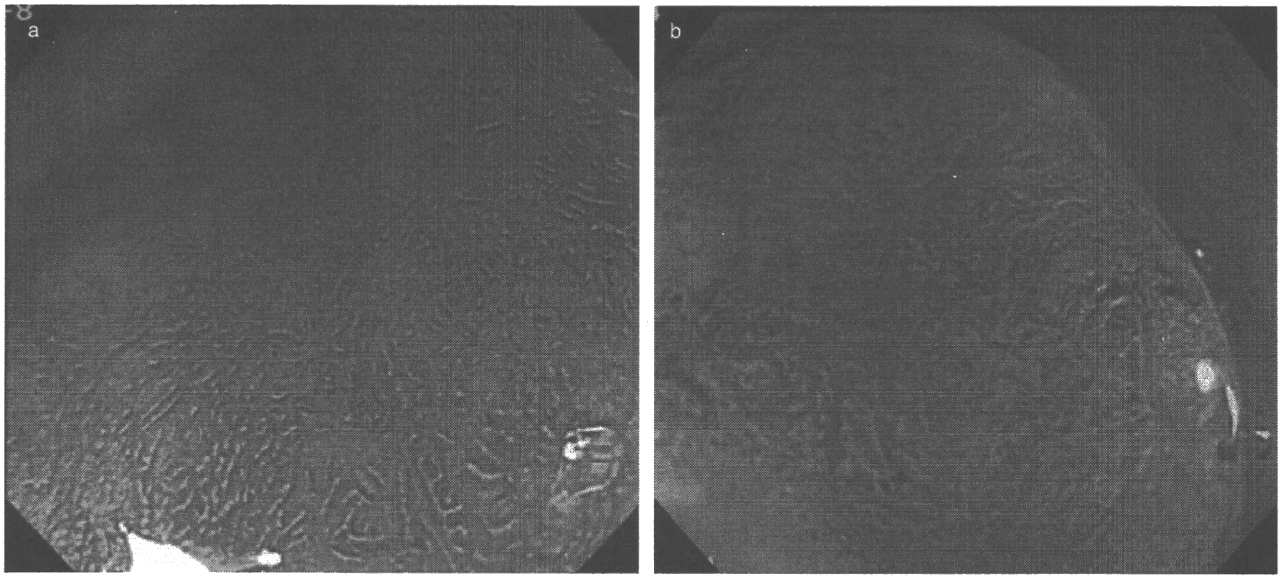

Figure 7 (a) Non-invasive pattern. (b) Invasive pattern.

Table 1 Clinicopathological characteristics of lesions

	Pedunculated type	Sessile type	Superficial type
Number of lesions	57	175	147
Tumor size (mean ± SD)	17.2 ± 6.5 mm	16.5 ± 8.5 mm	16.3 ± 8.6 mm
Histopathological diagnosis			
Intramucosal cancer	37	98	44
s.m.-s. (< 1000 μm)	6	8	26
s.m.-d. (≥ 1000 μm)	14 (24.6%)	69 (39.4%)	77 (52.4%)
Distribution			
Right colon	9 (15.8%)	43 (24.6%)	58 (39.5%)
Left colon	44 (77.2%)	60 (34.3%)	41 (27.9%)
Rectum	4 (7.0%)	72 (41.1%)	48 (32.6%)

SD, standard deviation; s.m.-d., submucosal deep invasion; s.m.-s., submucosal superficial invasion.

Histopathology

Resected specimens were fixed in a 10% buffered formalin solution, embedded on paraffin and then cut into 2–3 mm slices. Each section was stained with hematoxylin–eosin and then histopathologically diagnosed by a highly experienced pathologist. Histopathological diagnosis was based on the Vienna classification.[16] A microscope with a built-in ruler was used to determine the depth of s.m. invasion.

Statistical analysis

Among the three macroscopic subtypes, the proportion of s.m. invasion was compared using the χ^2-test. When characteristics showed a significant difference, we performed logistic regression including all such characteristics as part of the model. Statistical analyses were done with the SPSS 11.0 for Windows software package (SPSS, Chicago, IL, USA). Each test was two-sided and a P-value < 0.05 was defined as being statistically significant.

Results

Clinicopathological characteristics

Table 1 shows the clinicopathological characteristics of the early CRC examined in this study. The superficial type had a significantly higher frequency of s.m.-d. invasion compared to the pedunculated and sessile types (52.4% [77/147] vs 24.6% [14/57] and 39.4% [69/175], respectively). The pedunculated type was most commonly diagnosed in the left colon (77.2% [44/57]) in contrast to the sessile and superficial types, which were most commonly diagnosed in the rectum (41.1% [72/175]) and the right colon (39.5% [58/147]), respectively.

Endoscopic factors for submucosal deep invasion

In the pedunculated type, a larger tumor size (≥ 20 mm), loss of lobulation, excavation, the presence of an invasive pit pattern and

Table 2 Relationship between endoscopic factors and submucosal deep invasion in 57 pedunculated type lesions

		s.m.-d. ca./*n*	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≥ 20 mm	10/22	< 0.01	1.49	0.22–10.31	0.69
	< 20 mm	4/35				
Loss of lobulation	Present	12/28	< 0.01	3.15	0.47–21.01	0.24
	Absent	2/29				
Excavation	Present	7/11	< 0.001	2.52	0.36–17.47	0.35
	Absent	7/46				
Demarcated depressed area	Present	2/4	0.25	ND	ND	ND
	Absent	12/53				
Pit pattern	Invasive	7/9	< 0.0001	4.62	0.50–42.98	0.18
	Non-invasive	7/48				
Stalk swelling	Present	9/19	< 0.01	2.00	0.40–10.10	0.40
	Absent	5/38				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

Table 3 Relationship between endoscopic factors and submucosal deep invasion in 175 sessile type lesions

		s.m.-d. ca./*n*	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≥ 15 mm	53/96	< 0.0001	1.86	0.61–5.66	0.28
	< 15 mm	16/79				
Loss of lobulation	Present	63/92	< 0.0001	5.99	1.76–20.42	< 0.01
	Absent	6/83				
Excavation	Present	42/57	< 0.0001	1.51	0.45–5.05	0.50
	Absent	27/118				
Demarcated depressed area	Present	19/29	< 0.01	0.20	0.03–1.44	0.11
	Absent	50/146				
Pit pattern	Invasive	55/61	< 0.0001	52.74	10.89–255.33	< 0.0001
	Non-invasive	14/114				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

swelling of the stalk were each significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, however, there was no independent risk factor for s.m.-d. invasion (Table 2).

In the sessile type, the presence of a larger tumor size (≥ 15 mm), loss of lobulation, excavation, a demarcated depressed area and an invasive pit pattern were each significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, the independent risk factors for s.m.-d. invasion were loss of lobulation and the existence of an invasive pit pattern ($P < 0.01$, odds ratio = 5.99; and $P < 0.0001$, odds ratio = 52.74, respectively) (Table 3).

In the superficial type, fullness, fold convergency, a demarcated depressed area and an invasive pit pattern were significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, the independent risk factors for s.m.-d. invasion were the existence of fullness and an invasive pit pattern ($P < 0.01$, odds ratio = 9.25; and $P < 0.0001$, odds ratio = 209.67, respectively) (Table 4).

Pit pattern analysis

The clinical classification of pit patterns has proven to be effective in differentiating intramucosal or s.m.-s. invasion < 1000 μm from s.m.-d. invasion (≥ 1000 μm). The calculated sensitivity, specificity, positive predictive value, negative predictive value and accuracy are shown in Table 5. The overall accuracy for differentiating intramucosal or s.m.-s. invasion from s.m.-d. invasion was 84.2% in the pedunculated type, 88.6% in the sessile type and 92.5% in the superficial type. The diagnostic accuracy of the invasive pit pattern was lower for pedunculated type lesions than for the other two macroscopic subtypes.

Number of endoscopic factors analysis

Diagnostic accuracy based on the number of positive endoscopic factors observed during conventional endoscopy performed without magnification is shown in Table 6. When a particular lesion included four or more such endoscopic factors, overall accuracy was highest for the pedunculated type (86.0%). As for both the sessile and superficial types, however, overall accuracies of 81.1% and 80.3%, respectively, were highest when a particular lesion included two or more of the endoscopic factors.

Table 4 Relationship between endoscopic factors and submucosal deep invasion in 147 superficial type lesions

		s.m.-d. ca./n	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≥ 10 mm	68/123	0.11	ND	ND	ND
	< 10 mm	9/24				
Fullness	Present	66/86	< 0.0001	9.25	2.14–40.00	< 0.01
	Absent	11/61				
Fold convergency	Present	38/50	< 0.0001	1.99	0.50–7.97	0.33
	Absent	39/97				
Demarcated depressed area	Present	52/68	< 0.0001	1.92	0.45–8.15	0.37
	Absent	25/79				
Pit pattern	Invasive	76/86	< 0.0001	209.67	23.05–1907.48	< 0.0001
	Non-invasive	1/61				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

Table 5 Diagnostic analysis of invasive pit pattern by macroscopic type

	Macroscopic type		
	Pedunculated type	Sessile type	Superficial type
Sensitivity	50.0%	79.7%	98.7%
Specificity	95.3%	94.3%	85.7%
PPV	77.8%	90.2%	88.4%
NPV	85.4%	87.7%	98.4%
Overall Accuracy	84.2%	88.6%	92.5%

The χ^2-test evaluates differences in sensitivity and there were significant differences among all three groups ($P < 0.05$).
NPV, negative predictive value; PPV, positive predictive value.

Discussion

Diagnosis of submucosal deep invasive cancer

We investigated various endoscopic factors including high magnification diagnosis of pit patterns in order to evaluate the predictive factors for s.m.-d. invasion in three macroscopic subtypes of early CRC. A higher incidence of s.m.-d. invasion in the superficial type and a difference in the diagnostic accuracy for predicting s.m.-d. invasion between the pedunculated type and the other two macroscopic types were found in our study.

In the superficial type, fullness and existence of the invasive pit pattern were independent risk factors for s.m.-d. invasion. Yokota *et al.* reported that conventional endoscopic findings were subjective,[12] however, fullness may not be a universal factor for determining s.m.-d. deep invasion. In the sessile type, multivariate analysis showed that loss of lobulation and existence of the invasive pit pattern were each independent risk factors for s.m.-d. invasion. A total of 68 lesions were excluded because of the poor quality of their magnifying colonoscopy pictures, however, so there could very well be a bias towards better pit pattern diagnostic analysis results in this study for both the superficial and sessile types.

In the pedunculated type, we were unable to demonstrate any independent endoscopic factors despite using pit pattern analysis. In addition, a combination of factors in pedunculated type lesions examined without magnification indicated that size and stalk swelling together had the same degree of overall diagnostic accuracy as produced by an analysis of invasive pit pattern using magnification. These results indicated that it is difficult to estimate the depth of tumor invasion in pedunculated type lesions using current magnification methods.

Endoscopic diagnosis versus non-lifting sign

In previous studies, Uno *et al.* reported the clinical usefulness of the non-lifting sign to predict the depth of invasion prior to EMR for early CRC.[17] In addition, Ishiguro *et al.* classified s.m. extension of early colorectal cancer as s.m.1 (infiltration into the upper third of the s.m. layer), s.m.2 (middle third) or s.m.3 (lower third) according to the vertical level of s.m. invasion. They reported that the non-lifting sign indicated s.m.3 invasion had a sensitivity of 100% and a specificity of 83% although only 30.4% of s.m.2 cancers were non-lifting sign positive in their study.[18]

Our group reported that the sensitivity, specificity and accuracy of the non-lifting sign (61.5%, 98.4% and 94.8%, respectively) were insufficient in comparison with endoscopic diagnosis of invasion depth (84.6%, 98.8% and 97.4%, respectively).[19] Given these results, magnifying colonoscopy can be considered more effective than the non-lifting sign in distinguishing s.m.-d. invasive cancer based on the techniques and methods used in this study.

Magnifying colonoscopy versus endoscopic ultrasonography

We previously reported that high magnification colonoscopy was superior to endoscopic ultrasonography (EUS) for the determination of invasion depth in early CRC.[13] In contrast, Hurlstone *et al.* demonstrated the superiority of EUS mini-probe staging over magnification colonoscopy.[20] At the present time, it is unclear whether magnification colonoscopy or EUS is superior for staging purposes. There is a learning curve associated with both modalities so the results can be influenced by the skill and experience of the endoscopist performing the procedure.

Magnifying endoscopy

We routinely use magnifying colonoscopy because a magnifying endoscope enables standard conventional observations, but can

Table 6 Diagnostic analysis according to number of positive endoscopic factors

		Number of positive endoscopic factors				
		≥ 1	≥ 2	≥ 3	≥ 4	≥ 5
Pedunculated type	Sensitivity	92.7%	71.4%	64.3%	42.7%	14.3%
	Specificity	44.2%	67.4%	86.1%	100%	100%
	PPV	35.1%	41.7%	60.0%	100%	100%
	NPV	95.0%	87.9%	88.1%	84.3%	78.2%
	Overall accuracy	56.1%	68.4%	80.7%	86.0%	79.0%
Sessile type	Sensitivity	97.1%	87.0%	52.2%	13.0%	ND
	Specificity	46.2%	77.4%	90.6%	99.1%	ND
	PPV	54.0%	71.4%	78.3%	90.0%	ND
	NPV	96.1%	90.1%	74.4%	63.4%	ND
	Overall accuracy	66.3%	81.1%	75.4%	65.1%	ND
Superficial type	Sensitivity	100%	87.0%	45.5%	1.3%	ND
	Specificity	34.3%	72.9%	91.4%	100%	ND
	PPV	62.6%	77.9%	85.4%	100%	ND
	NPV	100%	83.6%	60.4%	48.0%	ND
	Overall accuracy	68.7%	80.3%	67.4%	48.3%	ND

ND, no data; NPV, negative predictive value; PPV, positive predictive value.

also provide images from low to high magnification using a one-touch operational system. It is possible to distinguish between non-neoplastic and neoplastic lesions and estimate depth of tumor invasion in less than 10 minutes. The insertion technique and manipulation of the magnifying endoscope also are similar to those of a conventional endoscope during colonoscopy.[21,22]

Treatment strategy

In considering therapeutic strategies, EMR should be the first-line treatment for intramucosal and s.m.-s. early CRC because it is less invasive. LN metastasis is more frequently present in s.m.-d. invasive cancer,[23,24] however, so we should avoid EMR for s.m.-d. invasive cancer because histopathological assessment is more difficult. In addition, incomplete EMR is thought to cause accelerated growth of any residual cancer and is also considered to be a positive risk factor for distant metastasis.[25,26] Recognizing the importance of reported endoscopic factors for predicting s.m.-d. invasion therefore is essential in determining the proper treatment choice in any given case.

For sessile and superficial type lesions endoscopically diagnosed as having an invasive pit pattern, a high percentage of cases revealed invasive cancer, particularly s.m.-d. cancer, so surgical resection is undoubtedly the appropriate treatment. Those lesions endoscopically diagnosed as having a non-invasive pattern, however, were mostly limited to the intramucosal layer, which makes EMR feasible. It is also technically possible now to remove large superficial lesions using the more recently developed endoscopic submucosal dissection procedure.[27–30]

In the pedunculated type, it is difficult to accurately estimate the depth of s.m.-d. invasion prior to endoscopic treatment, but the endoscopic resection of a pedunculated polyp is relatively easy from a technical point of view. It is recommended therefore that a pedunculated type lesion first be removed endoscopically followed by a histopathological determination of the depth of invasion. A surgical resection should then be performed when stalk invasion or lymph-vessel involvement has been revealed histopathologically.

Limitations

This was a retrospective study conducted in a single center so the results need to be confirmed in a prospective multi-center trial. In addition, only pedunculated, sessile and superficial lesion macroscopic subtypes were included in this study.

Conclusion

Pit pattern high magnification diagnosis proved to be useful for predicting s.m.-d. invasion in sessile and superficial type lesions, although it was not helpful with the pedunculated type. Consequently, diagnostic endoscopic treatment is advisable for pedunculated early CRC.

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BRIEF ARTICLE

Endoscopic diagnosis of cytomegalovirus gastritis after allogeneic hematopoietic stem cell transplantation

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Abstract

AIM: To clarify the endoscopic and clinical findings of cytomegalovirus (CMV) gastritis after allogeneic hematopoietic stem cell transplantation (allo-SCT).

METHODS: Between 1999 and 2005, 523 patients underwent allo-SCT at our hospital, and 115 of these patients with gastrointestinal symptoms underwent esophagogastroduodenoscopy.

RESULTS: CMV gastritis was diagnosed pathologically in seven patients (1.3%) with the other 108 patients serving as controls. Six of the seven patients developed positive CMV antigenemia, and five complained of abdominal pain. Development of abdominal pain preceded CMV antigenemia in four of the five patients. Endoscopic examination showed oozing (n = 2), erosion (n = 6), and redness (n = 5) in the seven patients with CMV gastritis, while the control patients showed oozing (n = 3), erosion (n = 24), and redness (n = 100). Erosion and oozing were more frequently documented in patients with CMV gastritis compared with the controls, and the differences were statistically significant (P = 0.0012 and 0.029, respectively). CMV inclusion bodies were documented in 12 of 14 biopsy specimens obtained from erosive lesions, while they were identified in 4 of 15 biopsy specimens obtained from lesions other than erosions (P = 0.0025).

CONCLUSION: This study suggests that erosion and oozing, as well as abdominal pain, are useful indicators in the diagnosis of CMV gastritis following allo-SCT.

Key words: Cytomegalovirus gastritis; Hematopoietic stem cell transplantation; Cytomegalovirus antigenemia; Esophagogastroduodenoscopy; Graft-versus-host disease

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INTRODUCTION

Cytomegalovirus (CMV) disease is a serious complication after allogeneic hematopoietic stem cell transplantation (allo-SCT)[1], which is widely accepted as a curative therapy for advanced hematological malignancies including leukemia and malignant lymphoma. CMV disease can involve many organs and the gastrointestinal (GI) tract is a common target[2].

CMV antigenemia is one of the most widely used methods to detect CMV reactivation in a variety of clinical settings[3]; however, it is of limited value in predicting and diagnosing GI CMV disease[4]. GI CMV disease is usually diagnosed based on pathological examination of endoscopically obtained mucosal biopsy specimens. Few reports have been published regarding endoscopic examination in diagnosing CMV gastritis after allo-SCT[5-7]. This study aimed to investigate endoscopic findings of CMV gastritis after allo-SCT in addition to its clinical features.

MATERIALS AND METHODS

Study patients

Between January 1999 and September 2005, 523 patients underwent allo-SCT at the National Cancer Center Hospital in Tokyo, Japan. Among them, 115 patients with GI symptoms underwent esophagogastroduodenoscopy (EGD). Written informed consent was obtained from all patients before EGD. We retrospectively reviewed records of medical, endoscopic and pathological examination in the 115 EGD patients. CMV gastritis was diagnosed pathologically in seven patients (1.3%) by hematoxylin-eosin staining and immunohistochemical staining with an anti-CMV antibody. The other 108 patients served as controls.

Endoscopic procedure

All EGD patients orally received 100 mL of a solution containing 1 g of pronase and 1 g of sodium bicarbonate to remove mucus and bubbles on the gastric mucosa before EGD. Antiperistaltic agents (scopolamine butylbromide 20 mg or glucagon 1 mg) and sedatives (pethidine hydrochloride 17.5-35 mg or midazolam 2-3 mg) were injected intravenously. Conventional endoscopic instruments (GIF Q240; Olympus Co, Ltd, Tokyo, Japan) were used, and biopsy specimens were obtained endoscopically from severely involved areas. When abnormal findings were not found, biopsy specimens were obtained from normal appearing areas.

Pathological examination

Biopsy specimens were fixed immediately in a 10% buffered formalin solution and subsequently stained with hematoxylin-eosin. All tissues were examined by expert pathologists. Diagnosis of CMV gastritis was based on histological identification of CMV inclusion bodies by hematoxylin-eosin staining and immunohistochemical staining with an anti-CMV antibody. Diagnosis of graft-versus-host disease (GVHD) was determined in accordance with a report published previously[8].

Management of CMV

All patients were monitored at least once a week for CMV reactivation by CMV antigenemia assay using monoclonal antibody against C7-HRP (Teijin, Tokyo, Japan) after engraftment.

A patient was considered to be infected with CMV when CMV antigenemia assay detected CMV in the blood. A patient was considered to have CMV disease when CMV was demonstrated in biopsy specimens by hematoxylin-eosin staining and immunohistochemical analysis. Ganciclovir was initiated when either more than 10 cells per 50 000 cells were positive according to the CMV antigenemia assay in patients transplanted from related donors, a single cell per 50 000 cells was positive in patients transplanted from unrelated donors, or a patient was diagnosed as having CMV disease[9].

Management of GVHD

Acute GVHD was graded according to the consensus criteria[10,11] and all patients with grades Ⅱ-Ⅳ acute GVHD were treated with 0.5-2.0 mg/kg per day of methylprednisolone.

Statistical analysis

Univariate analysis using Fisher's exact test was performed to compare differences in patient characteristics, clinical features, and endoscopic findings between the seven patients with CMV gastritis and the other 108 patients who had GI symptoms, but did not have CMV gastritis. Values of $P < 0.05$ were considered significant.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. There was a significant difference in the number of patients given tacrolimus with methotrexate as GVHD prophylaxis between the two groups ($P = 0.018$).

Clinical features

Five of the seven patients with CMV gastritis complained of abdominal pain, while 31 of the 108 control patients complained of abdominal pain ($P = 0.030$) (Table 2). The pain was localized in the upper abdomen in all four patients with CMV gastritis whose medical reports provided the specific location of their pain (Table 3). Three patients required significant analgesia (morphine hydrochloride for one and pentazocine hydrochloride for the other two). Abdominal pain improved with ganciclovir in four of the five patients with abdominal pain, and the remaining patient (Case 1) died of bacterial pneumonia without any improvement in CMV gastritis.

Watery diarrhea was found in four of the seven patients with CMV gastritis, and was complicated by intes-

Table 1 Patient characteristics with and without CMV gastritis

Variables		Patients with CMV gastritis (n = 7)	Patients without CMV gastritis (n = 108)
Median age (range)		47 (26-62)	45 (18-69)
Gender	Male/female	5/2	65/43
Underlying diseases	Acute leukemia	1	41
	Chronic leukemia	2	15
	Malignant lymphoma	3	21
	Myelodysplastic syndrome	1	22
	Others	0	9
Preparative regimens	Myeloablative/reduced-intensity	2/5	48/60
Stem cell sources	Marrow/peripheral blood/cord blood	3/3/1	39/64/5
GVHD prophylaxis	CSP alone/CSP + MTX/CSP + MMF/FK506 + MTX/FK506 Alone	2/3/0/2*/0	36/64/2/2*/4

CMV: Cytomegalovirus; GVHD: Graft-versus host disease; CSP: Cyclosporine; MTX: Methotrexate; MMF: Mycophenolate mofetil; FK506: Tacrolimus. *P = 0.018.

Table 2 Clinical features in patients with and without CMV gastritis

Variables			Patients with CMV gastritis (n = 7)	Patients without CMV gastritis (n = 108)
Gastrointestinal symptoms at EGD		Nausea	2	60
		Vomiting	1	26
		Abdominal pain	5[a]	31[a]
		Abdominal discomfort	2	23
		Hematemesis	1	2
		Tarry stool	2	6
		Watery diarrhea	4	32
		Appetite loss	0	40
CMV	Median onset of CMV gastritis	Days (range)	63 (33-167)	NA
	CMV antigenemia (C7-HRP) at EGD	Positive/negative/not done	6[b]/1/0	28[b]/71/9
		Median number of positive cells per 50 000 (range)	8[d] (0-143)	0[d] (0-167)
	Involved organs of CMV diseases	Esophagitis/duodenitis/enterocolitis/pneumonitis/retinitis	1/2/1/0/0	0/0/4/0/0
GVHD		Positive (clinical grade: Ⅰ/Ⅱ/Ⅲ/Ⅳ)	7[c] (2/2/3/0)	65[c] (45/10/9/1)

EGD: Esophagogastroduodenoscopy; NA: Not applicable. [a]P = 0.030, [b]P = 0.0026, [c]P = 0.044, [d]P = 0.0023.

Table 3 Clinical features of CMV gastritis

	Demographics	Gastrointestinal symptoms			CMV antigenemia assay	
	Age (yr), gender, diagnosis	Any symptoms	Abdominal pain		Onset (d)	Level at EGD (cells per 50000)
			Onset (d)	Localization in abdomen		
Case 1	34, male, CML	Abdominal pain, tarry stool	81	Upper abdomen	88	8
Case 2	43, female, MDS	Nausea, abdominal pain, tarry stool, hematemesis, watery diarrhea	53	No description	69	2
Case 3	60, male, AML	Abdominal pain, watery diarrhea	62	Upper abdomen	73	143
Case 4	48, female, ML	Abdominal pain, watery diarrhea	36	Upper abdomen	31	10
Case 5	47, male, ML	Abdominal pain, watery diarrhea	30	Upper abdomen	32	4
Case 6	62, male, CML	Abdominal discomfort	NA	NA	47	32
Case 7	26, male, ML	Nausea, vomiting, abdominal discomfort	NA	NA	NA	0[1]

[1]CMV antigenemia remained negative throughout clinical course. CML: Chronic myelocytic leukemia; MDS: Myelodysplastic syndrome; AML: Acute myelocytic leukemia; ML: Malignant lymphoma.

tinal GVHD in three of these four patients. Watery diarrhea improved with ganciclovir in a patient with CMV gastritis who had no evidence of intestinal GVHD.

All seven patients with CMV gastritis had GVHD, while 65 of the 108 control patients had GVHD (P = 0.044) (Table 2). Five of the seven patients with CMV gastritis had grade Ⅱ-Ⅳ GVHD that was being treated by corticosteroids.

CMV antigenemia assay

Six of the seven patients with CMV gastritis and 28 of the 108 controls showed positive CMV antigenemia (P =

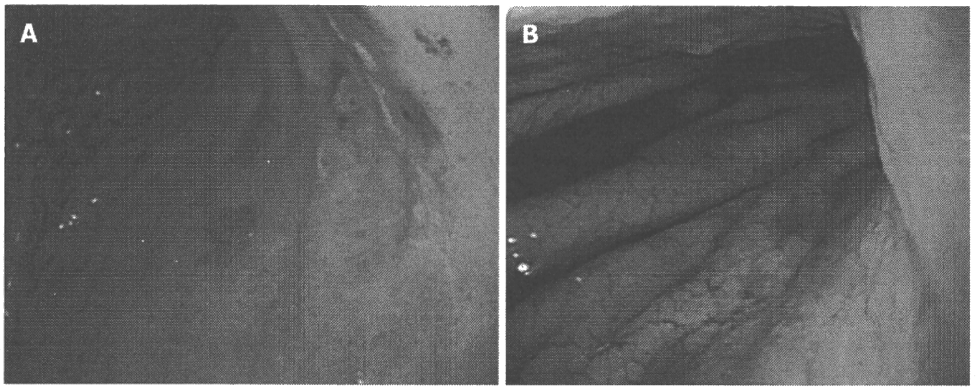

Figure 1 Erosion (Case 6). Multiple erosions are clearly shown in gastric body. A: Before indigo carmine dye spraying; B: After indigo carmine dye spraying).

Table 4 Endoscopic features in patients with and without CMV gastritis

Variables	Patients with CMV gastritis (n = 7)	Patients without CMV gastritis (n = 108)
Atrophic mucosa	3	36
Redness	5	100
Edema	2	9
Orange peel appearance	2	21
Mucosal sloughing	1	6
Erosion	6[b]	24[b]
Ulceration	0	2
Oozing	2[a]	3[a]

[a]P = 0.029, [b]P = 0.0012.

0.0026) (Table 2). The median number of positive cells in the CMV antigenemia test among the seven patients with CMV gastritis was 8 cells per 50 000 cells (range, 0-143) at the time of EGD.

Development of abdominal pain preceded the CMV antigenemia in four of the five patients who complained of it, and the median interval between onset of abdominal pain and the first positive CMV antigenemia was 7 d (range, -5 to 16 d) (Table 3).

Endoscopic findings

Erosion was observed in six of the seven patients with CMV gastritis and in 24 of the 108 control patients (P = 0.0012) (Table 4). The erosive lesions were located in the antrum (n = 2), body (n = 2), and antrum-body (n = 2) of the stomach. Two of the six patients had a solitary erosion, and the other four patients had multiple erosions of various sizes. Erosions were flat in four patients and raised in the other two. A representative example of erosion is shown in the accompanying figure; multiple erosions are clearly shown in the gastric body (Figure 1).

Oozing was observed in two of the seven patients with CMV gastritis and in three of the 108 control patients (P = 0.029). Oozing was located in the antrum with erosion (Case 3), and in the antrum-body with mucosal sloughing (Case 2).

Pathological findings

Detailed information regarding pathological findings is shown in Table 5. CMV inclusion bodies were documented in 12 of 14 biopsy specimens obtained from erosive lesions, while they were identified in 4 of 15 biopsy specimens obtained from lesions other than erosions (P = 0.0025) (Table 5).

Outcomes

Four patients died, and CMV disease was not the primary cause of death in any of them (Table 5). Two died from recurrences of their primary diseases, one died of bacterial pneumonia and one died of renal failure.

DISCUSSION

The present study clarifies the endoscopic findings of CMV gastritis following allo-SCT in addition to its clinical features. CMV gastritis was diagnosed pathologically in seven patients (1.3%) among 523 patients who underwent allo-SCT at our facility. The incidence is comparable to a previous study (1.7%)[12]. None of the seven patients died of CMV gastritis, while three patients complained of significant abdominal pain requiring analgesia which impaired their quality of life. CMV gastritis was a clinically important complication after allo-SCT.

No detailed information on clinical features of CMV gastritis has been previously reported. In the present study, abdominal pain was a common symptom of CMV gastritis. The pain was localized in the upper abdomen in all four patients whose medical reports provided the specific location of their pain. Ganciclovir administration improved abdominal pain in these four patients, supporting the likelihood that this symptom was attributable to CMV gastritis. Clinicians should pay particular attention to upper abdominal pain following allo-SCT as a possible symptom of CMV gastritis.

The association between watery diarrhea and CMV gastritis may be minimal as it remained unclear whether such diarrhea was due to CMV gastritis or overlapping intestinal GVHD. In the present study, ganciclovir improved symptoms in only one of four patients with diarrhea. In contrast, CMV gastritis was complicated by intestinal GVHD in three of those four patients. Our observations suggested that watery diarrhea in patients with CMV gastritis was more likely due to intestinal GVHD rather than the CMV gastritis itself.

Endoscopic findings characteristic of CMV gastritis

Table 5 CMV inclusion bodies and response to ganciclovir of CMV gastritis

	Positive specimens with CMV inclusion bodies/total specimens in EGD biopsy				Response to ganciclovir		Outcome	
	Total	Erosions	Mucosal sloughing	Other findings or normal mucosa	Abdominal pain	CMV antigenemia assay	Outcome	Cause of death
Case 1	1/2	1/2	None	0	Continued	Continued	Death	Bacterial pneumonia
Case 2	2/2	None	2/2[1]	0	Improved	Turned negative	Death	Recurrence of primary disease
Case 3	2/3	2/3[1]	None	0	Improved	Turned negative	Death	Renal failure
Case 4	5/7	4/4	None	1[2]/3	Improved	Turned negative	Alive	NA
Case 5	1/5	1/1	None	0/4	Improved	Turned negative	Alive	NA
Case 6	4/7	3/3	None	1[2]/4	NA	Turned negative	Alive	NA
Case 7	1/3	1/1	None	0/2	NA[3]	NA[4]	Death	Recurrence of primary disease
Case 7		26, male, ML		Nausea, vomiting, abdominal discomfort	NA	NA	NA	0[1]

[1]Oozing was accompanied in these findings; [2]The patient was not given ganciclovir, but CMV gastritis improved spontaneously; [3]The patient was not given ganciclovir, and CMV antigenemia remained negative throughout clinical course; [4]The patient was not given ganciclovir, and CMV antigenemia remained negative throughout clinical course.

after allo-SCT have not been fully investigated, but the present study indicates that erosion and oozing might be useful markers for early diagnosis of CMV gastritis. Vascular endothelium infected with CMV narrows vessels and induces local ischemia[13] eventually resulting in erosions and oozing. In fact, most CMV inclusion bodies were obtained from erosion sites. Erosions from CMV gastritis developed in all stomach sites and varied in size. Endoscopists should suspect CMV gastritis and obtain multiple biopsies whenever erosions are found in any stomach site.

In contrast, none of the seven patients with CMV gastritis had punched out ulcers which had previously been considered characteristic of GI CMV disease[14-16]. In the present study, early EGD might have enabled early diagnosis of CMV gastritis before progression to ulcers. In two patients (Cases 4 and 6), CMV inclusion bodies were identified pathologically from normal mucosa as well as erosions. This result demonstrates the necessity of biopsy even if only normal findings are identified when EGD is performed.

CMV antigenemia reflects the severity of CMV reactivation[3,17], but the clinical significance of CMV antigenemia remains unknown in the diagnosis of GI CMV disease because of the wide variation in positive findings, ranging from a low of 21%[4] to a high of 73%[18]. In this study, CMV antigenemia was positive in six of the seven patients with CMV gastritis. This result supports the usefulness of CMV antigenemia in the diagnosis of CMV gastritis. It should be noted that abdominal pain preceded CMV antigenemia in four of the five patients with positive CMV antigenemia and abdominal pain. Our observations suggest that elaboration of physical and endoscopic examinations is even more important than detection of CMV antigenemia in the early diagnosis of CMV gastritis.

Patients with GVHD, and patients given corticosteroids for treatment of GVHD, carry a high risk of CMV disease[19]. In this study, such increased risk was confirmed as all seven patients with CMV gastritis also had GVHD and five of them had grade Ⅱ-Ⅳ GVHD that was being treated by corticosteroids. GVHD, by itself and also accompanied by corticosteroid administration, are exacerbating factors in the existence of CMV gastritis.

The present investigation was a retrospective study based on our examination of medical records as well as endoscopic and pathological findings. The small size of the study does not exclude the possibility of unrecognized bias. Since EGD was not conducted in all allo-SCT recipients, underestimation of the frequency of CMV gastritis is a possibility. Consequently, further prospective evaluation is warranted to clarify the endoscopic findings for early diagnosis of CMV gastritis.

The results of this study suggest that endoscopic and clinical findings are useful indicators in the diagnosis of CMV gastritis following allo-SCT. Use of EGD is warranted for the establishment of an early diagnosis of CMV gastritis following allo-SCT.

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COMMENTS

Background

Cytomegalovirus (CMV) disease is a serious complication after allogeneic hematopoietic stem cell transplantation (allo-SCT), which is widely accepted as a curative therapy for advanced hematological malignancies including leukemia and malignant lymphoma. CMV disease can involve many organs and stomach is a common target.

Research frontiers

Few reports have been published regarding endoscopic examination in diagnosing CMV gastritis after allo-SCT. In this study, the authors demonstrate the endoscopic findings of CMV gastritis after allo-SCT in addition to its clinical features.

Innovations and breakthroughs

The present study indicated that erosion and oozing might be useful markers for early diagnosis of CMV gastritis.

Applications

Endoscopists should suspect CMV gastritis and obtain multiple biopsies whenever erosions are found in any stomach site when performing esophagogastroduodenoscopy in patients after allo-SCT.

Peer review

Although it does not really break new ground, this is an interesting manuscript on an important topic. The study presented here is a retrospective one with a small number of affected patients (7), but it offers some insight into this complex problem.

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ENDOSCOPY MINISERIES

Endoscopic resection of gastrointestinal lesions: Advancement in the application of endoscopic submucosal dissection

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Abbreviations
GIT, gastrointestinal tract; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LST, laterally spreading tumor; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor non-granular type.

Abstract

Curative endoscopic resection is now a viable option for a range of neoplastic lesions of the gastrointestinal tract (GIT) with low invasive potential. Risk of lymph node metastasis is the most important prognostic factor in selecting appropriate lesions for endoscopic therapy, and assessment of invasion depth is vital in this respect. To determine appropriate treatment, detailed endoscopic diagnosis and estimation of depth using magnifying chromoendoscopy is the gold standard in Japan. En bloc resection is the most desirable endoscopic therapy as risk of local recurrence is low and accurate histological diagnosis of invasion depth is possible. Endoscopic mucosal resection is established worldwide for the ablation of early neoplasms, but en bloc removal using this technique is limited to small lesions. Evidence suggests that a piecemeal resection technique has a higher local recurrence risk, therefore necessitating repeated surveillance endoscopy and further therapy. More advanced endoscopic techniques developed in Japan allow effective en bloc removal of early GIT neoplasms, regardless of size. This review discusses assessment of GIT lesions and options for endoscopic therapy with special reference to the introduction of endoscopic submucosal dissection into Western countries.

Introduction

The presence of lymph node metastasis is an important prognostic factor in gastrointestinal malignancy.[1,2] Lesions known to have a low risk of lymph node metastasis can be considered for curative endoscopic resection, thus avoiding radical surgery. Endoscopic mucosal resection (EMR) is now a well-established technique worldwide for the treatment of benign and small malignant lesions in the gastrointestinal tract (GIT).[3] Endoscopic submucosal dissection (ESD) is a more advanced technique and was pioneered by Japanese endoscopists.[4] It has become standard treatment in Japan for superficial esophageal and early gastric cancers and has recently been implemented in major centers to achieve en bloc resection of colorectal lesions that would otherwise necessitate piecemeal or surgical resection. Few centers offer ESD in the West, and there are currently no publications of significant patient cohorts. In the following article we give an overview of endoscopic resection of GIT lesions and consider the application of ESD in Western countries.

Assessment of GIT lesions

Histological assessment

Early or superficial gastrointestinal cancer is confined to the mucosa and submucosa, irrespective of the presence of lymph node metastasis.[5] Comparison between Eastern and Western publications has been difficult in the past due to a divergence in the histological definition of gastrointestinal neoplasia. One of the main differences was that lesions with high-grade intraepithelial neoplasia and no invasion of the lamina propria were defined as high-grade dysplasia in the West, but as intramucosal carcinoma in Japan. In an attempt to overcome these discrepancies, the Vienna Workshop produced a consensus classification, revised in 2002,

Table 1 The revised Vienna classification of gastrointestinal epithelial neoplasia

Category	Diagnosis
1	Negative for neoplasia
2	Indefinite for neoplasia
3	Mucosal low-grade neoplasia
	Low-grade adenoma
	Low-grade dysplasia
4	Mucosal high-grade neoplasia
	4.1 High-grade adenoma/dysplasia
	4.2 Non-invasive carcinoma (carcinoma *in situ*)
	4.3 Suspicious for invasive carcinoma
	4.4 Intramucosal carcinoma
5	Submucosal invasion by carcinoma

and now used worldwide.[6,7] High-grade dysplasia and intramucosal carcinoma are now considered subdivisions of the same group (Table 1).

Macroscopic assessment

Careful endoscopic diagnosis is essential in the selection of suitable lesions for endoscopic removal. The Paris classification of superficial neoplasia of the GIT allows for straightforward endoscopic diagnosis of early lesions, whilst simultaneously allowing estimation of depth, and therefore likely risk of lymph node metastasis (Fig. 1).[8] Lesions that are of mixed morphology, for example a superficial elevated lesion (IIa) with a centrally depressed area (IIc), can also be described logically using this system. Laterally spreading tumors (LST) of the colorectum are not described by the Paris classification and are defined as lesions $\geq$ 10 mm in diameter with a low vertical axis extending laterally along the interior luminal wall. LST are further subdivided into granular type (LST-G) and non-granular type (LST-NG), depending on surface appearance.

Magnifying chromoendoscopy

Detailed endoscopic diagnosis and estimation of depth using magnifying chromoendoscopy is the gold standard in Japan for determination of appropriate treatment. Standard endoscopic images can be enlarged up to 150×, enabling easier recognition of lesion margins and superior visualisation of surface architecture.[9] Lesion visualisation can be enhanced further when magnification is used in combination with dye spraying using stains such as Lugol's solution, indigo carmine and cresyl violet. Normal esophageal non-keratinized squamous epithelium is stained dark brown by Lugol's solution due to the presence of glycogen-rich granules, whereas dysplasia and carcinoma are left unstained. This method has proven to be successful in the detection of early esophageal lesions that might otherwise be missed. Indigo carmine is the most commonly used dye in Japan for early cancer screening of the stomach and colon and for differentiation between benign and malignant lesions in the colon. Pooling of the blue dye in grooves and depressed areas highlights mucosal irregularities. Crystal violet is an alternative dye that is absorbed across epithelial cell membranes accentuating mucosal patterns of gastric and colonic neoplasia.[10]

Colonic pit pattern classification

Whilst gastric mucosal changes can prove more difficult to assess due to gastric acid damage and presence of other pathologies, such as gastritis, clear magnified images can usually be obtained in the colon. Kudo *et al.* used magnifying endoscopy to observe the shape of colorectal crypt openings (pits) on the surface of normal bowel and colorectal tumors *in vivo*. They observed a distinct correlation between lesion type and pit pattern and devised a classification system that is now considered standard in Japan and specialist centers worldwide for the diagnosis of colorectal lesions (Fig. 2). Pit patterns I and II are found in the majority of non-neoplastic lesions; III_L and III_S are present predominantly in adenomas; while the type IV pit pattern is seen in 75% of adenomas, but also found in some carcinomas. The distribution of type V irregular-type (V_I) was found to be 61% in carcinomas, and the non-structural pit pattern (V_N) was present in over 93% of intramucosal and submucosal carcinomas.[11,12]

Once the characteristics of a lesion have been fully defined, the appropriate mode of treatment can be determined. The choice between surgery, EMR or ESD can be made using the methods described above; it will depend on several factors including lesion size, pathological differentiation and estimation of depth.

Endoscopic mucosal resection

EMR is a minimally invasive technique for effective curative treatment of early-stage GIT lesions with no invasive potential. It involves complete mucosal removal by excision though the submucosal layer of the gastrointestinal wall. Several EMR techniques have been described. Cap-assisted EMR is frequently used to excise early esophageal lesions; it involves fitting a transparent plastic cap to the tip of a standard endoscope. After submucosal injection to separate the lesion from the muscle layer, a crescent-shaped snare is deployed into a groove at the tip of the cap. After suction of the lesion into the cap, the snare is closed around the base and electrocautery is used to complete the excision.[13]

The 'inject and cut' method is safe and straightforward and is used extensively for colonic EMR. The submucosa is injected to create a fluid cushion before a snare is closed around the base of the lesion and current applied.[14] Less commonly employed techniques include the use of a double channel endoscope to lift the lesion with a grasper while a snare is deployed through the second channel, or use of a variceal ligation device to release a band around the lesion base before snare resection.[15,16] The 'non-lifting' sign has been reported in the past as a viable assessment tool for invasion depth of colonic lesions prior to resection.[17] Kobayashi *et al.*, however, were unable to reliably predict deep cancer invasion with the 'non-lifting' sign when compared with magnifying endoscopic diagnosis.[18]

Endoscopic submucosal dissection

ESD was developed in Japan to enable larger lesions of the GIT to be removed en bloc.[4] Figure 3 illustrates important steps in this procedure using gastric ESD as an example. The borders of the

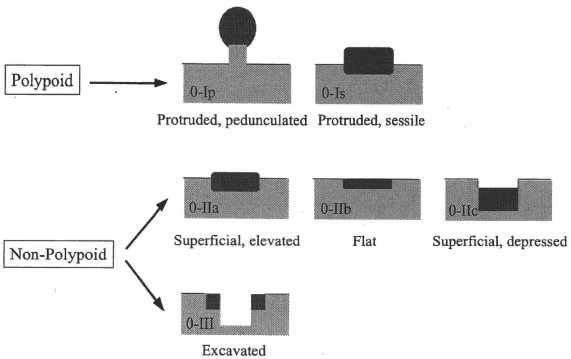

Figure 1 Classification of superficial neoplastic lesions of gastrointestinal tract.

lesion are initially highlighted using indigo carmine and marks placed 5 mm from the lateral edge using a needle knife (KD-1L-1; Olympus, Tokyo, Japan/Center Valley, PA, USA/Hamberg, Germany). Submucosal injection is used to lift the lesion from the muscularis propria, and is followed by one or more needle knife pre-cuts into the submucosa. Circumferential incision into the submucosa around the lesion using a specialized electrocautery knife is performed 5 mm outside the initial markings. Further submucosal injection takes place before submucosal dissection begins. A plastic cap can be attached to the endoscope at any time during the procedure to lift the lesion and to define tissue planes if required. Any procedural bleeding is controlled by careful hemostasis with coagulation current using the electrocautery knife, hot biopsy forceps or electrosurgical hemostatic forceps. The resected specimen is flattened and mounted on a cork or polystyrene block and oriented to facilitate histological examination.

The choice of electrocautery knife for ESD is dependent on position of the lesion and operator choice. At the National Cancer Center Hospital in Tokyo, the IT-2 knife (Olympus) with a three-pointed star-shaped blade, is used most commonly for gastric ESD, whereas the bipolar B knife (Xemex, Tokyo, Japan) is preferred for colonic ESD. The colonic mucosa is very thin and the narrow lumen makes endoscope manipulation more difficult, thereby increasing the risk of perforation.

The B knife was developed specifically to reduce perforation rate during colonic ESD by minimizing the application of high-frequency current to the muscle layer through current direction back from the knife towards the sheath tip.[19] This knife is currently only available in Japan. Colonic ESD can be slow, and once the submucosal plane has been established, the IT knife (KD-610L; Olympus) is frequently used to speed up the procedure. Carbon dioxide insufflation has proved safe and effective during lengthy colonic ESD, resulting in less abdominal pain and requirement of lower sedation doses compared to air insufflation.[20] Submucosal injection plays a vital role in endoscopic resection, enabling safe exclusion of the muscularis propria from the cutting zone. Glycerol and hyaluronic acid are used commonly in Japan to achieve a long-lasting submucosal cushion, thereby facilitating safe resection. They are often combined with epinephrine and indigo carmine to reduce bleeding and clearly define tissue planes.[21]

EMR or ESD?

The choice of endoscopic resection technique depends on a number of factors. One of the main limitations of EMR is the inability to remove lesions larger than 2 cm en bloc. Piecemeal removal is possible, but studies have shown that the risk of local recurrence is higher than one-piece resection.[22,23] It has, however, been shown that safe and complete resection can be achieved after piecemeal EMR in the colon if vigilant surveillance and careful removal of recurrent lesions is carried out.[24] The rate of perforation is higher after ESD compared to EMR, but ESD facilitates removal of much larger lesions en bloc, whilst being less invasive than major surgery. Most perforations can be treated endoscopically using clips without the need for surgical intervention. Hemorrhage is generally higher for ESD, although some studies do not include data on minor bleeding, so comparisons are difficult. Data from studies comparing complication rates of EMR and ESD are shown in Table 2,[22,25–29] and indications for endoscopic resection of GIT lesions are displayed in Table 3.[31–33]

Early esophageal neoplasms

Esophageal cancer is only the eighth most common malignancy worldwide, but survival is very poor with a 16% 5-year survival rate in the USA and 10% in the UK. High-risk areas include China, South and East Africa, South Central Asia and Japan (only in men) and squamous cell carcinoma is the most prevalent type.[26] In the Western world, adenocarcinoma arising from Barrett's mucosa has replaced squamous cell cancer as the predominant tumor type. Detection and cure of esophageal neoplasms at an early stage is therefore essential in high-risk groups. Esophagectomy used to be the only available management strategy for esophageal cancer, but significant complication rates make other treatment modalities

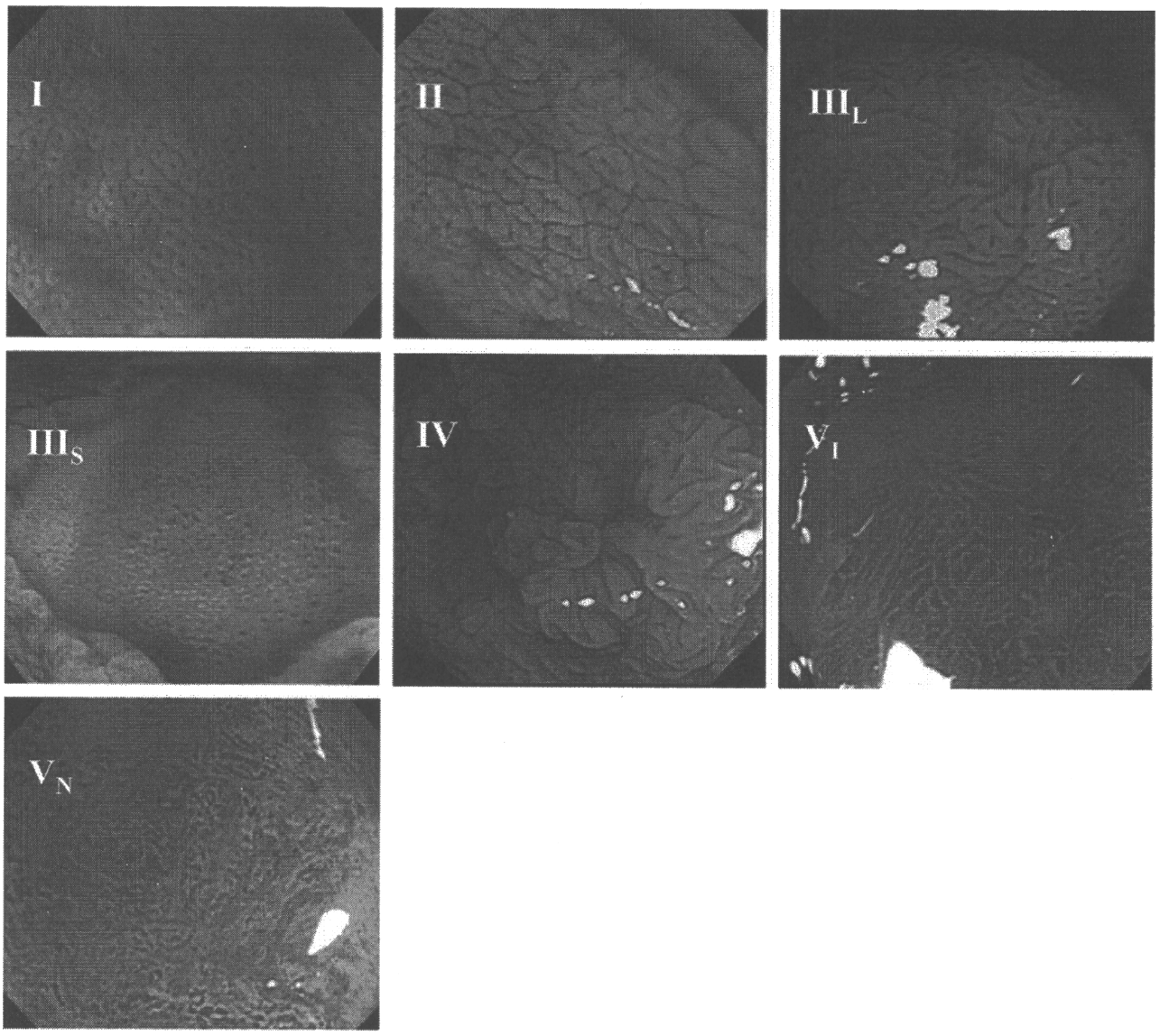

Figure 2 Pit pattern classification of colorectal neoplasia. I, roundish pits; II, stellar or papillary pits; III$_L$, large roundish or tubulart pits (larger than type I pits); III$_S$, small roundish or tubulart pits (smaller than type I pits); IV, branch-like or gyrus-like pits; V$_I$, irregular type; V$_N$, non structural type.

more attractive, especially for early-stage disease.[27] Photodynamic therapy for high-grade intraepithelial neoplasia and early adenocarcinoma arising from Barrett's mucosa has proven to be safe and effective and is the treatment of choice for non-localized lesions.[28] Endoscopic therapy is used increasingly to cure early esophageal lesions worldwide; ESD is now standard treatment in Japan.[30] The incidence of adenocarcinoma of the esophagus has risen in recent years in the West as a consequence of increased gastro-esophageal reflux disease and subsequent Barrett's mucosa.[34] This has led to the adoption of endoscopic surveillance programs in many centers, but the actual benefit of surveillance in terms of cost and survival is still uncertain; it remains a controversial issue.[35]

The prognosis of established early esophageal adenocarcinoma is dependent on depth of invasion, which in turn determines the risk of lymph node metastasis. Nigro *et al.* showed that lesions confined to the mucosa had a 7% risk of lymphatic metastasis, whereas 80% of those invading into muscularis propria had spread to lymph nodes.[36] This study, as with other early studies of esophageal adenocarcinoma, was small and involved only 37 patients. Since then, larger studies have shown that tumors of the mucosa and the superficial 500 μm (SM1) of the submucosa provide negligible risk of lymph node metastasis. Westerterp and colleagues demonstrated lymph node metastasis in only 1/79 mucosal and SM1 adenocarcinomas, while Stein *et al.* reported no lymphatic spread in 53 similar cases.[37,38]

Early squamous cell carcinoma of the esophagus has been much more extensively studied, in part, due to the routine use of endoscopic ablation in Japan. Patients with early squamous cell carcinoma, no lymph node metastasis on computed tomography scan and no evidence of a second primary cancer have been shown to

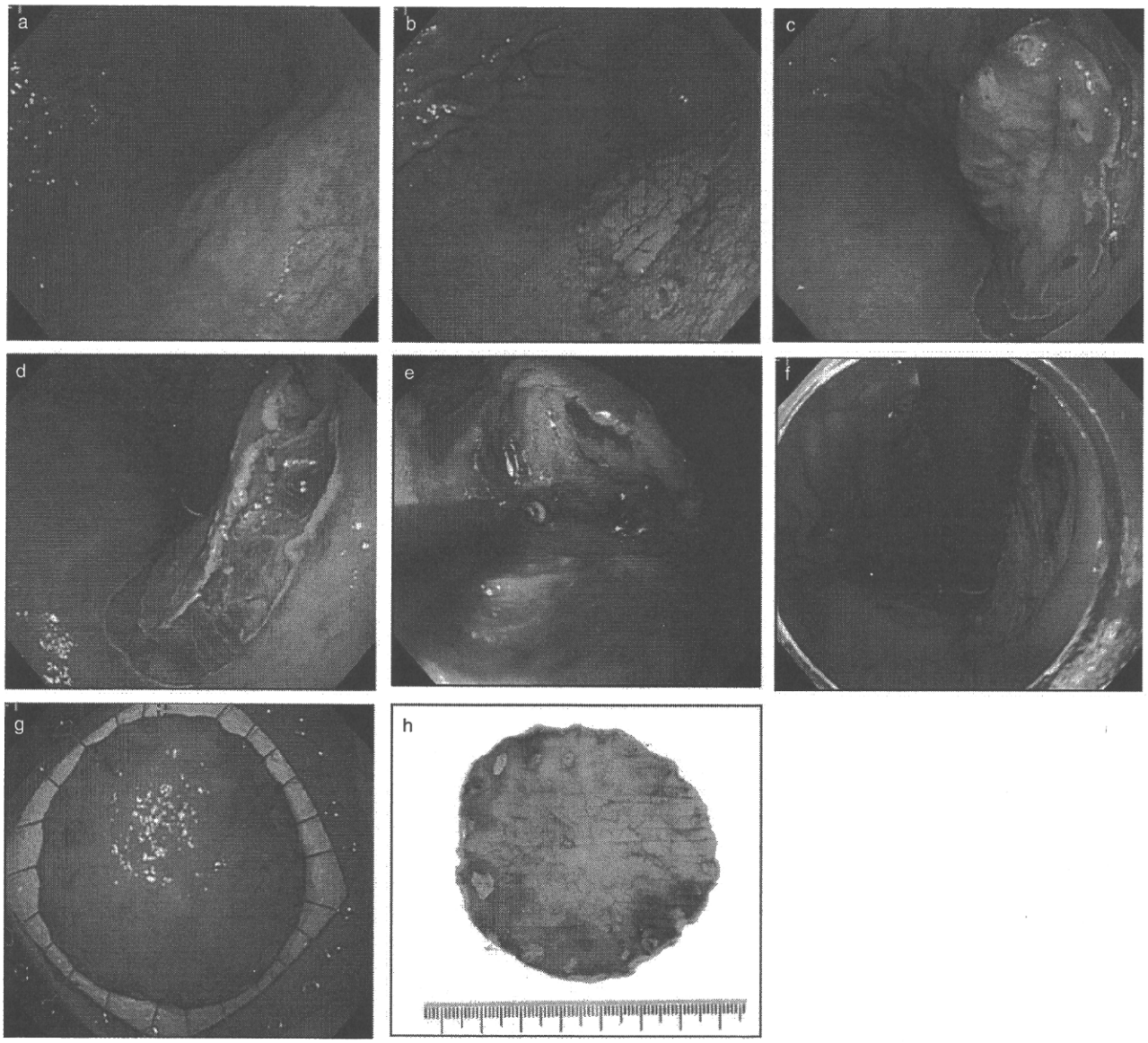

Figure 3 Gastric endoscopic submucosal dissection technique. a, conventional view; b, chromoendoscopy and marking of lesion margins; c, circumferential incision; d, submucosal injection; e, submucosal dissection; f, gastric wall defect after resection; g, mounted lesion; h, pathological specimen.

have a similar survival rate as the general population following endoscopic therapy.[39] Mucosal and superficial submucosal squamous cell cancers have an excellent prognosis due to low risk of lymph node metastasis. Tajima *et al.* reported on 240 patients after surgical resection of squamous cell cancer and showed that none of the mucosal or SM1 tumors had metastasized to lymph nodes.[40] Stein and colleagues found a higher rate of lymphatic spread of 7.7%, but this was based on just 26 mucosal/SM1 patients.[38]

Minimally invasive squamous cell esophageal cancer can be cured endoscopically; early detection is therefore crucial. In this context, the use of high-resolution video-endoscopy with adjuncts, such as chromoendoscopy and narrow-band imaging, are useful technologies. Although the cure rate is high, surveillance after endoscopic therapy is necessary due a significant risk of local recurrence.[41] Data on endoscopic treatment of early esophageal adenocarcinoma are limited; therefore, evidence-based treatment recommendations are not yet available.

Early gastric cancer

Although the worldwide incidence of gastric cancer is slowly declining, it is still the fourth most common malignancy and the second most frequent cause of cancer death. Five-year survival is relatively good in Japan at 40–60%, compared to about 20% in Western countries. Over 50% of gastric cancers diagnosed in Japan are early lesions, and this may explain the overall better survival.[30,42]

Table 2 Published reports comparing complication rates of EMR and ESD

Author	Site	EMR					ESD			
		Number of lesions	Removed en bloc %	Bleeding %	Perforation %	Recurrence %	Number of lesions	Removed en bloc %	Bleeding %	Perforation %	Recurrence %
Saito[25]	Colon	228	84.0	3.1 (minor)	1.3	14.5	145	33.0	1.4 (minor)	6.2	2.1
Oda[26]	Gastric	411	56.0	0.2 (transfused)	1.2	6.6	303	92.7	0.0 (major)	3.6	2.0
Shimura[27]	Gastric	48	31.3	12.5	0.0	35.4	59	88.1	13.6	3.4	1.7
Watanabe[28]	Gastric	125	63.6 (> 10 mm)	1.8	3.2	5.6	120	91.3 (> 10 mm)	0.0 (major)	4.2	2.5
Ishihara[42]	Oesophagus	52	10.9 (out of 46 lesions)	0.0	0.0	22.0	33	90.6 (out of 32 lesions)	0.0	0.0	3.1
Cao*[29]	All	2987	57.7	5.8	1.0	5.2	1804	94.6	9.2	4.5	0.3

*Meta-analysis of 15 studies of EMR and ESD.
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

Table 3 Indications for endoscopic resection of early gastrointestinal neoplasm

Lesion Position	Indication
Esophagus	Well- or moderately differentiated m1 or m2 SCC or AC < 20 mm, without venous or lymphatic involvement; less than a third of the circumference involved (to avoid risk of post-resection stricture formation) ER for Barrett's esophagus is still being studied
Stomach	Standard criteria: Well- or moderately differentiated AC and/or papillary carcinoma; cancer confined to mucosa IIa < 20 mm; cancer confined to the mucosa IIb, IIc < 10 mm, without evidence of lymphatic involvement Expanded criteria: Mucosal well-/moderately differentiated AC, irrespective of size, without ulceration; ≤ 30 mm with ulceration; if minute submucosal invasion is found then the size of the lesion is ≤ 30 mm, without venous or lymphatic involvement; mucosal undifferentiated AC ≤ 20 mm, without lymphovascular involvement or ulceration
Colorectum	Laterally spreading tumors High-grade dysplasia The indication for resection of mucosal or AC invading slightly into the SM is still being studied. ESD has been reported for resection of: - well- or moderately differentiated AC; cancer confined to the mucosa: IIa < 20 mm, IIb, IIc < 10 mm, without evidence of venous or lymphatic involvement - superficially invading the SM (< 500 μm from the muscularis mucosa); without venous or lymphatic involvement

AC, adenocarcinoma; ER, endoscopic resection; IIa, slightly elevated superficial tumor; IIb, flat superficial tumor; IIc, slightly depressed superficial tumor; m, mucosal; SCC, squamous cell carcinoma; SM, submucosa.

Gastrectomy with regional lymph node dissection was formerly the only available curative treatment for early gastric cancer. In 1996, the National Cancer Center Hospital (Tokyo) published their data describing over 1000 patients with intramucosal early gastric cancer who underwent surgical resection. This study provided some of the first evidence to suggest that radical surgery with lymphadenectomy was unnecessary for certain gastric cancers due to the extremely low incidence of spread to lymph nodes.[43] Curative endoscopic resection of early intramucosal gastric cancers has since become a valid therapeutic option, but until recently was restricted to small lesions less than 2 cm in size with no evidence of surface ulceration. Although other publications suggested that certain lesions invading into the submucosa also carried a low risk of progression, these studies were limited by small patient cohorts.[44–46]

Gotoda and colleagues published extensive data in 2000 that provided a more robust evidence base for the expansion of endoscopic resection criteria. They examined the presence of lymph node metastasis in 5265 patients who underwent gastrectomy with

Table 4 Early gastric cancer with no risk of lymph node metastasis

Tumor characteristics	Number of cases	95% confidence interval
Intramucosal Well-/moderately differentiated No lymphovascular invasion Irrespective of ulcer findings Tumor less than 3 cm in size	1230	0–0.3%
Intramucosal Well-/moderately differentiated No lymphovascular invasion No ulcer Irrespective of tumor size	929	0–0.4%
Intramucosal Poorly differentiated No lymphovascular invasion No ulcer Tumor less than 2 cm in size	141	0–2.6%
Minute submucosal penetration (SM1) Well-/moderately differentiated No lymphovascular invasion Tumor less than 3 cm in size	145	0–2.5%

lymph node dissection for early gastric cancer from two centers. Only 2.2% (65/3016) of intramucosal cancers were associated with regional lymph node metastasis. Of these lesions, lymph node metastasis was associated with poor differentiation, signet ring histology, lymphovascular invasion and lesions greater than 3 cm with surface ulceration. Specifically, intramucosal lesions without ulceration did not demonstrate lymph node metastasis irrespective of size. Gotoda *et al.* also showed that 18% of cancers with deeper invasion into the submucosal layer were associated with lymph node metastasis. However, lesions less than 3 cm in size with submucosal invasion less than 500 μm, well- or moderately differentiated histology and no evidence of lymphovascular involvement demonstrated no lymph node metastasis. Table 4 summarizes data from this study, showing the lesion types that displayed no evidence of lymph node metastasis.[47]

In 2004, the Japanese Gastric Cancer Association issued expanded criteria for the treatment of early gastric cancer based on this study.[48] Hirasawa and colleagues have since explored undifferentiated early gastric cancers in a similar population of 3843 Japanese patients. Undifferentiated lesions confined to the mucosa, less than 20 mm in diameter, without lymphovascular involvement or ulcer presence showed no lymph node metastasis. They proposed that endoscopic resection should also be considered for these lesions, thus further expanding the criteria for endoscopic management of gastric cancer.[49] Other studies of the risk of lymph node metastasis in poorly differentiated lesions have produced similar results, although they involved smaller patient numbers.[50–53]

Early lesions of the colorectum

Worldwide, colorectal cancer incidence ranks fourth in frequency in men and third in women. Despite a relatively good prognosis, rates of colorectal cancer are rising rapidly in countries such as Japan where the risk was previously low.[30] Important work done in the 1980s demonstrated that specific genetic alterations occurred in adenomas and carcinomas, suggesting that colorectal cancer development involved mutational activation of an oncogene and loss of tumor suppressor genes. This evidence led to the development of a genetic model for colorectal tumorigenesis, and to the suggestion that most carcinomas arise from benign adenomatous precursors.[54] In contrast, a proportion of colorectal cancers appear to arise from normal mucosa and do not follow the adenoma–carcinoma sequence. These de novo carcinomas tend to be small, depressed-type lesions and may have an increased invasive tendency.[55,56] Originally, depressed-type colorectal neoplasms were thought to exist only in Eastern populations, but their existence and invasive potential in the West have since been proven by groups from the UK and the USA.[57,58]

Intramucosal colorectal lesions have no risk of lymph node metastasis and can be cured by endoscopic resection.[59] Once the submucosa has been breached, the incidence of lymphatic spread rises to around 10%, but this is dependent on depth of invasion. Lesions with submucosal invasion less than 1000 μm have a low risk of lymph node metastasis and are good candidates for endoscopic therapy.[8] Kitajima *et al.* reported an overall incidence of lymph node metastasis in 865 submucosal invasive colorectal cancers of 10%. Poor differentiation, lymphatic invasion and venous invasion were significant risk factors for metastasis. They showed that pedunculated lesions with submucosal invasion less than 3000 μm and no evidence of lymphatic invasion displayed no evidence of lymph node metastasis. All sessile cancers with lymph node metastasis had invaded the submucosal layer by more than 1000 μm.[60]

Egashira and colleagues demonstrated a similar rate of lymph node metastasis of 9%, and identified submucosal invasion greater than 2000 μm as an independent risk factor. Their study was smaller, involving only 140 cancers, and cases were not subdivided into pedunculated and non-pedunculated.[61] With regard to pedunculated lesions, Haggitt identified stalk invasion as an important factor in predicting clinical outcome. Tumors extending beyond the stalk into the submucosa, but not reaching the muscularis propria (Haggitt level 4) were associated with poor outcome. This study was limited by moderate patient numbers ($n = 129$), a factor that should be taken into consideration in practical application.[62]

Special consideration should be given to LST of the colorectum. Uraoka *et al.* studied 511 colorectal LST and reported significant differences in depth of invasion between granular and non-granular lesions. LST-NG had a higher potential for malignancy compared to LST-G with frequency of submucosal invasion of 14% versus 7%. Whilst piecemeal resection was considered acceptable for LST-G type, en bloc resection was suggested as the best therapeutic approach for LST-NG type.[63]

The therapeutic approach to lesions of the colorectum is very much dependent on the accuracy of endoscopic diagnosis. Matsuda *et al.* recently carried out a large prospective study of 4215 lesions in 3029 consecutive patients between 1998 and 2005 at the National Cancer Center Hospital, Tokyo. All lesions were detected via the conventional endoscopic view and assessed using magnifying chromoendoscopy for evidence of invasive features according to pit pattern evaluation. They showed that 99.4% of lesions diagnosed endoscopically as 'non-invasive' were adenoma, high-grade dysplasia or adenocarcinoma with submucosal inva-

sion less than 1000 μm. Among lesions diagnosed with 'invasive' pattern, 87% were cancers with submucosal invasion deeper than 1000 μm. This is the first large-scale prospective study to validate the use of magnifying chromoendoscopy as a highly effective method in the prediction of invasion depth of colorectal neoplasms.[64]

Application of ESD in countries other than Japan

ESD is an appealing prospect for treatment of certain lesions of the GIT in the West, such as superficial carcinomas of the esophagus, high-grade dysplasia in Barrett's mucosa and large flat non-granular tumors of the colorectum. There are, however, a number of limitations to widespread use of ESD outside Japan.

Firstly, selection of appropriate lesions for ESD is crucial, and the diagnostic skills to facilitate this, including determination of lesion characteristics, are of great importance. Whilst optical magnification is used in Japan allowing up to 150× image enlargement, digital magnification is more commonly available in the West, providing views with less resolution. Chromoendoscopy is also a routine modality in GI lesion assessment in Japan, but rarely used outside specialist units in the West. Consequently, the ability to analyze lesion surface vascularity and pit pattern in detail and therefore lesion selection for ESD is limited. These assessment techniques are considered crucial in Japan to enable correct diagnosis of lesion type, depth and amenability to endoscopic treatment. Successful application of ESD in the West will certainly require a change in diagnostic technique and close reference to Japanese literature in selection of lesions for resection.

Secondly, ESD is a technically demanding procedure requiring a high level of endoscopic skill and intensive training. The learning curve is steep and involves animal model work in the first instance. Unlike Western countries, facilities for animal model training are readily available in Japan and materials such as the isolated pig stomach can be supplied at low cost. Initial ESD training in patients entails removal of small gastric lesions in the antrum under close expert supervision, and generally, at least 30 procedures are required to reach basic proficiency.[65] The likelihood of major complications for ESD of lesions in this position is low, even for endoscopists with less experience. The large lumen allows easy maneuvering and the risk of perforation is reduced due to the relative thickness of the gastric wall. Bleeding is common during ESD and safe hemostasis is one of the most important aspects of the procedure. However, acquiring skills for basic ESD maneuvers from the beginning of training is vital and the lower vascularity of the antral wall allows this due to reduced bleeding risk.

The incidence of early gastric cancer in the West is very low compared to Japan, so opportunities to perform training gastric ESD are few. Alternatively, rectal ESD is a comparatively safe procedure and may provide a useful training medium for Western endoscopists. Certain skills can be acquired during animal model training, but collaboration with expert Japanese endoscopists and training periods in their units may be helpful in order to reach the necessary skill level. Suzuki *et al.* recently reported their early experience of ESD as a modality to remove large sessile colorectal polyps at the Wolfson Endoscopy Unit, UK. Although only nine patients were enrolled in the study, en bloc resection was achieved in seven patients, with only one major complication of post-procedural bleeding requiring blood transfusion. Importantly, the ESD technique was acquired under the supervision of an expert.[66] Dinis-Ribeiro *et al.* published a case series of 19 gastric ESD from Portugal reporting only one hemorrhage and no perforations.[67]

Thirdly, ESD is considered more economical and less invasive compared to surgery. Nevertheless, mean hospital inpatient stay for ESD is 5 days and this could prove logistically difficult in the West where bed availability is often limited. In addition, it could be argued that laparoscopic surgery and transanal resection for colorectal lesions in the West are more established techniques, requiring a shorter or similar length inpatient stay; thus, they may be a more viable option.

Finally, management of GIT lesions using ESD in the West will undoubtedly require a multidisciplinary team. During each procedure, several endoscopists are often present in Japan, either to assist or monitor patients, and propofol is frequently given without anesthetists being present. However, although conscious sedation is standard practice in the UK, anesthetists would be required to administer propofol.[68] Practice varies worldwide, with anesthetist- or nurse-administered propofol common in Australia and the USA.[69] Endoscopy nurse training would also need to be addressed in the West, as ESD requires highly trained assistants as well as skilled technicians. Introduction of ESD into Western countries could be of huge benefit to the management of GIT lesions. However, close and supportive working relationships between endoscopists, pathologists and surgeons would be vital for it to succeed as a viable therapeutic option.

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Disclosure statement

The authors report no conflicts of interest in this work.

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