表2　ガイドライン病変と当センターにおける適応拡大病変

深達度	M癌				SM癌	
	潰瘍(−)		潰瘍(+)		≦SM1	SM1<
組織型	≦2cm	2cm<	≦3cm	3cm<	≦3cm	any size
分化型						
未分化型						

■ガイドライン病変
■適応拡大病変
■外科手術が第一であるが，検討の余地あり
■外科手術

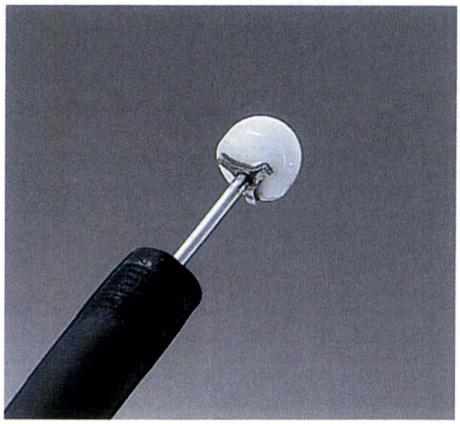

図1　ITナイフ2
（文献7,8より引用）

スチックキャップ法(EMR-C)法などのEMRが行われていたが，UL(+)病変や大きな病変は技術的に一括切除が困難であり，また分割切除後の遺残再発も問題となった[4,5]．しかしながら，粘膜下層に線維化を有するUL(+)病変は，病理学的検索でも粘膜筋板の同定が困難となるため，内視鏡治療が施行される際には，一括切除が必須であると考えられる[6]．ここにESDが登場したのである．小野らによりITナイフを用いたESDが臨床応用され，さらにセラミックボールの裏にブレードが追加された改良型のITナイフ2が開発された(図1)[7,8]．ITナイフをはじめとする種々のデバイスを用いたESDの開発により，従来のEMRと比較して高い一括断端陰性切除率が得られるようになり，またUL(+)病変に対する一括切除も可能となった[9]．

2 UL(+)早期胃癌に対するESDの技術的治療成績，問題点

1999年6月から2006年3月の間に，国立がんセンター中央病院で術前に分化型，M，3cm以下のUL(+)病変と診断しESDを行った早期胃癌316例(残胃，胃管病変，遺残再発病変，未分化癌，多発病変を除く)を，同期間の術前にガイドライン病変と診断しESDを行った早期胃癌951例と技術的側面から比較検討した．対象病変を内視鏡的に判断して1回の切除行為で終了したものを1回切除，1回切除でかつ

表3　ESDの技術的治療成績

	UL(+)病変 (n=316)	ガイドライン病変 (n=951)	p値
1回切除率	97.8%(309)	98.7%(939)	NS
一括断端陰性切除率	88.3%(279)	95.6%(909)	<0.01
切除時間中央値 (range)	75分(15～430)	50分(10～480)	<0.01
穿孔率	5.7%(18)	2.3%(22)	<0.01
後出血率	5.4%(17)	3.0%(29)	NS

表4　一括非断端陰性切除の原因

	UL(+)病変 (n=30)	ガイドライン病変 (n=30)	p値
切れ込み	8(26.7%)	1(3.3%)	0.03
凝固挫滅	2(6.7%)	4(13.3%)	NS
深達度診断	10(33.3%)	15(50.0%)	NS
範囲診断	9(30%)	10(33.3%)	NS
別病変	1(3.3%)	−	

病理組織学的に水平方向，垂直方向の切除断端が陰性であったものを一括断端陰性切除と定義した．

1回切除率はUL(+)病変で97.8%，ガイドライン病変で98.7%であり統計学的有意差は認められなかった．しかし，一括断端陰性切除率はUL(+)病変で88.3%，ガイドライン病変で95.6%であり，ガイドライン病変と比較して有意に低い結果であった．また，UL(+)病変の穿孔率は5.7%(18/316)，切除時間中央値は75分であり，それぞれガイドライン病変と有意差を認めた(表3)．さらに，1回切除であったが切除断端が陽性あるいは判定不能となった症例の原因を検討したところ，剝離中の病変内への切れ込みの割合がUL(+)病変で26.7%(8/30)，ガイドライン病変で3.3%(8/30)であり，有意にUL(+)病変に多かった(表4)．

UL(+)病変はガイドライン病変と比較して病変内への切れ込みや穿孔例が多かったが，これらは粘膜下層のfibrosisのため剝離ラインの同定が困難であるためと考えられる．UL(+)病変に対するESDでは，粘膜下層への局注で十分な挙上が得られないため，適切な剝離すべき方向を認識しづらく，深く切除すると穿孔をきたす．逆に深度が浅くなると病変部を切り込んでしまい，切除後の詳細な病理学的評価が困難になってしまう．このような合併症や不完全切除を避けるため，筆者らはUL(+)病変に対するESDにおいて次項に示すような手技的工夫で対応している．

3 治療手技

1．診　断

色素散布も含めた詳細な内視鏡観察により病変の質的診断，量的診断(腫瘍の側方進展範囲診断，深達度診断，潰瘍による線維化の程度ならびにその範囲の推測)を行う(図2，3)．深達度診断が困難である際には，超音波内視鏡(endoscopic ultrasonography；EUS)を補助的に用いることもあるが，一般にUL(+)病変に対するEUSでの深達度診断は困難とされており，陥凹内隆起，壁の厚み，ヒダの太まりや融合等内視鏡上明らかな粘膜下層浸潤を示唆する所見がなければESDの適応としてよいと考える[10-12]．

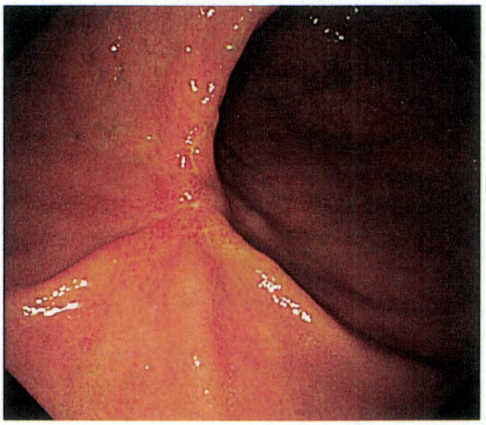

図2　通常観察

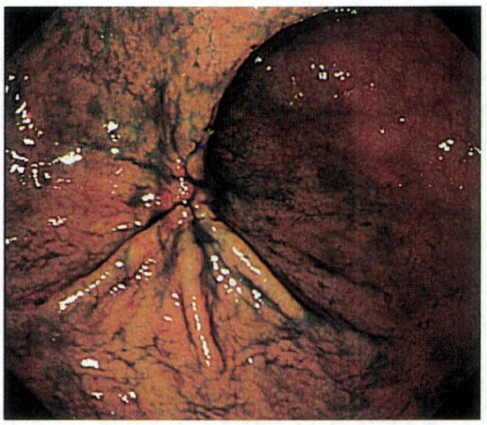

図3　色素散布

2．マーキング

UL(+)病変を前述のように病変内に切れ込むことなく，かつ穿孔をきたさずに一括切除を行うには，正確な剝離ラインを同定することが必要である．ITナイフの粘膜下層剝離は筋層直上の層に到達することが肝要であるが，線維化を有する部位から粘膜切開を開始すると，その後も瘢痕域を処理せざるを得ず，適切な深度を得るのが困難である．そのため，広めのマーキングをおいて線維化のない部分から処置を行うことが推奨される(図4)．

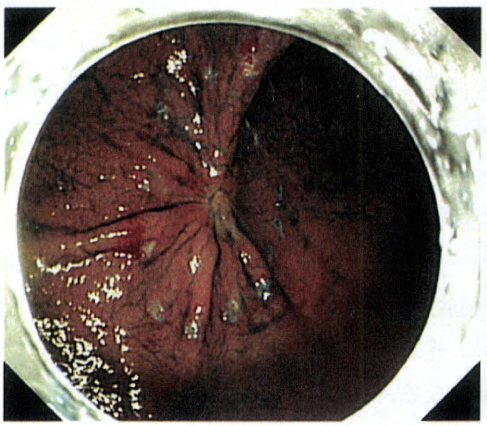

図4　マーキング

3．粘膜切開，瘢痕周囲の粘膜下層剝離

正確な剝離ラインを認識するために非常に大切なことは，潰瘍瘢痕部の処理の前に，その周囲を筋層直上の剝離深度で確実に処理しておくことに尽きる．線維化のない潰瘍瘢痕部の周囲を均等に処理して瘢痕中心部を最後に残すように剝離すると，胃壁の走行が明確となり剝離すべき方向が認識しやすくなる(図5)．近接すると，剝離済みスペースの筋層の走行と瘢痕近傍の線維化のない粘膜下層から，剝離すべき方向を視認

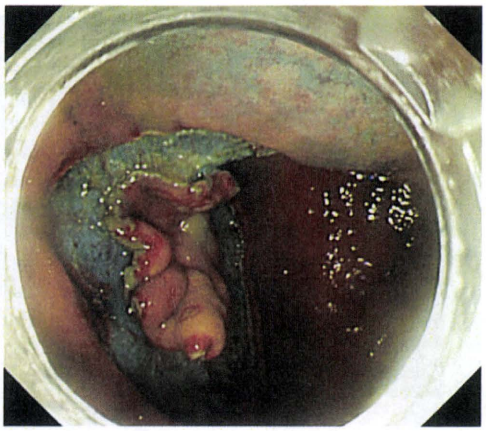

図5　瘢痕周囲の剝離

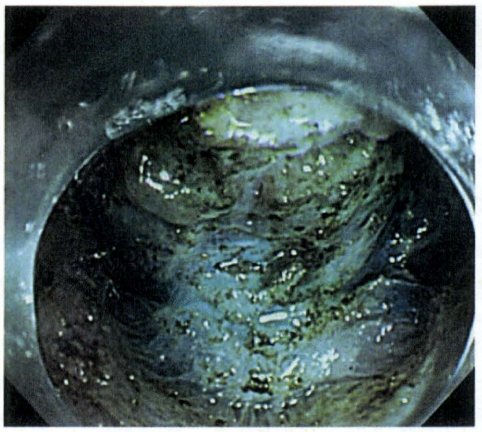

図6　瘢痕部の剝離

することが可能となる(図6)．なお，瘢痕近傍には潰瘍に伴う新生血管が豊富であるため，出血にも注意が必要である．

4．瘢痕部の剝離

線維化が強い瘢痕部は，粘膜下層に局注が入らず良好な隆起が得られない．UL-Ⅱsであれば，瘢痕層の下をITナイフにて剝離可能なこともある．しかし，UL-Ⅲsとなると，ITナイフで粘膜下層剝離を行う際に，経験的には通常通りのテンションのかけ方だと粘膜層側にナイフが滑ってしまい，病変内に切れ込みをきたしてしまうことが多い．一方で，これを防ぐため無理に剝離深度を深くすることは，穿孔のリスクを高めると思われる．

適切な剝離深度を得るためのポイントは，前述のように剝離済みスペースから剝離ラインを想定して，少しずつ粘膜下層剝離を行うことである．無理に盲目的な剝離を行うと粘膜への切れ込みや穿孔につながるため，先端アタッチメントを用いた近接の視野確保が必要となる．さらに針状メスなどの先端系デバイスを用いて，左右の剝離済みスペースから筋層の走行を推測

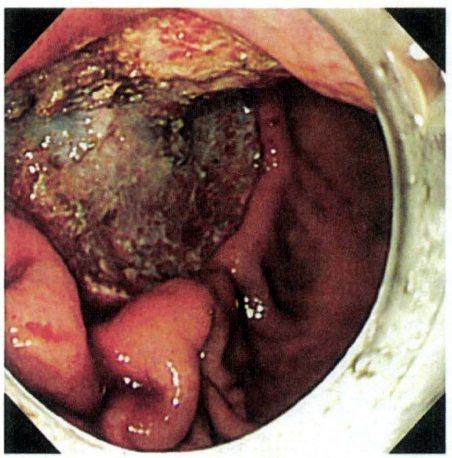

図7　剝離後

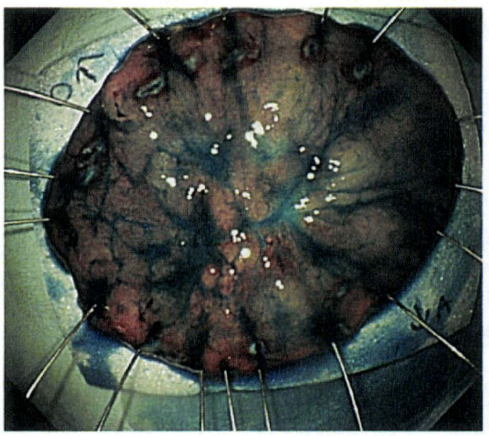

図8　切除標本

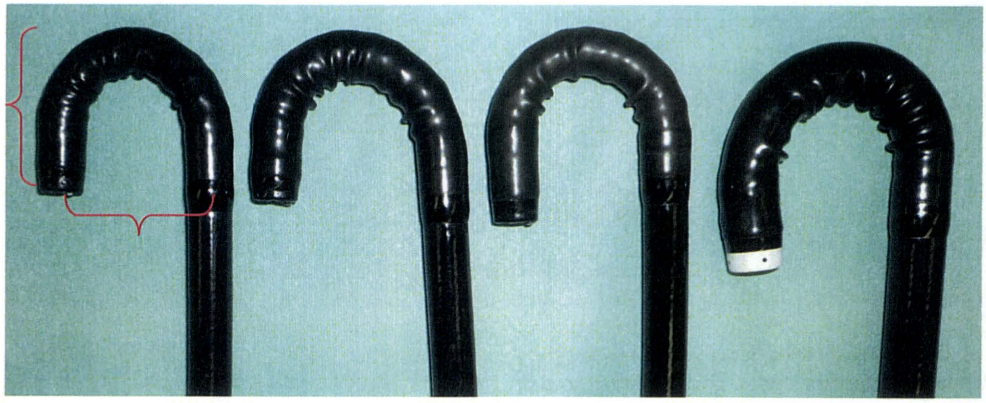

図9　スコープごとの先端硬性部の違い

しつつ，シャープかつ精密に剝離を行い，瘢痕中心部の剝離を終了させる(図7，8)．

5．その他

潰瘍瘢痕部の剝離の際には先述のように近接の視野確保が必須であるが，胃角部小彎，胃体部小彎前壁等，近接困難な部位は先端硬性部の長いスコープを用いて視野確保を行う必要があり，スコープごとの特性を熟知しておくことが重要と考える(図9)．また，施行時間が長くなることから，病変によっては全身麻酔も考慮した適切な周術期管理が必要となる．

おわりに

早期胃癌における内視鏡治療は，ESDの登場により低侵襲，機能温存，術後のQOLの点で優れた縮小治療として認められてきている．ESDの開発，技術の進歩に伴い，UL(+)病変に対しても一括切除ならびに詳細な病理学的検索が可能になった．一方で手技的難易度は高く，穿孔の頻度はガイドライン病変より高率である．線維化が強い病変や穹窿部病変などは，さらに高度な技術と時間を要すると考えられるため，先駆施設への紹介等も考慮すべきである．

根治が期待できる早期胃癌を対象に治療を行っている以上，盲目的な適応拡大は避けるべきである．各々の技量を考慮して，切除困難と考えられる病変に対しては，最初から標準治療である外科手術を選択することも大切である．

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Frequency of Lymph Node Metastasis to the Splenic Hilus and Effect of Splenectomy in Proximal Gastric Cancer

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Abstract. *Background: The purpose of this study was to investigate the clinicopathological characteristics and frequency of lymph node metastasis to the splenic hilus in proximal gastric cancer and the effect of splenectomy. Patients and Methods: Three hundred and forty-nine patients undergoing total gastrectomy for primary proximal gastric cancer were included. Among these patients, lymph node metastasis to the splenic hilus was histologically assessed in 201 cases. Results: The incidence of lymph node metastasis to the splenic hilus was 31 cases (15.4%). No lymph node metastasis to the splenic hilus was detected in any T1 and T2 tumors located at the lesser curvature and anterior wall. No significant difference was observed between the survival rates of patients with and without splenectomy in each stage. Conclusion: Our findings indicated that gastrectomy with spleen preservation may be recommended at least in patients with T1 or T2 tumors located at the lesser curvature and anterior wall.*

Established gastric cancer treatment guidelines (1) indicate that "the standard operation for advanced gastric cancer is gastrectomy with D2 lymph node dissection" and that "advanced gastric cancer involving the upper third portion is recommended for treatment by total gastrectomy including splenectomy for dissection of lymph nodes located at the splenic hilus". Pancreaticosplenectomy with lymph node dissection at the splenic hilus and around the splenic artery for advanced gastric cancer has often been performed. However, pancreaticosplenectomy is not recommended for gastric cancer patients without direct invasion of the pancreas because this procedure does not increase their survival rate (2, 3). Furthermore, it was reported that splenectomy may increase postoperative morbidity (3, 4). Therefore, gastrectomy with spleen preservation was indicated as a potential less-invasive operation for patients without lymph node metastasis to the splenic hilus. Currently, gastrectomy with spleen preservation for early gastric cancer is a common procedure, and a randomized prospective controlled trial for proximal gastric cancer designed by the Japan Clinical Oncology Group 0110 (JCOG 0110) (5), which will reveal the clinical significance of splenectomy in patients with advanced tumors without lymph node metastasis to the splenic hilus or along the splenic artery, is underway. Currently, however, the indications for splenectomy in proximal gastric cancer remain controversial.

Based on these background data, we performed a retrospective analysis of the frequency of lymph node metastasis to the splenic hilus and the effect of splenectomy on the survival of patients who underwent total gastrectomy for primary proximal gastric cancer.

Patients and Methods

Between January 1991 and December 2006, total gastrectomy was performed in 349 patients with primary proximal gastric cancer in our institute. The mean age of the patients (237 men and 112 women) was 62.9 years (range: 21-90 years). Among the 349 patients, lymph node metastasis to the splenic hilus was histologically assessed in 201 patients who underwent splenectomy or pancreaticosplenectomy. The great pancreatic artery was preserved in patients who underwent pancreas-preserving splenectomy. The rates of lymph node metastasis to the splenic hilus were retrospectively assessed in the patients who underwent splenectomy in accordance with the clinicopathological characteristics. The survival rates of patients with or without splenectomy were assessed. The clinical and pathological diagnoses and classifications were determined according to the Japanese classification of gastric carcinoma (6). Depth of tumor invasion was classified as follows: T1, tumor invasion of the mucosa and/or muscularis mucosa or submucosa; T2, tumor invasion of the muscularis propria or submucosa.

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Key Words: Proximal gastric cancer, splenectomy, lymph node metastasis, splenic hilus.

Table I. *Clinicopathological findings of patients with proximal gastric cancer who underwent total gastrectomy with or without splenectomy.*

	Splenectomy (−) (n=148)	Splenectomy (+) (n=201)	*P*-value
Age (years; range)	65.0 (29-90)	61.3 (21-88)	0.005
Gender (M/F)	97/51	140/61	0.486
Tumor size (mm; range)	66.5 (1-240)	79.0 (6-385)	0.019
Macroscopic type			<0.001
Early	56	21	
Advanced	92	180	
Histological type			0.632
Differentiated	68	86	
Undifferentiated	80	115	
Combined resection			
Pancreaticosplenectomy	0	33	
Splenectomy	0	168	
Stage			<0.001
I	64	52	
II	30	36	
III	19	60	
IV	35	53	
Lymph node metastasis			0.001
N0	68	63	
N1	42	51	
N2	34	65	
N3	4	22	
Liver metastasis			0.726
No	144	193	
Yes	4	8	
Peritoneal metastasis			0.007
No	126	173	
Yes	22	28	
Other distant metastasis			0.728
No	145	199	
Yes	3	2	

Table II. *Clinicopathological findings of patients underwent total gastrectomy with splenectomy for proximal gastric cancer.*

	Splenic hilus node metastasis		*P*-value
	− (n=170)	+ (n=31)	
Age (years; range)	62.2 (21-88)	56.7 (33-76)	0.023
Gender (M/F)	123/47	17/14	0.082
Tumor size (mm; range)	75.4 (6-385)	97.2 (9-180)	0.035
Macroscopic type			0.210
Early	20	1	
Advanced	150	30	
Histological type			0.005
Differentiated	80	6	
Undifferentiated	90	25	
Liver metastasis			0.205
No	165	28	
Yes	5	3	
Peritoneal metastasis			<0.001
No	153	20	
Yes	17	11	
Other distant metastasis			0.703
No	169	30	
Yes	1	1	

Statistical analysis was conducted using StatView version 5.0 (SAS Institute, Cary, NC, USA). The significance of differences was determined by the χ^2 test, Student's *t*-test and logistic regression. The cumulative survival rate was calculated using the Kaplan-Meier method and the log-rank test. The level of significance was set at $p<0.05$.

Results

Clinicopathological factors. The clinicopathological findings of 148 patients without splenectomy and 201 patients with splenectomy are shown in Table I. In the splenectomy group, more advanced tumors were observed. On the other hand, early or extremely severe cases with peritoneal dissemination were recognized in the spleen-preserving group. The clinicopathological findings of the patients with splenectomy are shown in Table II. Overall, 31 patients (15.4%) had metastasis to the lymph nodes of the splenic hilus. Significant differences were found for age, tumor size, histological type and peritoneal metastasis. In multivariate analysis, age was the only predictive factor (Table III).

The frequency of lymph node metastasis to the splenic hilus was associated with the location and depth of tumor invasion (Table IV). Tumors with lymph node metastasis to the splenic hilus were more frequently located at the greater curvature (38.5%), posterior wall (27.8%), had circumferential involvement (22.8%), and had invaded more deeply than the serosa. Among all T1 and T2 tumors located at the lesser curvature and anterior wall, no lymph node metastasis to the splenic hilus was observed.

Prognosis. In the splenectomy group, the cumulative 5-year survival rate of patients with lymph node metastasis to the splenic hilus was 15%, whereas the corresponding rate in patients without such metastasis was 49% (Figure 1; $p<0.001$). Among 31 patients with lymph node metastasis to the splenic hilus, 23 died of gastric cancer and 1 died of another disease. Regarding recurrence or metastasis, 16 patients had associated peritoneal metastasis, 3 lymph node metastasis and 1 patient each local recurrence, liver metastasis and lung metastasis, respectively.

The survival curves of patients with and without splenectomy in each stage are shown in Figure 2. The cumulative 5-year survival rates of patients with and without

Table III. *Multivariate logistic regression analysis of independent risk factors for lymph node metastasis to the splenic hilus.*

	P-value	Odds ratio	CI
Age (years)			
<60	0.035	2.85	1.08-7.52
≥60	-	1	
Gender			
Male	-	1	
Female	0.406	1.51	0.57-3.95
Tumor size (mm)			
<50	-	1	
≥50	0.064	4.34	0.92-20.51
Macroscopic type			
Early	-	1	
Advanced	0.776	1.37	0.15-12.29
Histological type			
Differentiated	-	1	
Undifferentiated	0.081	2.93	0.88-9.78
Liver metastasis			
No	-	1	
Yes	0.422	2.49	0.27-23.03
Peritoneal metastasis			
No	-	1	
Yes	0.056	2.95	0.97-8.96
Other distant metastasis			
No	-	1	
Yes	0.526	3.44	0.08-155.7

CI, Confidence interval.

Table IV. *Frequency of lymph node metastasis to the splenic hilus associated with location and depth of tumor invasion.*

	M	SM	MP	SS	SE	SI	Total (%)
Less	0/4	0/5	0/10	0/39	1/15	1/3	2/76 (2.6%)
Ant	0/0	0/1	0/2	0/9	1/6	0/1	1/19 (5.3%)
Gre	0/0	0/0	1/2	1/4	2/5	1/2	5 / 1 3 (38.5%)
Post	0/1	0/2	0/4	2/12	4/11	4/6	1 0 / 3 6 (27.8%)
Circ	0/0	0/0	0/1	2/13	9/35	2/8	1 3 / 5 7 (22.8%)
Total	0/5 (0%)	0/8 (0%)	1/19 (5.3%)	5/77 (6.5%)	17/72 (23.6%)	8/20 (40.0%)	31/201 (15.4%)

M, Mucosa; SM, submucosa; MP, muscularis propria; SS, subserosa; SE, serosa; SI, invasion of adjacent structures; Less, lesser curvature; Ant, anterior wall; Gre, greater curvature; Post, posterior wall; Circ, circumferential involvement.

splenectomy were 84% and 84% in stage I, 57% and 60% in stage II, 28% and 52% in stage III, and 18% and 7% in stage IV, respectively. No significant differences were observed between the two groups.

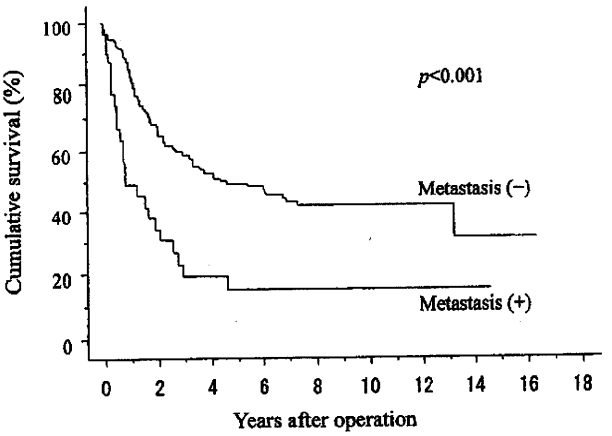

Figure 1. *Survival curves of patients who underwent total gastrectomy and splenectomy with or without lymph node metastasis to the splenic hilus.*

Table V. *Postoperative complications following total gastrectomy with or without splenectomy.*

	Splenectomy (−) (n=148)	Splenectomy (+) (n=201)	*P*-value
Bleeding	0	2 (1.0%)	0.616
Anastomotic leakage	5 (3.4%)	12 (6.0%)	0.389
Pancreatic fistula	0	17 (8.5%)	<0.001
Peritoneal abscess	3 (2.0%)	10 (5.0%)	0.249
Anastomotic stenosis	3 (2.0%)	2 (1.0%)	0.728
Intestinal obstruction	2 (1.4%)	1 (0.5%)	0.788
Cardiac disease	1 (0.7%)	2 (1.0%)	0.749
Pulmonary disease	8 (5.4%)	8 (4.0%)	0.711
Liver dysfunction	1 (0.7%)	2 (1.0%)	0.749
Renal dysfunction	0	0	-
Other	13 (8.8%)	18 (9.0%)	0.956

Morbidity and mortality. The postoperative complications following total gastrectomy with or without splenectomy during the hospitalization are shown in Table V. Postoperative complications were encountered in 32 patients (21.6%) without splenectomy and 55 patients (27.4%) with splenectomy. The major complications were anastomotic leakage, pancreatic fistula and peritoneal abscess. A significant difference in the complications was only observed for pancreatic fistula. Pancreatic fistula was observed in 4 out of 33 patients (12.1%) with pancreaticosplenectomy. Only 1 patient with splenectomy died from postoperative bleeding.

Discussion

The incidence of metastasis to the splenic hilar lymph nodes was reported to be around 10% in proximal gastric cancer (7-9). Lymphangiograms have revealed that the lymphatics

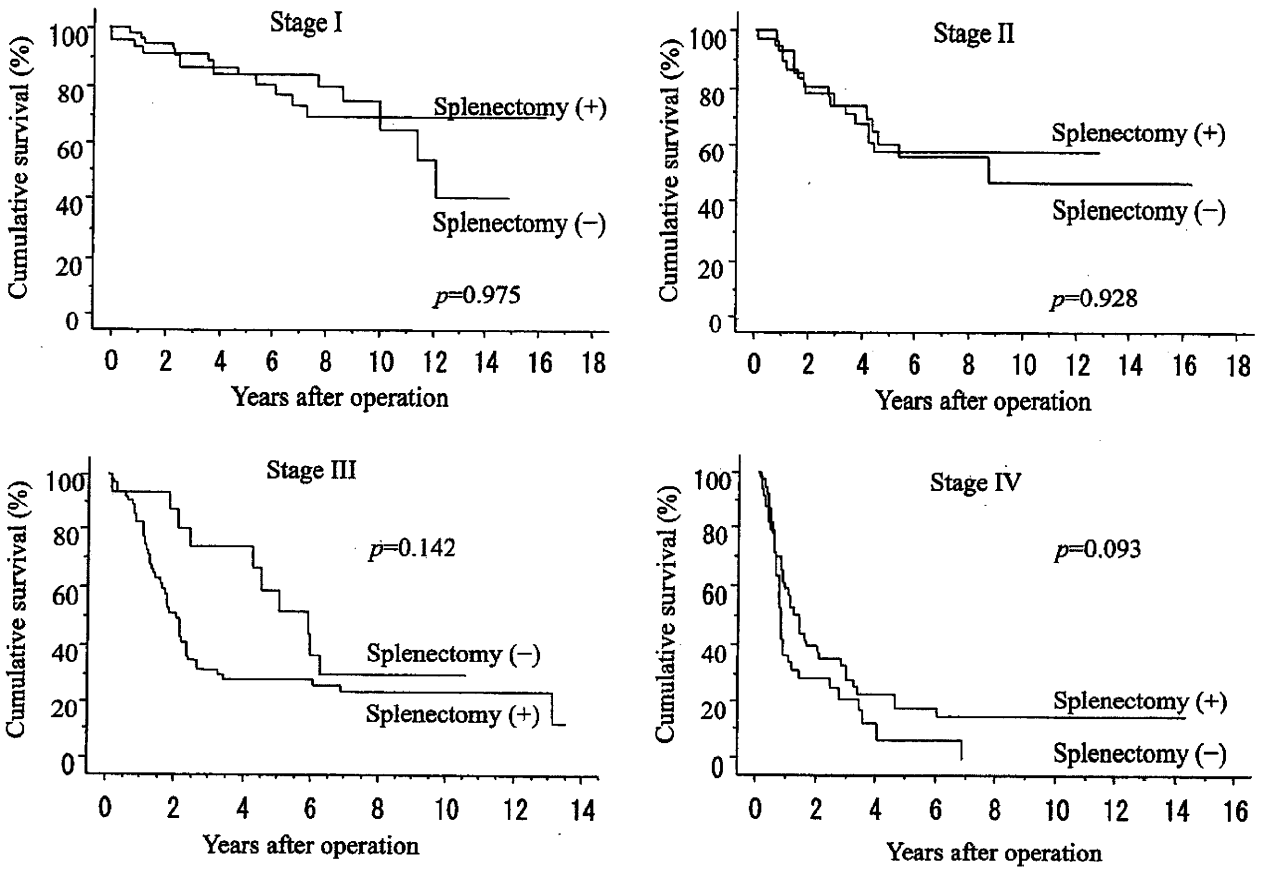

Figure 2. *Survival curves of patients who underwent total gastrectomy with or without splenectomy in each stage.*

from the upper left part of the stomach drain into the splenic hilar nodes and travel to the nodes around the celiac trunk through the splenic artery (10). This drainage route passes along not only the left gastroepiploic artery and short gastric artery, but also the posterior gastric artery, and this anatomical background agrees with the finding that splenic hilar node metastases were more frequent in tumors located at the greater curvature, posterior wall and circumferential involvement.

Although extended lymph node dissection has become a standard surgical procedure for gastric cancer in Japan, it has not shown a clear survival benefit in randomised clinical trials (11, 12) and a meta-analysis (13) in Western countries. The main reason for leaving the spleen is to resect lymph nodes in station 10, because it is impossible to resect them at the splenic hilus without splenectomy. The problems associated with simultaneous splenectomy during surgery for gastric cancer are its contribution to prognosis and the frequency of postoperative complications. A prospective randomised study comparing patients with and without splenectomy in Western countries revealed that splenectomy did not influence the survival in localized stages of gastric cancer, that is stages IA, IB, II, IIIA (14). A Japanese prospective randomised trial is in progress (5). Although the previous studies did not improve patient survival (3, 15-21), some conferred a survival benefit (10, 22-25). Regarding the survival benefit of splenectomy, previous studies have reported that the spleen in advanced gastric cancer patients produced suppressor T-cells, which might improve the survival *via* tumor-induced immunosuppression (25-28). In the present study, there was no significant difference in survival for each stage between patients with and without splenectomy. Furthermore, among postoperative complications in patients with splenectomy, only pancreatic fistula was more frequent and associated with surgical technique, but did not increase mortality.

In conclusion, from the standpoint of survival benefit, splenectomy did not exhibit any significance for primary proximal gastric cancer. Furthermore, for all T1 and T2 tumors located at the lesser curvature and anterior wall, gastrectomy with spleen preservation may be recommended as a standard operation.

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Risk factors for cardiac and pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment

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Background and study aims: Bleeding and perforation are major complications of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC), but post-ESD stenosis represents a severe delayed complication that can result in clinical symptoms such as dysphagia and nausea. The aims of this study were to determine the risk factors and evaluate the clinical treatment for post-ESD stenosis.

Methods: A total of 2011 EGCs resected by ESD at our institution between 2000 and 2005 were reviewed retrospectively. Resection was defined as cardiac when any mucosal defect was located in the squamocolumnar junction, and as pyloric when any mucosal defect was located < 1 cm from the pylorus ring. Post-ESD stenosis was defined when a standard endoscope could not be passed through the stenosis. We examined the incidence of post-ESD stenosis, its relationship with relevant factors, and the clinical course of post-ESD stenosis patients.

Results: Post-ESD stenosis occurred with seven of 41 cardiac resections (17%) and eight of 115 pyloric resections (7%). Circumferential extent of the mucosal defect of > 3/4 and longitudinal extent > 5 cm were each significantly related to occurrence of post-ESD stenosis with both cardiac and pyloric resections. All 15 affected patients were successfully treated by endoscopic balloon dilation.

Conclusions: A circumferential extent of the mucosal defect of > 3/4 or longitudinal extent of > 5 cm in length were both demonstrated to be risk factors for post-ESD stenosis, in both cardiac and pyloric resections, and endoscopic balloon dilation was shown to be effective in treating post-ESD stenosis.

Introduction

Currently, endoscopic resection is a widely accepted treatment for early gastric cancer (EGC) when the risk of lymph node metastasis is diagnosed as being very low or negligible [1–3]. Endoscopic submucosal dissection (ESD) is a new endoscopic resection method that facilitates one-piece resection even in patients with large or ulcerative lesions, thereby reducing local recurrence [4–9].

Although bleeding and perforation remain the most common complications, post-ESD stenosis represents a severe delayed complication that may result in clinical symptoms such as dysphagia and nausea. It is thought that post-ESD stenosis is caused by the removal of a large area when lesions are located near either the cardia or the pylorus, but only one case series about post-ESD stenosis in gastric ESDs has been reported so far [10]. The aims of this study were to determine the risk factors for post-ESD stenosis and evaluate the clinical treatment of post-ESD stenosis patients.

Patients and methods

We performed ESD with curative intent on 2011 EGCs in 1819 consecutive patients at the National Cancer Center Hospital in Tokyo between January 2000 and December 2005. Written informed consent was obtained from all patients before their ESD procedures. The median age of patients was 68 years (range 27–94) and the male/female ratio was 3.92 (1449/370). The ECG lesions were located in the upper third of the stomach in 326 instances, the middle third in 887, and the lower third in 798. Resection was defined as cardiac when any mucosal defect was located in the squamocolumnar junction, and as pyloric when any mucosal defect was located < 1 cm from the pylorus ring.

	Cardiac resection n = 41	Pyloric resection n = 115
Age, median years (range)	68 (41 – 85)	70 (37 – 90)
Gender, n (%)		
Male	36 (88)	75 (65)
Female	5 (12)	40 (35)
Concomitant disease, n (%)		
Diabetes mellitus	4 (10)	8 (7)
Liver cirrhosis	0 (0)	5 (4)
Chronic heart failure	2 (5)	3 (3)
Autoimmune disease	0 (0)	3 (3)
Chronic renal failure	0 (0)	2 (2)
Circumferential extent of mucosal defect, n (%)		
≤ 1/2	28 (68)	81 (70)
1/2 – 3/4	6 (15)	16 (14)
> 3/4	7 (17)	18 (16)
Longitudinal extent of mucosal defect, n (%)		
≤ 5 cm	39 (95)	109 (95)
> 5 cm	2 (5)	6 (5)
Location of mucosal defect (center), n (%)		
Lesser curve	32 (78)	32 (28)
Anterior wall	3 (7)	32 (28)
Greater curve	2 (5)	22 (19)
Posterior wall	4 (10)	29 (25)
Perforation*, n (%)		
No	37 (90)	113 (98)
Yes	4 (10)	2 (2)
Lesion macroscopic type, n (%)		
Elevated	14 (34)	32 (28)
Depressed	24 (59)	65 (56)
Elevated and depressed	3 (7)	18 (16)
Depth of invasion, n (%)		
Mucosal	29 (71)	99 (86)
Submucosal	12 (29)	16 (14)
Ulcer finding, n (%)		
Absence	37 (90)	94 (82)
Presence	4 (10)	21 (18)

Table 1 Characteristics of patients with cardiac and pyloric resections.

*All patients with perforations were successfully treated by endocopic clipping.

ESD procedures were performed with sedation using midazolam and pentazocine and began with identification of the lesion margins which were then marked with a needle knife. Submucosal injections were used to lift the mucosa followed by a circumferential mucosal incision around the lesion. Finally, submucosal dissection of the lesion was performed with an insulation-tipped knife (Olympus Medical Systems, Tokyo, Japan) [5]. The curative success of the ESDs was subsequently determined pathologically. As a general rule, we performed an additional gastrectomy with lymph node dissection after a noncurative ESD in which a resected specimen was diagnosed as indicating a possible risk of nodal metastasis, such as showing submucosal deep invasion or positive lymphatic invasion. [11] When a resected specimen was diagnosed as showing a curative resection, we usually performed an endoscopy to check the healing progress of the ESD mucosal defect 2 – 3 months later. If patients had undergone cardiac or pyloric resection or had any clinical symptoms, we carried out endoscopy earlier than 2 – 3 months after ESD. We then followed up the patients every 6 months or annually.

Post-ESD stenosis risk factors

Post-ESD stenosis was diagnosed by endoscopy and defined as existing when a standard 10-mm diameter endoscope could not be passed through an existing stenosis.

We reviewed the clinical records, endoscopic images, and endoscopic and pathological reports for all patients. Patients with cardiac and pyloric resection lesions were divided into two groups, that is, with and without post-ESD stenosis. The two groups were compared with regard to age, gender, concomitant disease that might affect ESD ulcer healing, circumferential extent of the mucosal defect, longitudinal extent of the mucosal defect, gastric location of the center of the mucosal defect, occurrence of perforation during ESD, macroscopic type of the lesion, depth of invasion, and finding of the presence of an ulcer.

The extent of the circumferential mucosal defect was classified into ≤ 1/2, 1/2 – 3/4 or > 3/4. The extent of the longitudinal mucosal defect was divided into ≤ 5 cm and > 5 cm. The gastric location of the center of the mucosal defect was categorized as lesser curve, anterior wall, greater curve, or posterior wall. These classifications were made by an experienced endoscopist who reviewed endoscopic images without being aware of the clinical outcomes.

	Post-ESD stenosis		*P* value
	None n = 34	Present n = 7	
Age, mean years (range)	68 (41 – 85)	73 (54 – 80)	n. s.
Gender, n (%)			
Male	31	5 (14)	n. s.
Female	3	2 (40)	
Concomitant disease, n (%)			
Diabetes mellitus	3	1 (25)	n. s.
Chronic heart failure	2	0 (0)	n. s.
Circumferential extent of mucosal defect, n (%)			
≤ 3/4	34	0 (0)	< 0.01
> 3/4	0	7 (100)	
Longitudinal extent of mucosal defect, n (%)			
≤ 5 cm	34	5 (13)	0.03
> 5 cm	0	2 (100)	
Location of mucosal defect (center), n (%)			
Lesser curve	26	6 (19)	n. s.
Anterior wall	3	0 (0)	
Greater curve	2	0 (0)	
Posterior wall	3	1 (25)	
Perforation*, n (%)			
No	30	7 (19)	n. s.
Yes	4	0 (0)	
Lesion macroscopic type, n (%)			
Elevated	12	2 (14)	n. s.
Depressed	19	5 (21)	
Elevated and depressed	3	0 (0)	
Depth of invasion, n (%)			
Mucosal	24	5 (17)	n. s.
Submucosal	10	2 (17)	
Ulcer finding, n (%)			
Absent	31	6 (16)	n. s.
Present	3	1 (25)	

Table 2 Risk factors for post-ESD stenosis following cardiac resection.

n. s., not significant.

*All patients with perforations were successfully treated by endocopic clipping.

Macroscopic lesion types were classified endoscopically as elevated type, depressed type, or elevated and depressed type, based on data collected from the endoscopic reports. Depth of invasion and the presence of an ulcer were determined pathologically, according to the findings from the pathological reports.

Clinical treatment of post-ESD stenosis patients

The clinical treatment of post-ESD stenosis patients was also investigated in our study. Endoscopic balloon dilation was indicated for post-ESD stenosis patients complaining of any clinical symptoms. A 15 – 18-mm or 18 – 20-mm wire-guided balloon dilator (CRE Wire-Guided Balloon Dilation Catheter; Boston Scientific, Natick, Massachusetts, USA) was used without fluoroscopic guidance. Endoscopic balloon dilation was performed once or twice a week as necessary whenever the degree of post-ESD stenosis was severe. The interval was extended gradually to every 2 weeks and then every month as the patient's condition improved, and endoscopic balloon dilation was continued until the patient's post-ESD stenosis and clinical symptoms were resolved completely.

Data were analyzed using the chi-squared test, Fisher's exact test or the Student *t* test as appropriate (Statview; Abacus Concepts, Berkeley, California, USA). Value differences of $P < 0.05$ were considered statistically significant.

Results

Post-ESD stenosis risk factors

Post-ESD stenosis was associated with 15 of the 2011 lesions (0.7 %) previously treated by ESD, in 15 of the 1819 patients. Of the other 1804 patients, 209 underwent gastrectomies because the ESDs were noncurative, while 84 received their first follow-up endoscopy examinations at other hospitals with no subsequent referrals to our hospital. None of the remaining 1511 patients showed signs of post-ESD stenosis, either at the first follow-up endoscopy after ESD at our hospital to check the healing progress of the mucosal defect or at any of their subsequent follow-up examinations.

All 15 post-ESD stenosis cases were induced by ESDs involving either the cardiac or pyloric resections that had comprised 41 of the 326 upper third lesions (13 %) and 115 of the 798 lower third lesions (14 %), respectively (**Table 1**). Post-ESD stenosis occurred following seven of the 41 cardiac resections (17 %) and eight of the 115 pyloric resections (7 %). All of the post-ESD stenosis patients were diagnosed before undergoing a routine first follow-up endoscopy examination, because each of the seven stenosis patients who had undergone cardiac resection experienced dysphagia while all eight of the pyloric resection stenosis patients suffered from severe nausea, with six of them actually vomiting due to the large amount of residual food in their stomachs.

Table 3 Risk factors for post-ESD stenosis following pyloric resection.

	Post-ESD stenosis		*P* value
	None n = 107	Present n = 8	
Age, mean years (range)	70 (37 – 90)	74 (51 – 83)	n. s.
Gender, n (%)			
Male	70	5 (7)	n. s.
Female	37	3 (8)	
Concomitant disease, n (%)			
Diabetes mellitus	8	0 (0)	n. s.
Liver cirrhosis	5	0 (0)	n. s.
Chronic heart failure	3	0 (0)	n. s.
Autoimmune disease	3	0 (0)	n. s.
Chronic renal failure	2	0 (0)	n. s.
Circumferential extent of mucosal defect, n (%)			
≤ 3/4	97	0 (0)	< 0.01
> 3/4	10	8 (44)	
Longitudinal extent of mucosal defect, n (%)			
≤ 5 cm	107	2 (2)	< 0.01
> 5 cm	0	6 (100)	
Location of mucosal defect (center), n (%)			
Lesser curve	29	3 (9)	n. s.
Anterior wall	29	3 (9)	
Greater curve	21	1 (5)	
Posterior wall	28	1 (3)	
Perforation*, n (%)			
No	105	8 (7)	n. s.
Yes	2	0 (0)	
Lesion macroscopic type, n (%)			
Elevated	28	4 (13)	n. s.
Depressed	62	3 (5)	
Elevated and depressed	17	1 (6)	
Depth of invasion, n (%)			
Mucosal	93	6 (6)	n. s.
Submucosal	14	2 (13)	
Ulcer finding, n (%)			
Absent	88	6 (6)	n. s.
Present	19	2 (10)	

n. s., not significant.
*All patients with perforations were successfully treated by endocopic clipping.

The median period from ESD to the diagnosis of post-ESD stenosis was 22 days (range 16 – 33) in the cardiac resection patients and 27 days (range 15 – 46) in the pyloric resection patients.

The data for post-ESD stenosis following cardiac and pyloric resections are shown in **Table 2** and **Table 3**, respectively. A circumferential mucosal defect > 3/4 in extent and a longitudinal mucosal defect > 5 cm in extent were each significantly related to the development of post-ESD stenosis in both cardiac and pyloric resections.

Clinical treatment of post-ESD stenosis patients

Each of the 15 post-ESD stenosis patients required endoscopic balloon dilation treatment. The clinical symptoms related to the stenosis were completely resolved in every patient in response to either single (one patient) or repeated (14 patients) endoscopic balloon dilation sessions. The median number of dilations and the median period from the first to the last dilation are shown in **Table 4**. No complications were observed after any endoscopic balloon dilation treatments.

Two patients, one each with post-ESD stenosis following cardiac resection and pyloric resection, underwent an additional gastrectomy with lymph node dissection following endoscopic balloon dilation treatment because their resected ESD specimens were subsequently pathologically diagnosed as showing a possible risk of lymph node metastasis. Those two patients were excluded from the analysis of follow-up data after repeated endoscopic balloon dilation treatment. During the median follow-up period of 36 months (range 2 – 63 months) for the other 13 post-ESD stenosis patients, the patency of the cardiac and pyloric lumens was well maintained and there were no further symptoms. The patient with the 2-month follow-up period subsequently received medical care at another institution with no further referral to our hospital.

Discussion

In the past, the accepted indications for conventional endoscopic mucosal resection (EMR) of EGC were a small intramucosal cancer ≤ 2 cm in size, of a differentiated histological type, and without an ulcer finding. This was because of technical limitations associated with the EMR procedure [4]. More recently, however, indications for the endoscopic resection of EGC have been expanded, based on a very low or negligible risk of lymph node metastasis

	Cardiac resection	Pyloric resection	*P* value
Number of dilations, median (range)	5 (1 – 14)	9 (7 – 40)	n. s.
Period of dilation treatments, median days (range)	42 (1 – 120)	50 (28 – 198)	n. s.

n. s., not significant

Table 4 Endoscopic balloon dilation treatment in patients with post endoscopic submucosal dissection (ESD) stenosis following cardac and pyloric resections.

as determined from a large number of surgical EGC cases [3, 4, 12]. The expanded indications include lesions > 20 mm and ulcerated lesions that would otherwise be difficult to resect by means of conventional EMR. Both kinds of lesions were previously resected by surgery, but the relatively new ESD technique has been developed to achieve the one-piece resection of even large and ulcerated lesions [4 – 9].

The number of EGC patients who undergo endoscopic resection is increasing in Japan because of the expanded indications and technical improvements mentioned above. Consequently, the number of endoscopic resection-related complications has also increased, so endoscopists must be aware of both the risk factors and the incidence of complications as well as knowing how to effectively treat such complications. Although cases of bleeding and perforation related to ESD of EGC have previously been reported [5, 13, 14], so far only one case series about post-ESD stenosis in gastric ESDs has been published [10].

This is the first study to determine the incidence of post-ESD stenosis in EGC lesions and the associated risk factors. The present study has shown that a circumferential mucosal defect of extent > 3/4 and a longitudinal mucosal defect of extent > 5 cm were each significantly related to the development of post-ESD stenosis in both cardiac and pyloric resections. Similar results have been reported in a study investigating esophageal stenosis after EMR of superficial esophageal cancer [15]. Knowledge of the risk factors associated with the subsequent development of post-ESD stenosis will allow endoscopists to better anticipate the likelihood of this complication.

Bleeding and perforation are complications that usually happen during ESD or within 24 hours after the procedure [5, 13, 14] so immediate treatment is normally required in such cases. In contrast, however, it is thought that post-ESD stenosis manifests itself several weeks after ESD, during the actual healing process. In this study, the median period from ESD to the diagnosis of post-ESD stenosis was 22 days in cardiac resection stenosis cases and 27 days in pyloric resection stenosis cases. Appropriate endoscopic follow-up to check for the subsequent presence of post-ESD stenosis, therefore, is recommended for patients with either of the identified risk factors for this complication. In order to minimize or prevent post-ESD stenosis-related symptoms from occurring, however, it may be advisable to start balloon dilation before the stenosis actually develops in such patients.

The clinical significance of post-ESD stenosis is that it decreases a patient's quality of life. In the present study, all 15 post-ESD stenosis patients developed a clinical symptom that was successfully relieved by either single (one patient) or repeated (14 patients) endoscopic balloon dilation treatment, and the patency of the cardiac and pyloric lumens was well maintained during a sufficiently lengthy follow-up period. Based on our findings, endoscopic balloon dilation can be regarded as an effective therapy for post-ESD stenosis although the number of patients was limited in this study. Similar effectiveness of endoscopic balloon dilation for the treatment of esophageal stenosis after EMR of superficial esophageal cancer has also been reported [15]. Patients with stenosis following pyloric resection required more balloon dilation procedures over a longer period compared with those with cardiac resections, although there was no significant difference between the two groups, probably once again because of the small number of patients involved (**Table 4**). In our study there were no complications after any of the balloon dilations, but the number of patients was limited and perforations related to endoscopic balloon dilation have been reported [10], so enhanced efforts should be made to preclude the development of post-ESD stenosis in the first place. In this regard, there is a recent case report of a biodegradable esophageal stent effective for patients with esophageal stenosis after ESD [16] that may be useful in preventing post-ESD stenosis from developing in patients with cardiac or pyloric resections.

In conclusion, the results of this retrospective study demonstrate that cardiac or pyloric resections in which the extent of the mucosal defect is > 3/4 circumferentially or > 5 cm longitudinally carry a risk for the occurrence of post-ESD stenosis, and that endoscopic balloon dilation can be an effective treatment for such post-ESD stenosis.

Competing interests: None

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Risk of perforation during endoscopic submucosal dissection using latest insulation-tipped diathermic knife (IT knife-2)

Endoscopic submucosal dissection (ESD) enables en bloc resection of lesions regardless of tumor size or location. The insulation-tipped (IT) diathermic knife (Olympus Medical Systems Corp., Tokyo, Japan) is a proven endoscopic device for ESD [1,2]. ESD gastric perforations using the IT knife usually happen during submucosal dissection [3]. However, we present an ESD perforation case that occurred when an IT knife-2, an improved version of the IT knife [4], was being used for circumferential mucosal incision.

A 59-year-old man presented a superficial depressed-type 20-mm lesion (**Fig. 1**), histologically diagnosed as a well-differentiated adenocarcinoma. Under sedation and following submucosal injection of normal saline solution, an initial incision was performed using a needle knife (Olympus Medical Systems Corp.). After the tip of the IT knife-2 had been inserted into the initial incision (**Fig. 2a**), an unexpected perforation occurred during the circumferential mucosal incision (**Fig. 2b**, **Video 1**). The resection was discontinued and the perforation was successfully closed using endoscopic clips (**Fig. 3**).

A recent study evaluated the use of the IT knife-2 over the original IT knife, reporting a significantly shorter operating time with no significant changes in the en bloc resection and complication rates [4]. The addition of a three-pronged blade directly beneath the insulation tip of the IT knife-2 seems to be the reason for an increased cutting ability from a vertical view, an enhanced lateral cutting capability, and a greater facility to hook the tissue edge prior to cutting (**Fig. 4a** and **b**). However, it is our belief that the perforation reported here would not have occurred if the original IT knife had been used at the time. Therefore, more gentle manipulation than that required with the original IT knife should be adopted during circumferential mucosal incision, especially by endoscopists who are inexperienced in the use of this recently developed device.

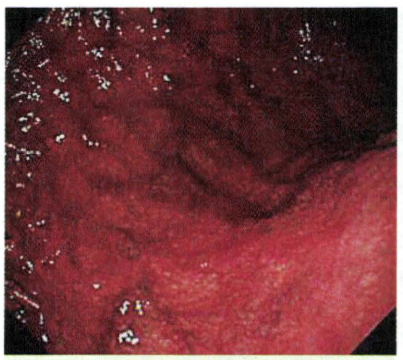

Fig. 1 Endoscopic finding of early gastric cancer. A superficial depressed lesion located in the posterior wall of the lower gastric body was revealed by conventional endoscopy.

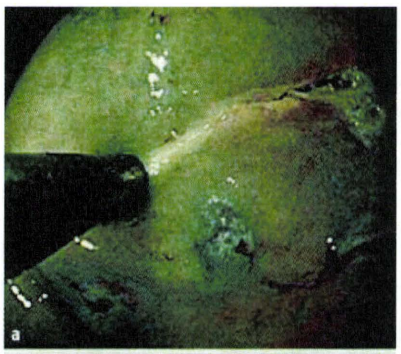

Fig. 2 Circumferential mucosal incision. **a** Circumferential mucosal incision had just begun using the insulation-tipped (IT) knife-2 from the point of small initial incision made with a needle knife. **b** Perforation occurred at the beginning of the circumferential mucosal incision.

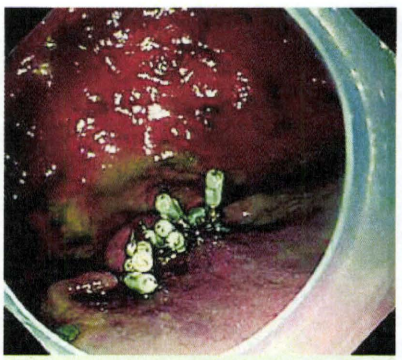

Fig. 3 Closure of the perforation was successfully performed using endoscopic clips.

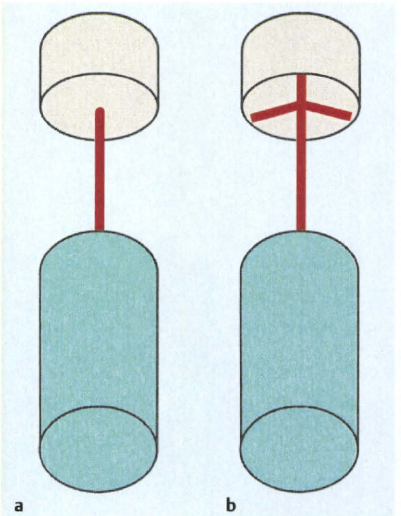

Fig. 4 The difference between the original IT knife and the IT knife-2. **a** There is no blade underneath the insulation tip of the original IT knife. **b** The IT knife-2 has a three-pronged blade directly beneath the insulation tip.

Video 1

Endoscopic submucosal dissection gastric perforation using the IT knife-2 during circumferential mucosal incision.

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Mixed-histologic-type submucosal invasive gastric cancer as a risk factor for lymph node metastasis: feasibility of endoscopic submucosal dissection

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Background and study aims: The clinicopathologic features of gastric cancers containing a mixture of differentiated-type and undifferentiated-type components remain uninvestigated. We evaluated the risk of lymph node metastasis and the feasibility of endoscopic submucosal dissection (ESD) for the treatment of mixed-histologic-type gastric cancers.

Patient and methods: We histologically classified 376 cases of gastric cancer with submucosal invasion into four types (differentiated type, differentiated-type-predominant mixed type, undifferentiated-type-predominant mixed type, and undifferentiated type) and studied the clinicopathologic relations of each type to lymph node metastasis. Lymphatic invasion was evaluated by D2-40 immunostaining.

Results: The overall prevalence of lymph node metastasis in gastric cancer with submucosal invasion was 16.5% (62/376). The prevalence of lymph node metastasis was 36.5% (23/63) in undifferentiated-type-predominant mixed type, which was significantly higher than those in the other three types ($P < 0.001$ vs. differentiated type, $P = 0.013$ vs. differentiated-type-predominant mixed type, and $P = 0.003$ vs. undifferentiated type). Lymphatic invasion, a depth of invasion of 500 µm or more from the lower margin of the muscularis mucosae (SM2), tumor size above 30 mm, and undifferentiated-type-predominant mixed histologic type were independent risk factors for lymph node metastasis. Submucosal cancers without these four risk factors were free of lymph node metastasis (0/41; 95% confidence interval 0%–8.6%).

Conclusions: Undifferentiated-type-predominant mixed-type gastric cancer with submucosal invasion carries a high risk of lymph node metastasis. ESD can be indicated for gastric cancer with submucosal invasion provided that the following conditions indicating a low risk of metastasis are met: a depth of invasion of no more than 500 µm or more from the lower margin of the muscularis mucosae (SM1), no lymphatic invasion, a tumor size of no more than 30 mm, and a proportion of undifferentiated components below 50%.

Introduction

Early gastric cancer is defined as a carcinoma that is confined to the mucosa or submucosa (depth of invasion from the lower margin of the muscularis mucosae < 500 µm, SM1; depth of invasion from the lower margin of the muscularis mucosae ≥ 500 µm, SM2), irrespective of the presence or absence of lymph node metastasis [1]. Pathologically, gastric cancer can be broadly divided into two types according to the presence or absence of tubular structures: these are the differentiated type and the undifferentiated type [1]. Characteristically, undifferentiated gastric cancer carries a higher risk of lymph node metastasis than does differentiated gastric cancer [2–5]. However, in some cases gastric cancer includes a mixture of differentiated and undifferentiated components. Gastric cancers that include a mixture of differentiated and undifferentiated components are classified according to the predominant histologic type by the Japanese Classification of Gastric Carcinoma [1].

Many studies have examined lymph node metastasis in early gastric cancer. The incidence of lymph node metastasis in intramucosal gastric cancer is estimated to be 2% [2,3,6,7]. Lymph node metastasis is present in about 20% of all cases of gastric cancer with submucosal invasion [4,5,8–10]. Cancer with SM2 invasion, undifferentiated-type cancer, and lymphatic invasion are independent risk factors for lymph node metastasis [2,4,5]. However, the advent of new devices such as insulation-tipped knives, the development of techniques for endoscopic submucosal dissection (ESD) [11], and a better understanding