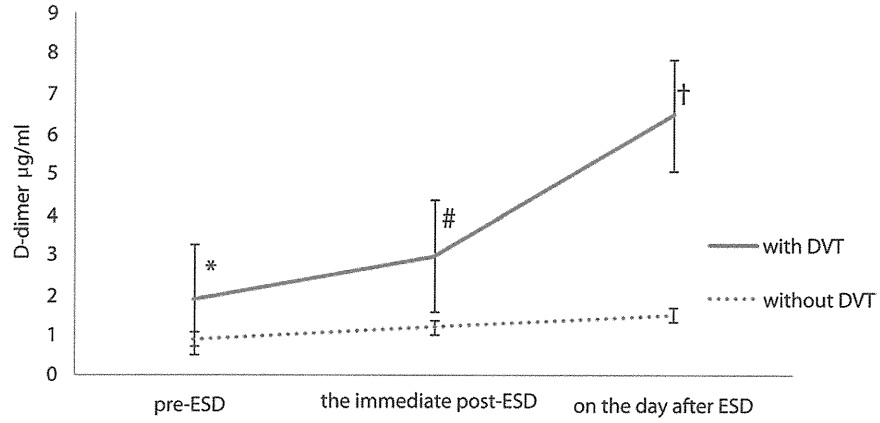

Figure 1. Differences in perioperative D-dimer levels in patients undergoing ESD. After interactions for times and groups of D-dimer levels had been statistically confirmed, D-dimer levels were compared between patients with versus without DVT at each time point. D-dimer levels were higher in patients with than without DVT at all time points examined. *DVT,* deep vein thrombosis; *ESD,* endoscopic submucosal dissection.

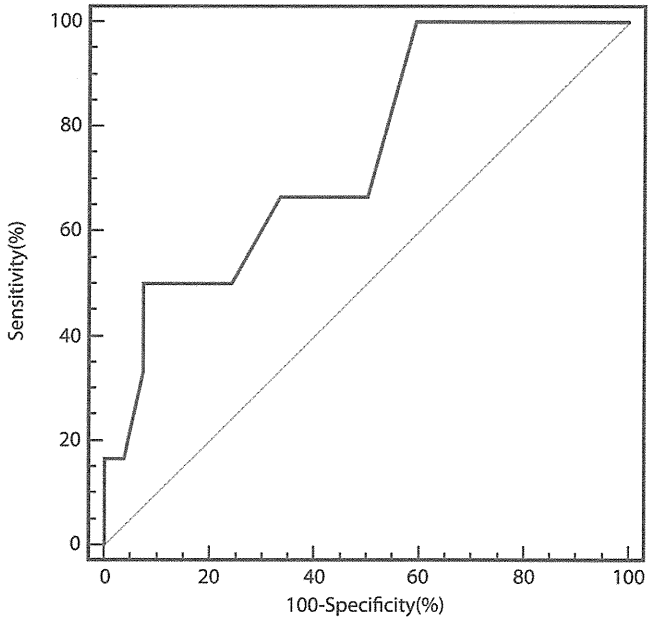

Figure 2. Receiver operating characteristic curve of D-dimer levels before endoscopic submucosal dissection. The curves are plotted with sensitivity (*y value*) and [100 − specificity] (*x value*).

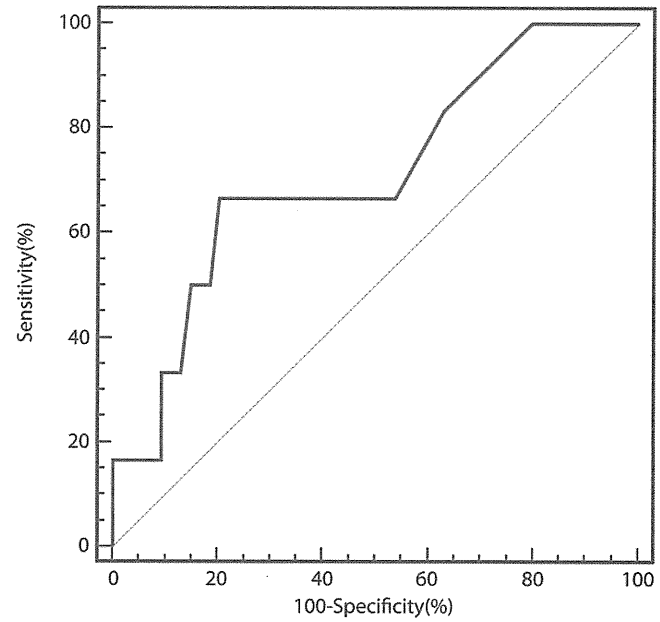

Figure 3. Receiver operating characteristic curve of D-dimer levels measured immediately after endoscopic submucosal dissection. The curves are plotted with sensitivity (*y value*) and [100 − specificity] (*x value*).

chosen by using the distance to the ROC curve and the Youden index for the D-dimer level the day after ESD. The resulting cut-off point was 1.9 μg/mL (sensitivity 83.33%; specificity 79.63%) for patients who underwent ESD (Table 1).

Factors in association with DVT development identified through univariate analyses

Based on the ROC curve analysis results and optimal cut-off points of D-dimer levels determined earlier, a D-dimer level above 1.9 μg/mL the day after ESD was used in univariate analyses.

As shown in Table 2, univariate analysis demonstrated that a high D-dimer level the day after ESD (P = .0009; 95% CI, 1.264-48.357; OR, 7.818) and comorbidities (P = .0267; 95% CI, 1.450-58.367; OR, 9.200) were significantly associated with the development of DVT. However, no other risk factors examined in the present study were significantly associated with DVT development.

Warfarin therapy was started for 6 patients with DVT 3 days after ESD, and disappearance of the thrombus was confirmed by ultrasonography 3 to 6 months after ESD in all patients.

DISCUSSION

This is the first prospective study to assess the incidence of DVT after ESD for gastric neoplasia. The overall fre-

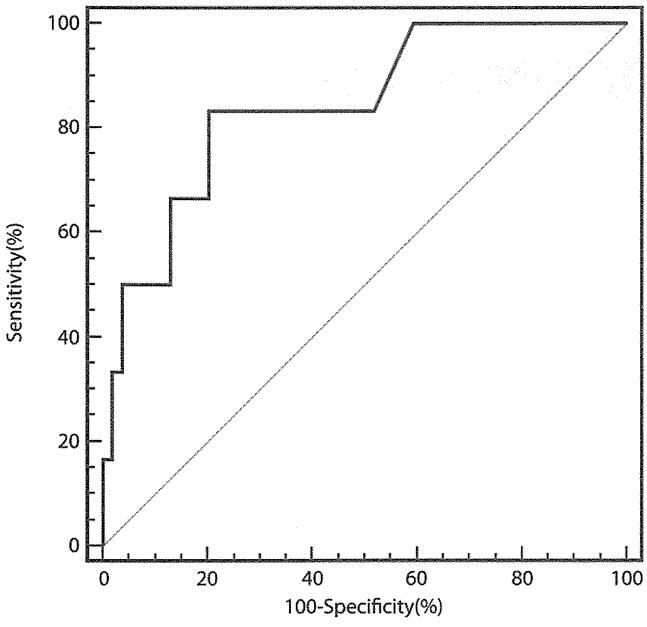

Figure 4. Receiver operating characteristic curve of D-dimer levels measured the day after endoscopic submucosal dissection. The curves are plotted with sensitivity (*y value*) and [100 − specificity] (*x value*).

quency of asymptomatic DVT after ESD was 10.0%. The incidence of objectively confirmed, hospital-acquired VTE is approximately 40% to 60% after major orthopedic surgery.[1] The overall incidence of VTE also has been shown to be approximately 20% for abdominal surgery without appropriate thromboprophylaxis.[14] The risk of thromboembolism with an ESD procedure was shown to be moderate, in this study, in accordance with American College of Chest Physicians guidelines.[1] For patients who are at moderate risk for VTE and also have a high risk of bleeding, the guidelines recommend using mechanical thromboprophylaxis (intermittent pneumatic compression, venous foot pump, and/or graduated compression stockings).

The American Society of Clinical Oncology VTE guideline panel has recommended that all hospitalized patients with cancer be considered for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications. The following treatment-related factors were identified as VTE risk factors in patients with malignant disease: recent major surgery, current hospitalization, active chemotherapy, active hormonal therapy, current or recent antiangiogenic therapy, current erythropoiesis-stimulating agent use, and the presence of central venous catheters. However, endoscopic therapies have not yet been demonstrated to be treatment-related risk factors for VTE. Although ESD treatment is not considered to be more invasive than abdominal surgery, the risk for thromboembolism (DVT) with ESD was moderate, that is, almost the same level as that of abdominal surgery. One explanation for these findings may be that ESD procedures often require patients to remain in the same position for prolonged periods with the use of intravenous sedation. In addition, the increased intraabdominal pressure created by air insufflations during ESD may cause venous pooling in the legs, via vessel wall damage, as suggested by animal studies of pneumoperitoneum.[15] Therefore, it may be more appropriate for air insufflations during ESD to use rapidly absorbed CO_2 gas in order to prevent gas accumulation in the intestine.

A D-dimer level exceeding 1.9 μg/mL the day after ESD was thought to be the most reliable marker associated with DVT development. D-dimer levels, especially the day after ESD, appear to have specific features for DVT development in patients undergoing ESD. The D-dimer is a marker of endogenous fibrinolysis and should therefore be detectable in patients with VTE.[16] The D-dimer assay has generally been reported to be a sensitive but nonspecific marker of DVT, thus making it a good rule-out test with appropriate pretest probability.[17,18] D-dimer levels usually show large individual deviations and could be elevated by bleeding and coagulation during the ESD procedure. Although we could not estimate precise amounts of bleeding during ESD procedures in this study, individual deviations in D-dimer levels could be corrected by the analysis procedure used in the present study. Furthermore, no patients needed blood transfusions in this study. In our experience, bleeding that requires blood transfusion appears to affect D-dimer levels. Although it is difficult to estimate precise amounts of bleeding during ESD procedures, in cases requiring transfusion, the volume of blood transfused might have to be assessed to determine the impact of bleeding during ESD procedures on D-dimer levels. In patients undergoing orthopedic or general surgery, D-dimer levels the day after surgery varied widely because of differences in internal hypercoagulability and surgical procedures, such as the amount of bleeding and frequencies of transient coagulation. Despite this variability, Dindo et al[19] reported that D-dimer levels do not increase after superficial surgery (no opening of the abdominal cavity, such as open hernia repairs), although D-dimer levels after general abdominal surgery are elevated even in patients without DVT. On the other hand, in our study of patients undergoing ESD, which does not involve opening the abdominal cavity, there were no significant changes in D-dimer levels at any of the time points examined in patients without DVT. However, D-dimer levels after ESD in patients with DVT were significantly elevated and were higher than in those patients without DVT. D-dimer levels are more specifically related to DVT after ESD. This is different from D-dimer levels after general abdominal surgeries, which are elevated even in patients without DVT.

Univariate analysis demonstrated that a high D-dimer level the day after ESD and comorbidities were significantly associated with the development of DVT, but other predictors were not. Because DVT development is complicated by some factors, multivariate analysis is desirable to evaluate predictors for DVT development after ESD.

TABLE 1. Cut-off points of D-dimer levels the day after ESD, showing optimal performance for diagnostic accuracy of DVT development

D-dimer levels (μg/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Likelihood ratio	Distance to ROC curve*	Youden index†
≥0.4	100	0	10		1	1	0
>0.8	100	40.74	15.8	100	1.69	0.5926	0.4074
>0.9	83.33	48.15	15.2	96.3	1.61	0.5446	0.3148
>1.9	83.33	79.63	31.2	97.7	4.09	0.2632	0.6296
>2	66.67	79.63	26.7	95.6	3.27	0.3906	0.4630
>2.2	66.67	87.04	36.4	95.9	5.14	0.3576	0.5371
>2.4	50	87.04	30	94	3.86	0.5165	0.3704
>4.4	50	96.3	60	94.5	13.5	0.5013	0.4630
>4.6	33.33	96.3	50	92.9	9	0.6677	0.2963
>4.7	33.33	98.15	66.7	93	18	0.6670	0.3148
>5.6	16.67	98.15	50	91.4	9	0.8335	0.1482
>7.9	16.67	100	100	91.5		0.8333	0.1667
>23.3	0	100	90			1	0

ESD, Endoscopic submucosal dissection; *DVT,* deep vein thrombosis; *PPV,* positive predictive value; *NPV,* negative predictive value; *ROC,* receiver operating characteristic.
*Distance to ROC curve = $\surd[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$.
†Youden index = sensitivity + specificity − 1.

However, in this study, multivariate analysis could not be done with such a small number of outcomes to assess. Further studies are necessary to permit meaningful multivariate analysis.

Interestingly, statistically significant differences in D-dimer levels between patients with DVT and without DVT were demonstrated not only immediately after ESD and the day after ESD but also before ESD. Mukubo and Kawamata[10] reported that patients with rheumatoid arthritis, a typical chronic inflammatory disease, have higher D-dimer levels preoperatively than patients with non-inflammatory osteoarthrosis, and that the D-dimer level was still elevated 1 week after the operation. This observation means that distinct disorders could show different perioperative hemostatic changes. These findings indicate that intrinsic or comorbid factors might be involved in DVT development after ESD in patients with gastric neoplasms.

The incidence of VTE had been considered to be lower in Japan than in Western countries. However, the mortality rate from PTE is rapidly increasing in Japan according to reports of routine autopsy examinations and has become comparable to that in Western countries, because this disease is now more often correctly diagnosed, Japanese lifestyles have become westernized, and the BMI has increased.[1,20] We showed that the overall frequency of DVT after ESD was 10.0%. However, all 6 patients with DVT were asymptomatic, and if ultrasonography of the lower limbs had not been performed, we would not have detected the DVT. In addition, the occurrence of PTE, a clinically serious condition, is thought to be rare after ESD because early ambulation is usually allowed, unlike orthopedic surgeries, in our setting. Nevertheless, when prolonged bed rest is required because of special situations such as ESD complications (perforation or late bleeding), a serious condition such as PTE might, on rare occasions, develop. Our results raise the possibility that greater awareness of the need for VTE prophylaxis is required.[21]

In conclusion, patients undergoing ESD were considered to be at moderate risk, as defined by the American College of Chest Physicians guidelines, for thromboembolism. D-dimer levels, especially on the day after ESD, appear to have specific features associated with DVT development in patients undergoing ESD. Because of the high incidence of DVT after ESD procedures, mechanical thromboprophylaxis should be considered in these patients, except for those with comorbidities, such as arterial circulatory deficits, cellulitis or thrombophlebitis of the lower limbs, congestive heart failure, and acute myocardial infarction, which might be aggravated by thromboprophylaxis. However, mechanical thromboprophylaxis has yet to be assessed by an interventional, randomized trial. Thus, further study is needed to determine appropriate

TABLE 2. Factors in association with DVT development identified through univariate analyses

Characteristic	Univariate analysis DVT, no. (%) Absence	Presence	*P* value
Sex			.7680
Female	14 (25.9)	2 (33.3)	
Male	40 (74.1)	4 (66.7)	
Age, y			.2212
<65	11 (20.4)	0 (0)	
≥65	43 (79.6)	6 (100)	
BMI (kg/m^2)			.6840
<25	41 (75.9)	5 (83.3)	
≥25	13 (24.1)	1 (16.7)	
Anti-thrombotic drugs			.9114
Not used	44 (81.5)	5 (83.3)	
Used	10 (18.5)	1 (16.7)	
Warfarin	1 (1.85	1 (16.7	.0551
Aspirin	6 (11.1)	0 (0)	.3894
Ticlopidine	1 (1.85)	0 (0)	.7368
Ethyl icosapentate	1 (1.85)	0 (0)	.7368
Dipyridamole	1 (1.85)	0 (0)	.7368
Comorbidity			.0267
Absence	49 (90.7)	3 (50.0)	
Presence	5 (9.3)	3 (50.0)	
Stroke	2 (3.70)	0 (0)	.6316
Heart failure	2 (3.70)	1 (16.7)	.1669
Renal failure	0 (0)	2 (33.3)	.0001
COPD	1 (1.85)	0 (0)	.7368
Operative time, min			.2839
<100	21 (38.9)	1 (16.7)	
≥100	33 (61.1)	5 (83.3)	
D-dimer level the day after ESD (μg/mL)			.0009
≤1.9	43 (79.6)	1 (16.7)	
>1.9	11 (20.4)	5 (83.3)	

DVT, Deep vein thrombosis; *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease; *ESD,* endoscopic submucosal dissection.

thromboprophylaxis recommendations for patients undergoing ESD.

REFERENCES

1. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:381S-453S.
2. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-9.
3. Yamamoto H, Kawata H, Sunada K, et al. Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy 2003;35:690-4.
4. Gotoda T, Kondo H, Ono H, et al. A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. Gastrointest Endosc 1999;50:560-3.
5. Oka S, Tanaka S, Kaneko I, et al. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. Gastrointest Endosc 2006;64:877-83.
6. Rosch T, Sarbia M, Schumacher B, et al. Attempted endoscopic en bloc resection of mucosal and submucosal tumors using insulated-tip knives: a pilot series. Endoscopy 2004;36:788-801.
7. Wells PS, Brill-Edwards P, Stevens P, et al. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. Circulation 1995;91:2184-7.
8. Freyburger G, Trillaud H, Labrouche S, et al. D-dimer strategy in thrombosis exclusion—a gold standard study in 100 patients suspected of deep venous thrombosis or pulmonary embolism: 8 DD methods compared. Thromb Haemost 1998;79:32-7.
9. Brill-Edwards P, Lee A. D-dimer testing in the diagnosis of acute venous thromboembolism. Thromb Haemost 1999;82:688-94.
10. Mukubo Y, Kawamata M. Higher preoperative D-dimer value remain high postoperatively in patients with rheumatoid arthritis compared with those with osteoarthrosis. J Anesth 2006;20:51-3.
11. Gotoda T, Yanagisawa A, Sasako M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000;3:219-225.
12. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:299S-339S.
13. Akobeng AK. Understanding diagnostic tests 3: receiver operating characteristic curves. Acta Paediatr 2007;96:644-7.
14. Sakon M, Maehara Y, Yoshikawa H, et al. Incidence of venous thromboembolism following major abdominal surgery: a multi-center, prospective epidemiological study in Japan. J Thromb Haemost 2006;4: 581-6.
15. Jorgensen JO, Gillies RB, Lalak NJ, et al. Lower limb venous hemodynamics during laparoscopy: an animal study. Surg Laparosc Endosc 1994;4: 32-5.
16. Caprini JA, Glase CJ, Anderson CB, et al. Laboratory markers in the diagnosis of venous thromboembolism. Circulation 2004;109:I4-8.
17. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349: 1227-35.
18. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med 2004;140:589-602.
19. Dindo D, Breitenstein S, Hahnloser D, et al. Kinetics of D-dimer after general surgery. Blood Coagul Fibrinolysis 2009;20:347-52.
20. Sakuma M, Konno Y, Shirato K. Increasing mortality from pulmonary embolism in Japan, 1951-2000. Circ J 2002;66:1144-9.
21. Fujita S, Hirota S, Oda T, et al. Deep venous thrombosis after total hip or total knee arthroplasty in patients in Japan. Clin Orthop Relat Res 2000; 375:168–74.

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Primary gastrointestinal follicular lymphoma involving the duodenal second portion is a distinct entity: A multicenter, retrospective analysis in Japan

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We conducted a multicenter, retrospective study to determine the anatomical distribution and prognostic factors of gastrointestinal (GI) follicular lymphoma (FL). This study included 125 patients with stage I and II_1 GI–FL. Of the 125 patients, the small intestine was examined in 70 patients, with double-balloon endoscopy and/or capsule endoscopy. The most frequently involved GI–FL site was the duodenal second portion (DSP) (81%), followed by the jejunum (40%); 85% of patients with involvement of the DSP also had jejunal or ileal lesions. The absence of abdominal symptoms and macroscopic appearance of multiple nodules were significantly present in the DSP-positive group. During a median follow up of 40 months, six patients showed disease progression. Patients with involvement of the DSP had better progression-free survival (PFS) than those without such involvement ($P = 0.001$). A multivariate analysis revealed that male sex, the presence of abdominal symptoms, and negative involvement of the DSP were independently associated with poor PFS. In conclusion, most patients with GI–FL have duodenal lesions associated with multiple jejunal or ileal lesions. Gastrointestinal follicular lymphomas involving the DSP might be a distinct entity showing a favorable clinical course. (*Cancer Sci* 2011; 102: 1532–1536)

Primary gastrointestinal (GI) follicular lymphoma (FL) has been regarded as a relatively rare malignant disease, accounting for 1–3.6% of primary non-Hodgkin lymphomas of the GI tract.[1] In Japan, because screening for gastric cancer is common, asymptomatic patients can undergo routine endoscopic examinations. In recent years, however, this lymphoma has been increasingly reported.[2,3] Gastrointestinal follicular lymphomas are clinically indolent, harbor t(14;18) translocation similar to nodal follicular lymphomas,[4,5] and most tumors remain localized in the GI tract.[4]

The International Workshop classification (Lugano classification) is used for the clinical staging of common GI lymphomas, such as gastric mucosa-associated lymphoid tissue (MALT) lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, and Burkitt's lymphoma.[6] To date, the applicability of Lugano clinical staging to GI–FL has not been examined. Gastrointestinal follicular lymphomas are frequently found in the duodenum, but also involve other parts of the small intestine, as often detected by double-balloon endoscopy (DBE) or capsule endoscopy (CE).[7–9] However, there are no accurate data on the distribution of GI–FL in the whole GI tract of a large series of patient studies. Moreover, the clinical behavior of GI–FL, including overall and progression-free survival, has not been clarified. As well as this, ways of therapy are various, and there is no consensus.

We therefore conducted a multicenter, retrospective study of a large number of patients with GI–FL, in order to analyze the anatomical distribution of the tumors, clinical characteristics, and response to therapy, and to elucidate the prognostic factors for this disease.

Materials and Methods

Patient selection. Invitations to join the study were sent to members of the Japan Gastrointestinal Lymphoma Study Group, and 18 participating institutes in Japan formed the GI–FL Working Group. The method used was a questionnaire-based enquiry requesting clinical and pathological data from databases at each institute. The inclusion criteria were: patients diagnosed as having GI–FL by upper and lower endoscopies, together with biopsy, and tumor cells immunohistochemically positive for both CD10 and BCL2 proteins.

A total of 191 patients who had been diagnosed with GI–FL between 1996 and 2009 were retrospectively registered. We excluded 66 patients with stage II_2 and IV, because it was not clear whether the primary site was GI or nodal origin. We also excluded two patients with grade 3B, because these patients are

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managed as DLBCL and have separate molecular and clinical entities, ranging from grades 1 and 2 to 3A.[10,11] In 70 of the 125 patients, the small bowel was examined by DBE and/or CE (DBE only: 32 patients, CE only: 1 patient, both DBE and CE: 38 patients). The remaining 55 patients were examined by upper and lower endoscopies. Duodenal second portion (DSP) is detectable by routine upper endoscopy. Some of these patients were included in previous studies.[7,8] The diagnosis of FL, including the histological grade (1, 2, and 3A), was made according to the World Health Organization classification criteria.[12] The clinical staging of each patient was determined according to the Lugano classification.[6] Stage I, according to Lugano staging, could involve multiple segments of the GI tract. Involved Field Radiation Therapy (IF-RT) is sometimes considered for duodenal involvement alone, and this appears to be rare in this series. In addition, the FL international prognostic index (FLIPI) was used for the evaluation of patient status.[13] Staging methods, including computed tomography scans and/or PET and/or MRI were performed in all patients. Bone marrow biopsy was performed for all patients in the initial staging assessment. After treatment, upper and lower endoscopies (including DBE or CE) were performed and evaluated by biopsy for restaging. All study protocols were approved by the institutional review board at each institute and complied with all provisions of the Declaration of Helsinki.

Distribution and macroscopic classification. To determine the FL-affected sites, we anatomically subdivided the GI tract into the esophagus, stomach, duodenum (first to fourth portions), jejunum, ileum, cecum, colon, and rectum.

Endoscopically, the majority of GI–FL manifest as multiple small polyps or whitish nodules.[2,4,7–9] Although this macroscopic appearance can be categorized as lymphomatous polyposis type, endoscopists now prefer to use the term ''multiple nodules'' (MN).[2,4,8,9] We therefore classified the tumors macroscopically into MN and other types (superficial, polypoid, ulcerative, diffuse, and unclassified) for the purpose of this study.[14] The definition of lymphomatous lesions in the GI tract was based on the endoscopic findings and/or biopsy of the lesion.

Treatment and response. Patients underwent one of the following initial treatment modalities: (i) watch and wait; (ii) rituximab containing anthracycline-based chemotherapy; (iii) rituximab monotherapy; (iv) surgical resection and chemotherapy; or (v) surgery alone. The anthracycline-based regimens used were as follows: cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP); rituximab with CHOP (R-CHOP); or cyclophosphamide, pirarubicin, vincristine, and prednisolone, as previously described.[15,16] Antitumor responses were assessed after initial chemotherapy or at the end of treatment, and were classified as complete response (CR), partial response, no change, or progressive disease (PD), as previously described.[17]

Statistical analysis. Overall survival (OS) was measured from the date of diagnosis to the date of death or the last follow-up visit.[18] Progression-free survival (PFS) was measured from the date of diagnosis to the date when PD was first documented or when death occurred. Time to the next treatment was measured from the last day of primary treatment (when patients were treated) or from the date of diagnosis (when patients were not treated upon diagnosis) to the first date when treatment began. The probabilities of OS and PFS were calculated by the Kaplan–Meier method, and the values were compared using the log-rank test. All variables that influenced the prognosis with a probability of <0.1 were used for the multivariate Cox regression analysis. Other statistical differences were assessed using chi-squared test or Fisher's exact test. Although P-values < 0.05 were regarded as statistically significant, Bonferroni's correction was applied for multiple comparisons. All statistical analyses were performed using the SPSS software package (version 14.0; Chicago, IL, USA).[19]

Results

Patient characteristics. Patient characteristics are summarized in Table 1. The median age of the 125 patients was 59 years (range: 34–84 years). There was no obvious sex trend; the male : female ratio was 53% versus 47%. Ninety-six patients (77%) were asymptomatic when the disease was detected. Twenty-nine (23%) had abdominal symptoms, such as abdominal pain, abdominal discomfort, intestinal obstruction, or diarrhea.

Macroscopically, 80% of tumors were classified as MN type. Histologically, all tumors were found to be grade 1 or 2 (low grade). According to the Lugano classification, the clinical stages were as follows: stage I in 108 patients (86.4%), and stage II_1 in 17 patients (13.6%). The serum lactate dehydrogenase level was elevated in three patients (3%).

Table 1. Baseline patient characteristics of primary gastrointestinal follicular lymphomas

Characteristic	Values (%)
Age (years)	34–84
Median	59
Sex	
Male	66 (53)
Female	59 (47)
Clinical symptoms (n = 125)	
Abdominal pain	10 (8)
Abdominal discomfort	13 (10)
Intestinal obstruction	5 (4)
Diarrhea	1 (1)
Absent	96 (77)
Macroscopic type (n = 110)	
Multiple nodules (LP)	88 (80)
Polypoid	13 (12)
Ulcerative	5 (5)
Diffuse	2 (2)
Unclassified	2 (2)
Site of involvement (n = 125)	
Esophagus	0 (0)
Stomach	2 (2)
Duodenum	111 (89)
Bulbus	6 (5)
Second portion	101 (81)
Third or fourth portion	36 (29)
Jejunum	50 (40)
Ileum	28 (22)
Cecum	2 (2)
Colon	1 (1)
Rectum	2 (2)
Histological grade (n = 115)	
Low grade (grade 1–2)	115 (100)
Stage (Lugano) (n = 125)	
I	108 (86.4)
II_1	17 (13.6)
Serum LDH (n = 108)	
Normal	105 (97)
Elevated	3 (3)
FLIPI score (n = 107)	
Low	96 (90)
Intermediate	11 (10)

DLBCL, diffuse large B-cell lymphoma; FLIPI, follicular lymphoma international prognostic index; LDH, lactate dehydrogenase; LP, lymphomatous polyposis.

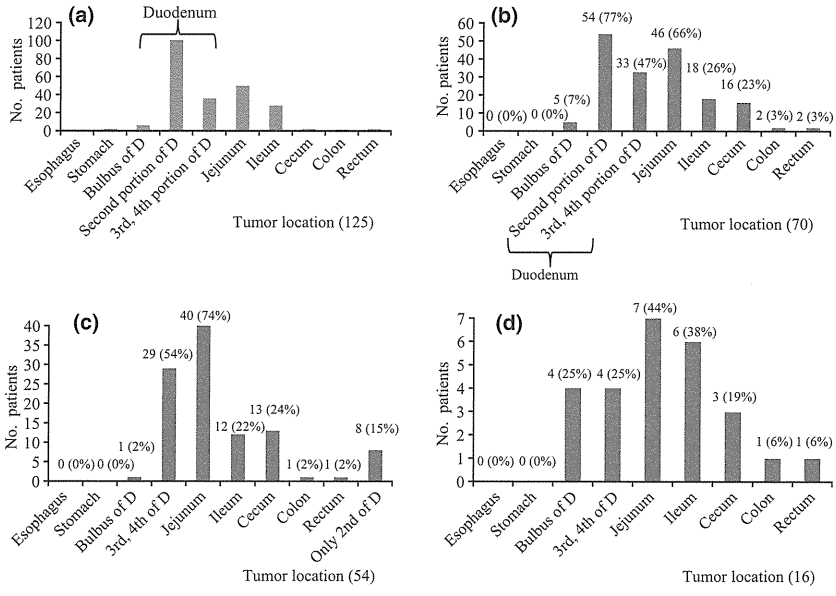

Fig. 1. Anatomical distribution of gastrointestinal follicular lymphoma. (a) Distribution of tumors in all patients (n = 125). Duodenal second portion (DSP) was the most frequent site. (b) Tumor location in 70 patients whose whole gastrointestinal tract was examined by double-balloon endoscopy and/or capsule endoscopy. Duodenum (D) is most commonly involved, followed by the jejunum. (c) Tumor location in patients whose whole gastrointestinal tract was examined, and DSP involvement was found (n = 54). Tumor locations were mainly in the small intestine. (d) Tumor location in patients whose whole gastrointestinal tract was examined, and DSP involvement was not found (n = 16). Tumor locations were mainly in the small intestine.

Distribution of tumors. The distribution of tumors in the GI tract is shown in Table 1 and Figure 1(a). The most frequent site was the DSP, followed by the jejunum. Figure 1(b–d) shows tumor locations in patients who were examined by DBE or CE. Of the 70 patients in whom the whole GI tract was surveyed, 63 had tumors in the duodenum (90%). Involvement of the DSP was found in 54 patients (77%). Figure 1(c) exhibits tumor locations in patients with involvement of the DSP. Eight of 54 patients (15%) with DSP involvement had tumors only in the DSP, whereas the other 46 patients (85%) with DSP involvement had extensive involvement within the small intestine; predominantly the jejunum (74%). Figure 1(d) shows tumor locations in patients without involvement of the DSP. In this group, most of the tumors were also located in the small intestine, and they tended to be found more frequently in the jejunum (44%). We also analyzed the affected segments of patients with or without involvement of the DSP (DSP-positive group or -negative group). In the DSP-positive group, the mean number of affected segments was 2.8 (range: 1–5). However, in the DSP-negative group, the mean number was 1.63 (range: 1–4).

Comparison between patients with and without DSP involvement. Table 2 shows the clinicopathological features of patients of the DSP-positive group or -negative group. Asymptomatic patients were significantly more frequent in the DSP-positive group than in the DSP-negative group (82% *vs* 54%, P = 0.0035). Macroscopically, the MN type was significantly more prevalent in the DSP-positive than the DSP-negative group (80% *vs* 29%, $P < 0.0001$). In addition, DSP-positive patients tended to be younger than DSP-negative patients.

Treatment and response. Thirty-three patients received no treatment (watch and wait), 42 patients were treated with immunochemotherapy with R-CHOP or R-CHOP-like regimens, and 29 patients were treated with rituximab alone. The other patients underwent surgery (n = 3), radiotherapy (n = 1), or *Helicobacter pylori* eradication (n = 3).

In total, CR was achieved in 61 patients (49%): 39 patients treated with R-CHOP or R-CHOP-like immunochemotherapy, 20 patients who received rituximab monotherapy, one of four patients who underwent surgery, one of three patients who underwent *Helicobacter pylori* eradication, and one of 33 patients who received no treatment (watch and wait). All four patients who underwent surgery had GI obstruction (ileus), but it is not known exactly whether they had major bleeding. The median duration of first response was as follows: R-CHOP or R-CHOP-like immunochemotherapy, 4 months (range: 0.7–13 months); rituximab monotherapy, 9 months (range: 3–60 months); and *Helicobacter pylori* eradication, 27 months.

Table 2. Comparison of clinicopathological findings between patients with duodenal second portion (DSP) involvement and without involvement

Characteristics	n	DSP positive (n = 101)	DSP negative (n = 24)	P-value*
Age (years)				
Median		59	65.5	0.022
Sex				
Male	66	52	14	0.546
Female	59	49	10	
Abdominal symptoms (n = 125)				
Absent	96	83	13	**0.0035**
Present	29	18	11	
Macroscopic type (n = 110)				
Multiple nodules	88	81	7	**<0.0001**
Others	22	3	19	
Serum LDH (n = 108)				
Normal	105	85	20	0.538
Elevated	3	3	0	
FLIPI score (n = 107)				
Low	96	79	17	0.441
Intermediate	11	8	3	

*$P < 0.0055$ is significant using Bonferroni's correction, as indicated by bold values. DSP, duodenal second portion; FLIPI, follicular lymphoma international prognostic index; LDH, lactate dehydrogenase.

Survival and prognostic factors. During a median follow up of 40 months (6–148 months), no patients died of primary disease. Six of 125 patients (5%) showed PD (Two patients were DSP positive, and four were DSP negative). The initial therapies for these PD patients were R-CHOP or R-CHOP-like immunochemotherapy (Two patients), watch and wait (Three patients), and

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Table 3. Results of univariate analysis for possible prognostic factors

Parameter	PFS		
	n	5-yr (%)	*P*-value*
Sex			
Female	60	98	**0.031**
Male	56	86	
Age (years)			
59 or younger	67	95	0.164
60 or older	49	92	
Abdominal symptoms			
Absent	90	97	**0.008**
Present	26	84	
DSP involvement			
Positive	97	98	**<0.001**
Negative	19	70	
Macroscopic type			
Multiple nodules	86	95	0.229
Others	19	88	
Hemoglobin level			
120 g/L or greater	81	95	0.393
Less than 120 g/L	18	100	
Serum LDH			
Normal	98	96	0.745
Elevated	3	100	
FLIPI score			
Low	90	97	0.34
Intermediate	10	88	
Therapy			
Watch and wait	33	86	0.921
Rituximab alone	29	92	
R-CHOP or R-CHOP like	42	97	

*Assessed by the log-rank test. Bold values indicate significance of $P < 0.05$. BM, bone marrow; DSP, duodenal second portion; FLIPI, follicular lymphoma international prognostic index; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone.

rituximab alone (One patient). The OS and PFS rates after 5 years were 100% and 93%, respectively.

Table 3 shows the results of the Kaplan–Meier analysis for possible prognostic factors for PFS. Patients with DSP involvement had significantly better PFS than those without DSP involvement (PFS, $P < 0.001$; Fig. 2). Other parameters, including absence of abdominal symptoms and female sex, were also associated with better PFS.

In the multivariate analysis, three factors (negative involvement of the DSP, male sex, and abdominal symptoms) were found to be independently and significantly associated with poor PFS (Table 4).

Discussion

Follicular lymphoma is one of the most frequent indolent lymphomas, and most are of nodal origin. However, recently, GI–FL has often been found by endoscopic examinations. The objective of this analysis was to determine the distribution of GI–FL in the GI tract, including extensive areas of the small intestine, and to determine new biological parameters for tumor progression. We found that the DSP was the most common site of involvement for GI–FL. Furthermore, most patients with duodenal involvement (85%) had extensive distribution throughout the small intestine, including the duodenum. These findings are similar to those of a smaller study by Nakamura *et al.*[7] and Kodama *et al.*[8] Among the patients whose entire GI tract was

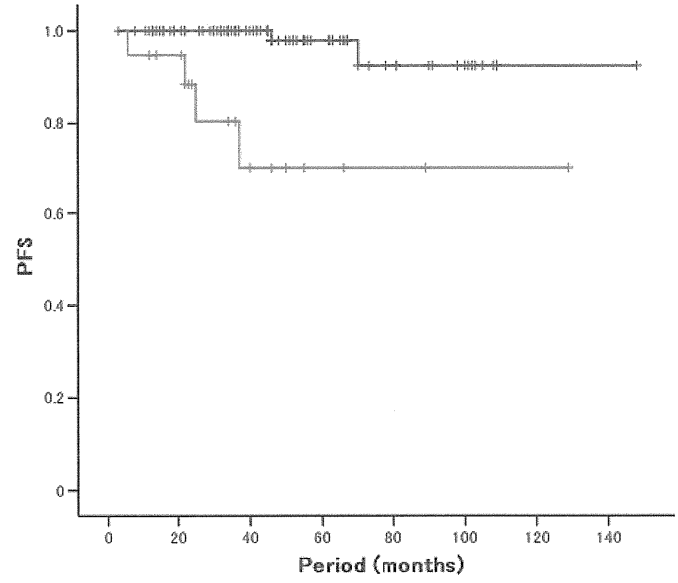

Fig. 2. Progression-free survival (PFS) of patients with gastrointestinal follicular lymphoma. PFS of patients with duodenal second portion (DSP) involvement (blue line, $n = 97$) and those without DSP involvement (green line, $n = 19$) (stage I and II_1; $P < 0.001$) are shown.

Table 4. Prognostic factors for progression-free survival in the multivariate analysis

Parameter	Hazard ratio (95% confidence interval)	*P*-value
Duodenal second portion involvement (–)	73.14 (5.84–915.72)	0.001
Abdominal symptoms (+)	18.07 (1.80–181.76)	0.014
Sex, male	67.86 (3.12–1476.06)	0.007

examined, the predominant site of involvement was the small intestine. Damaji *et al.*[20] examined 25 patients with GI–FL, and found that the most frequent site of involvement was the small intestine, with a predilection for the ileum and ileocecal region, followed by the duodenum. The difference between their findings and ours might depend on the number of patients. The Lugano classification was originally proposed for gastric lymphoma, and its applicability to GI–FL needs to be examined in detail. In this regard, the distribution of FL within the GI tract might be important to consider.

In the stage IV patient series, 21 of 41 patients (51%) had bone marrow involvement without any distant lymph node lesion. In these patients, GI–FL could be regarded as a primary tumor site. In the present study, we excluded these stage IV patients, because the tumor origin was unclear. However, this stage IV patient series will need further study in order to understand pathogenesis of GI–FL. In the stages I and II_1 patients, negative involvement of the DSP, male sex, and abdominal symptoms were found to be independently and significantly associated with poor PFS. In this analysis, DSP involvement was also an independent prognostic factor, but the 95% confidence interval was rather wide. The progression of patients in this series was so small (6 patients) that it might have influenced the results. Many DSP-positive patients might have their disease detected by medical check-up, because the duodenum is routinely examined in medical check-ups in Japan. It might also relate to lower tumor volume, which could correspond to increased PFS. The whole GI tract was examined in 70 patients.

The other 55 patients did not have the jejunum and ileum examined, as the DBE has only been applied since 2004. However, DSP lesions can be well detected by upper endoscopy (esophagogastroduodenoscopy), even in the other 55 patients. The progression of lymphomatous GI lesions, especially in the small intestine, is notoriously elusive. Moreover, patients were followed up according to each physician's policy, as this study was retrospective. There are limitations in this study.

We previously reported that in contrast to other FL, duodenal FL lacked follicular dendritic cells (FDC), and moreover, it had an immunoglobulin heavy-chain gene deviation from other FL, which resembled that of MALT lymphoma.[21,22] It has been reported that FL cells interact with FDC within the tumor, and that the presence of FDC gives a growth advantage to the lymphoma cells.[5] Thus, we can assume that the absence of FDC might have contributed to lower histological grades and slower tumor progression of duodenal FL. We previously examined the CD21 expression, which is the FDC marker in 30 FL samples of the DSP. Twenty-seven samples (90%) lacked FDC expression, and 17 samples, which had monoclonal bands by PCR examinations, showed an immunoglobulin heavy-chain gene deviation.[5] All of these patients were included in the present study. Taken together, the present results might indicate that GI–FL involving the DSP is distinct from other GI–FL. Of note, the duodenum itself is not uniform for FL.

According to the FLIPI score, 96 of our patients (90%) were classified into a low-risk group, a certain proportion of whom actually showed PD.

Histological transformation of FL to DLBCL is an important event, and is associated with high mortality rates. Montoto *et al.*[23] demonstrated that the risk of histological transformation by 10 years was 28%, and that risks for this transformation included advanced disease stage and a high-risk FLIPI score. In our patient group, no patient transformed to DLBCL. Our median follow-up duration was 40 months (6–148 months), but at this stage, GI–FL is still in the early days of development; longer periods of follow up are needed for a more thorough analysis of possible disease transformation.

In conclusion, GI–FL distribution assessment by DBE or CE showed that GI–FL was most frequently found in the duodenum, especially the DSP. Three risk factors (negative involvement of the DSP, sex, and abdominal symptoms) were found to be novel risk factors for the progression of GI–FL. Further prospective studies are required to establish optimal clinical strategies for GI–FL, including diagnosis and treatment.

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Disclosure Statement

The authors have no conflicts of interest.

References

1 Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distribution of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol* 1998; **9**: 717–20.
2 Yoshino T, Miyake K, Ichimura K *et al.* Increased incidence of follicular lymphoma in the duodenum. *Am J Surg Pathol* 2000; **24**: 688–93.
3 Sato Y, Ichimura K, Tanaka T *et al.* Duodenal follicular lymphomas share common characteristics with mucosa-associated lymphoid tissue lymphomas. *J Clin Pathol* 2008; **61**: 377–81.
4 Shia J, Teruya-Feldstein J, Pan D *et al.* Primary follicular lymphoma of the gastrointestinal tract: a clinical and pathologic study of 26 cases. *Am J Surg Pathol* 2002; **26**: 216–24.
5 Takata K, Sato Y, Nakamura N *et al.* Duodenal and nodal follicular lymphomas are distinct: the former lacks activation-induced cytidine deaminase and follicular dendritic cells despite ongoing somatic hypermutations. *Mod Pathol* 2009; **22**: 940–9.
6 Rohatiner A, d'Amore F, Coffier B *et al.* Report on a work shop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. *Ann Oncol* 1994; **5**: 397–400.
7 Nakamura S, Matsumoto T, Umeno J *et al.* Endoscopic features of intestinal follicular lymphoma: the value of double-balloon enteroscopy. *Endoscopy* 2007; **39**: E26–7.
8 Kodama M, Kitadai Y, Shishido T *et al.* Primary follicular lymphoma of the gastrointestinal tract: a retrospective case series. *Endoscopy* 2008; **40**: 343–46.
9 Higuchi N, Sumida Y, Nakamura K *et al.* Impact of double-balloon endoscopy on the diagnosis of jejuoileal involvement in primary intestinal follicular lymphomas: a case series. *Endoscopy* 2009; **41**: 175–8.
10 Wahlin BE, Sander B, Christensson B *et al.* CD8+ T-cell content in diagnostic lymph nodes measured by flow cytometry is a predictor of survival in follicular lymphoma. *Clin Cancer Res* 2007; **13**: 38–97.
11 Karube K, Guo Y, Suzumiya J *et al.* CD10$^-$ MUM1+ follicular lymphoma lacks BCL2 gene translocation and shows characteristic biologic and clinical features. *Blood* 2007; **109**: 3076–9.
12 Harris NL, Swerdlow SH, Jaffe ES *et al.* Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th edn. Lyon: IARC, 2008; 220–6.
13 Solal-Celigny P, Roy P, Colombat P *et al.* Follicular lymphoma international prognostic index. *Blood* 2004; **104**: 1258–65.
14 Nakamura S, Matsumoto T, Iida M *et al.* Primary gastrointestinal lymphoma in Japan: a clinicopathologic analysis of 455 patients with special reference to its time trends. *Cancer* 2003; **97**: 2462–73.
15 Hara T, Tsurumi H, Goto N *et al.* Phase II study of rituximab combined with THP-COP as first-line therapy for patients younger than 70 years with diffuse large B cell lymphoma. *J Cancer Res Clin Oncol* 2010; **136**: 65–70.
16 Czuczman MS, Weaver R, Alkzweny B *et al.* Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. *J Clin Oncol* 2004; **22**: 4711–6.
17 Shimada K, Matsue K, Yamamoto K *et al.* Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. *J Clin Oncol* 2008; **26**: 3189–95.
18 Fischbach W, Dragosics B, Kolve-Goebeler ME *et al.* Primary gastric B-cell lymphoma: results of a prospective multicenter study. The German–Austrian Gastrointestinal Lymphoma Study Group. *Gastroenterology* 2000; **119**: 1191–202.
19 Mori M, Kobayashi Y, Maeshima AM *et al.* The indolent course and high incidence of t(14;18) in primary duodenal follicular lymphoma. *Ann Oncol* 2010; **21**: 1500–5.
20 Damaji G, Verkarre V, Delmer A *et al.* Primary follicular lymphoma of the gastrointestinal tract: a study of 25 cases and a literature review. *Ann Oncol* 2003; **14**: 623–9.
21 Yoshino T, Akagi T. Gastric low-grade mucosa-associated lymphoid tissue lymphomas: their histogenesis and high-grade transformation. *Pathol Int* 1998; **48**: 323–31.
22 Kagami Y, Jung J, Choi YS *et al.* Establishment of a follicular lymphoma cell line (FLK-1) dependent on follicular dendritic cell-like cell line HK. *Leukemia* 2001; **15**: 148–56.
23 Montoto S, Davies AJ, Matthews J *et al.* Risk and clinical implications of transformation of follicular lymphoma to diffuse large B cell lymphoma. *J Clin Oncol* 2007; **25**: 2426–33.

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Ⅱ．診療の進歩

1．原因不明消化管出血

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要　旨

原因不明消化管出血（OGIB）は，原因検索追求の程度・再発性の有無により多種の消化管病変を含む．本邦では上下部消化管内視鏡を施行して原因が不明な消化管出血をここに含むことができるが，出血源が上下部内視鏡で検索が困難な小腸に存在するとは限らない．小腸内視鏡の進歩により50％近いOGIBの出血源を発見・診断・治療可能になった．同時に非ステロイド性抗炎症薬服用OGIB患者の出血源が高率に小腸潰瘍性病変であることが明らかとなり対策が求められている．

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Key words　原因不明消化管出血，カプセル内視鏡，バルーン内視鏡，NSAID起因性小腸粘膜傷害

はじめに

消化管出血患者の10から20％程度は初回の出血源検索で出血源を同定できない．これらの患者の約半数は出血を繰り返すとされ，入院の反復や多量の輸血を必要とする[1]．これら出血源が特定できない消化管出血を原因不明消化管出血（obscure gastrointestinal bleeding：OGIB）と称している．通常検査である上下部内視鏡検査で出血源が特定できない病変が多いことからOGIBの患者には小腸出血が多く含まれている．従来小腸病変の検索には小腸造影を用いなければ全小腸の評価は困難であり，内視鏡検査である術中内視鏡やプッシュ式小腸鏡などは侵襲が大きい上に，小腸全長の評価は極めて難しかった．近年開発され小腸内視鏡に革命をもたらしたカプセル内視鏡やバルーン内視鏡に加えて血管造影の進歩やCT（computed tomography）精度の向上が，小腸疾患診療に大きな変革をもたらした．新しい内視鏡は開腹手術しか方法がなかった多くの小腸疾患の内視鏡治療を可能とし，小腸診療に新しい道を切り開いてきている．ここではOGIBの概念や近年の診断・治療について概説する．

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1. 原因不明消化管出血（OGIB）とは

本来，原因不明の消化管出血とは，さまざまな検査を施行して原因が不明の消化管出血，という意味であるので，どのような検査をどれくらい施行して原因が不明なのかで意味が大きく異なってくる．最近日本では，上部消化管および下部消化管内視鏡検査で出血源が不明な消化管出血をOGIBと定義した（第5回カプセル内視鏡の臨床応用に関する研究会2010・日本カプセル内視鏡研究会用語委員会）．ここで上部消化管とは十二指腸Vater乳頭部より口側を指し，また下部消化管とは大腸である．米国消化器病学会では2007年に上下部消化管内視鏡検査，小腸X線検査（小腸造影のほかにCTなどによるバーチャル小腸検査を含む）を行っても出血源が不明な消化管出血をOGIBと定義しており，本邦の定義と異なっている．従って文献を読む場合には注意が必要で，常にOGIBをどのように定義しているのかを確認する必要がある．

消化管出血の10から20%程度は初回の出血源検索で出血源が同定できない．これらの患者の約半数は出血を繰り返し，35%～75%の患者が2回目の上部消化管内視鏡を，6%の患者が下部消化管内視鏡を繰り返し行われたと報告されている[1]．消化管出血で上下部消化管に出血源がなければ基本的に出血源はその間にある．近年この間，つまりVater乳頭部より回腸末端までの小腸を中部消化管と呼称している．ではOGIBが中部消化管出血（mid gastrointestinal bleeding）と同義であるかといえばそうではない．出血源が上下部消化管に存在するが上下部消化管内視鏡検査では診断が困難な出血源も少なくないため，このOGIBのなかにはそれら同定されなかった上下部消化管出血が含まれるためである．従ってOGIBの出血源として同定された病変には食道静脈瘤・十二指腸潰瘍・大腸憩室出血など様々な中部消化管出血以外の病変が含まれる．原因不明とは限らないが，中部消化管出血は全消化管出血の5%程度と考えられている[1]．

2. 顕在性出血と潜在性出血

OGIBは顕在性出血と潜在性出血に大きく分けられている．顕在性出血（overt bleeding）とは下血や血便などの可視的出血で，出血が持続している（on going）と出血の既往（previous）に分けられている．下血（melena）は通常上部消化管出血でみられる黒色便を，血便（hematochezia）は通常下部消化管で認められる赤色便（鮮血便）を指すものとして用語が定義されていることに留意して欲しい．潜在性消化管出血とは再発または持続する鉄欠乏性貧血および/または便潜血陽性患者と定義される．便潜血陰性の患者を消化管出血とすることに違和感を覚えるが，便潜血検査は，ヘモグロビン法，グアヤック法などで測定する対象が異なること，感度は人為的に設定されたものであること，間欠的出血では検出が困難な場合があることなどの理由により便潜血陰性でも消化管出血を否定することはできない．この潜在性消化管出血の定義は消化管出血であることが前提であるので，消化管出血以外である尿路出血や性器出血などの消化管出血以外の出血は除外されており，消化管出血による鉄欠乏性貧血だが出血が捕らえられていない症例をここに分類している．定義にこだわる理由は，消化管出血以外の出血源を精査することなく，鉄欠乏性貧血をOGIBと安易に診断することに警鐘するためである．

3. 原因不明消化管出血（OGIB）の診断

小腸検査には現在カプセル内視鏡，バルーン内視鏡，小腸造影，血管造影が主力となり，CTや体外式超音波も試みられている．さまざまな

表 1. 各種小腸検査法の特徴

	利点	欠点	得意な分野	苦手な分野
カプセル内視鏡検査	侵襲が少なく安全性が高い 微小病変でも高診断能 検査に技術が不用	1.5% 程度に滞留 画像読影に時間が必要 治療・生検ができない	血管性病変(小型を含む) 潰瘍性病変 濾胞性リンパ腫	粘膜に異常のない病変 粘膜下腫瘍，憩室
バルーン内視鏡検査	生検・治療・点墨が可能 選択的挿入が可能 大型病変を見落とさない	穿孔・膵炎などの合併症 麻酔などが必要 癒着などで挿入困難	腫瘍性病変 狭窄病変精査 出血している病変	止血小型血管性病変 高度癒着後方病変
小腸造影検査	狭窄・瘻孔も描出可能 小腸全長の評価可能	凹凸がないと描出困難 良好な画像には技術が必要	狭窄を有する病変 Crohn病	血管性病変
血管造影検査	出血性病変の精査・治療 腫瘍性病変の診断	止血時出血源診断困難	出血病変 腫瘍性病変	止血病変 潰瘍性病変
造影CT検査	侵襲が少なく安全性が高い 短時間で検査可能	小型病変の診断困難	腫瘍性病変 出血有無の評価	潰瘍性病変 小型血管性病変
CTバーチャル小腸検査	侵襲が少なく安全性が高い	手技の確立が不十分 施行できる施設はわずか	腫瘍・狭窄の評価 大型病変	小型病変
体外式超音波検査	侵襲がなく安全性が高い	小腸全長の評価困難 手技の確立が不十分	腸閉塞原因検索 Crohn病の狭窄精査	小型病変

小腸検査法の詳細については今号の特集における他稿の参照をお願いするが，概略を表1に示した．近年急速に世界に広まっている小腸検査法がカプセル内視鏡とバルーン内視鏡である．カプセル内視鏡は，患者に対する身体的な負担が少なく，偶発症も嚥下困難のない患者ではカプセルの滞留以外に重篤なものがないため，スクリーニング検査には最適である．カプセル内視鏡は病変を観察，指摘することに主な有用性があり，患者負担の少ないことから経過観察にも優れている．しかし，生検して組織学的に確定診断することや，内視鏡治療に用いることはできない．一方バルーン内視鏡は通常内視鏡のほぼすべての処置が可能で，経口的・経肛門的に2回検査を施行すれば癒着のない小腸であれば90% 以上で全小腸のいずれの部位にも到達が可能である．バルーン内視鏡はこのように全小腸の検査が可能であり，術中内視鏡検査の需要を激減させた．しかし，バルーン内視鏡は小腸内に長く挿入するため疼痛が強く，セデーションなしには検査が困難である．また，誤嚥・腸管穿孔や膵臓の圧迫などで膵炎になる合併症が報告され，患者に対する侵襲はカプセル内視鏡と比較してはるかに大きい．そこで，狭窄が認められない小腸では，カプセル内視鏡をスクリーニングに用いて病変を指摘し，バルーン内視鏡を用いて指摘された病変に対して精査，治療を行うというのが両内視鏡をもちいた基本的戦略である[2]．

当院におけるOGIBに対するカプセル内視鏡による出血源検出率は40% 程度であるが，これはOGIB患者に1回だけカプセル内視鏡を施行した場合の診断率で，患者の出血直後に施行した場合では診断率は増加する．特に出血中の患者であれば出血を同定することにより出血部位を診断できる．この場合腸管内血液のために出血源をカプセル内視鏡で診断できないが，カプセル内視鏡による病変位置の検出により，臨床的診断・治療のプロセスは大きく進歩する[3]．2010年8月に行われた第1回カプセル内視鏡・ダブ

ルバルーン内視鏡合同国際会議(1st International Conference on Capsule Endoscopy and Double Balloon Endoscopy：ICCD 2010)において，鉄欠乏性貧血に長期間便潜血陽性を認めるOGIB患者におけるカプセル内視鏡の病変検出率は80%近いと報告された．カプセル内視鏡の第一目標は病変の診断よりも病変の検出なのである．カプセル内視鏡で病変の位置や性格を推定できれば，バルーン内視鏡での精査，治療時の患者の負担，検査時の人的，時間的負担が減少し，より適切なものとなる．内視鏡診断では，バルーン内視鏡と比較してカプセル内視鏡は微小血管性病変の検出を得意とするが，粘膜に異常を認めない粘膜下腫瘍や憩室などでは病変を指摘できないことが少なくない．粗大病変を確実に指摘できるバルーン内視鏡と診断面においても良い補完関係にある．

OGIBはカプセル内視鏡やバルーン内視鏡の一番の適応と考えられている．われわれの施設では，持続的に出血している場合は一期的に診断・治療を完結しうるダブルバルーン内視鏡を可能な限り積極的に行っている．この場合，血液残渣の影響をうけず，また病変部位に近づくと腸液が赤味を帯びてくることで出血部位の同定の助けになることから，前処置を施行しない経口的挿入としている．しかし，バルーン内視鏡は1人では困難なので緊急内視鏡ができないことが少なくない．その場合は直ちにカプセル内視鏡を行う．また，出血が既に止まっている症例，または鉄欠乏性貧血に便潜血検査陽性を伴う症例のように非顕性出血症例では，カプセル内視鏡で病変の存在診断を行い，後日バルーン内視鏡で質的診断や治療を行うようにしている．カプセル内視鏡では硬いカプセルが病変に接触して出血を誘発し，待期的な検査で責任病変が解ることも多い．われわれの施設では，検査後追跡調査を行った108例のOGIB患者のうち52例で出血源を同定できたことを報告し[4]，OGIB患者の約半数の症例の出血源を特定することができるようになったが，この割合は本邦における他施設とほぼ同様な割合である．

4. 原因不明消化管出血（OGIB）の出血源

中部消化管が出血源の場合は通常の上下部消化管内視鏡検査では同定できないためOGIBとなる．この中部消化管出血の出血病変には地域差が認められていて，西欧では約70%が血管性病変，アジアでは45%が潰瘍性病変と報告されている[1]．当施設では確定診断したOGIBの出血源は現在，腫瘍性病変25%，血管性病変35%，潰瘍性病変30%，小腸外病変10%程度であるが，この割合は変化傾向にある．カプセル内視鏡・バルーン内視鏡登場当初は繰り返す消化管出血や鉄欠乏性貧血で長年悩まされた患者が優先検査対象で，比較的高頻度に良性の腫瘍性病変を診断した．図1はリンパ管腫であるがこの腫瘍の成長は遅く，良性腫瘍であるため輸血していれば致死的ではない．このような長年患者を悩ませた腫瘍の検出は減少傾向で，近年は非ステロイド性抗炎症薬（NSAID）起因性小腸粘膜傷害による小腸潰瘍の検出が急増している．カプセル内視鏡保険適応において，カプセル内視鏡の使用はNSAID起因性小腸傷害に対しては慎重であることが求められていた．NSAID起因性小腸傷害ではまれに膜様狭窄（図2）という狭窄病変が出現し，その狭窄にカプセルが滞留と呼ばれる詰まりを起こすことが危惧されたためである．近年，このNSAID起因性小腸傷害でのカプセル滞留の頻度は少ないこと，もし滞留しても膜様狭窄は狭窄が薄いためバルーン内視鏡で拡張してカプセルの摘出が可能なことが多いことがわかった．このため多くの施設においてOGIB精査目的でNSAID服用者にカプセル内視鏡を施行するようになり，当施設でも近年使用頻度が増加したため，NSAID起因性潰瘍性病変の検出