LY grade

Lymphatic tumor emboli were graded as follows according to the total number of LY per case: 0, LY0; 1 to 2, LY1; 3 to 9, LY2; and 10 or more, LY3. The frequency of N was calculated according to LY grade. According to Guidelines for the Clinical and Pathological Studies on Carcinoma of the Esophagus issued by the Japanese Society for Esophageal Diseases, small numbers of ly were classified as ly1, moderate numbers of ly as ly2, and large numbers of ly as ly3 [19]. The frequency of N was then calculated according to ly grade.

LY density

For each case, LY density was calculated as the number of LY per 20 high-power fields (HPF) at the deepest site of tumor invasion and the surrounding region.

Results

D2-40 immunostaining permitted the identification of lymphatic vessels, thereby facilitating the detection of LY. This technique allowed LY to be accurately pinpointed in tumor tissue and stroma, often not feasible with conventional pathological techniques (Fig. 2).

The number of LY detected per case ranged from 0 to 2,460, and the number of V detected ranged from 0 to 1,799. The correlation coefficient for the number of LY and the LY density was 0.702, indicating a significant positive correlation ($p < 0.0001$). The median (range) LY density according to LY grade was 0 for LY0, 1 (0–2) for LY1, 3 (1–4) for LY2, and 7.5 (2–71) for LY3. Both LY and V were highest in sm3 cases. All m1 and m2 cases were LY− and N−. In m3, LY was positive in about 50% of cases, whereas N was positive in about 20%. In sm1, sm2, and sm3, LY was positive in 60%–70% of cases. In about 47% of sm1 cases, N was positive, but this figure rose to about 63% in sm3 cases. The frequency of V increased in parallel with the depth of invasion, and V was positive in all sm3 cases. Like LY, ly was negative in m1 and m2 cases. However, ly was slightly less frequent than LY in m3 and more frequent than LY in sm1, sm2, and sm3 (Table 1).

We divided sm1 cases into those with a depth of invasion of 200 μm or less from the lower margin of the muscularis mucosae (≤200 μm group) and those with a depth of invasion of greater than 200 μm (>200 μm group) and compared LY and N between these two groups. The presence of LY was positive in 2 (33.3%) of 6 cases in the ≤200 μm group and 10 (90.9%) of 11 cases in the >200 μm group, and N was positive in 1 (16.7%) of 6 cases in the ≤200 μm group and 8 (72.7%) of 11 cases in the > 200 μm group. The frequencies of both LY+ and N+ were significantly higher in the >200 μm group ($p = 0.0276$, 0.0498).

As for the relation between LY and N according to the depth of invasion, in m3 all LY− cases were N−. In submucosal cancer, N was positive in one sm1 case and two sm2 cases, although LY was negative. In the sm1 case, the depth of invasion was 350 μm from the lower margin of the muscularis mucosae. In sm3, 10 (83%) of 12 LY + cases were N+, representing a very high frequency.

The correlation coefficient for the number of LY and the number of N was 0.609, indicating a significant positive correlation ($p < 0.0001$) (Fig. 3). Multiple regression analysis was performed with the number of lymph node metastases as the dependent variable and LY, V, tumor size, tumor thickness, and depth of invasion as independent variables. Only LY and V were found to significantly correlate with N (Table 2). Next, to determine whether LY is a predictor of N, we calculated the sensitivity, specificity, accuracy, positive predictive value, negative predictive value, positive posterior probability increase, negative posterior probability increase, likelihood of a positive test, and likelihood of a negative test for LY. These values were also similarly calculated for ly. Although sensitivity did not significantly differ between LY and ly, specificity, accuracy, and positive predictive value were higher for LY than for ly. In addition, the false positive rate was lower for LY than for ly (Table 3).

As for the relation of N to LY grade and ly grade, the frequency (%) of N increased with higher grades of both LY and ly. The increment in the frequency of N was similar for both LY grade and ly grade. Even in LY1, 39% of cases were N+. In LY2, this figure rose to 82%, and in LY3 all cases were N+. Lymphatic tumor emboli grade strongly correlated with N. A similar trend was seen for ly

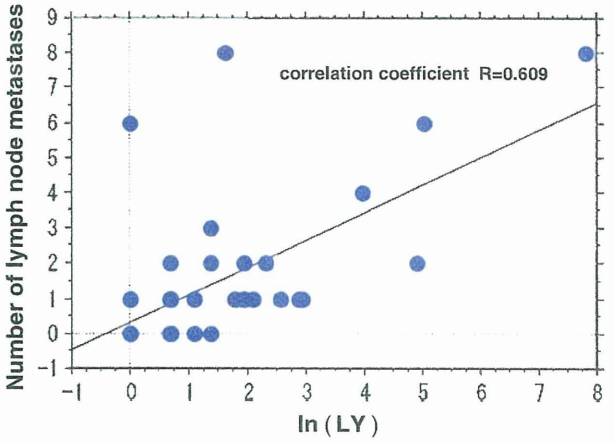

Fig. 3 Correlation between the number of lymph node metastases and the number of lymphatic tumor emboli detected on D2-40 immunostaining

Table 2 Dependent variables and independent variables[a]

	Regression coefficient	Standard error	Standardized regression coefficient	*t* Value	*p* Value
LY	0.029	0.009	4.901	3.129	0.0026
V	−0.037	0.013	−4.442	−2.863	0.0056
Length	0.003	0.011	0.036	0.222	0.8251
Width	−0.005	0.019	−0.044	−0.287	0.7752
Thickness	0.088	0.066	0.15	1.331	0.1875
Depth of invasion	0.559	0.369	0.146	1.515	0.1344
Intercept	0.043	0.405	0.043	0.107	0.9155

[a] Dependent variables represent the number of lymph node metastases per case; independent variables include number of lymphatic tumor emboli (LY), number of venous tumor emboli (V), length, width, thickness and depth of invasion

Length longitudinal diameter of the tumor; *Width* widest diameter of the tumor; *Thickness* distance from the surface to the invasion front of the tumor

Table 3 Relation between lymphatic tumor emboli and lymph node metastasis, prevalence, sensitivity, specificity

	LY		ly	
	+	−	+	−
Lymph node metastasis				
N+	25	3	27	1
N−	17	30	24	23
	LY		ly	
Prevalence	37.3%		37.3%	
Sensitivity	89.3%		96.4%	
Specificity	63.8%		48.9%	
Accuracy	73.3%		66.7%	
False positive rate	36.2%		51.1%	
False negative rate	10.7%		3.6%	
Positive predictive value (PPV)	59.5%		52.9%	
Negative predictive value (NPV)	90.9%		95.8%	
Positive posterior probability increase	22.2%		15.6%	
Negative posterior probability increase	53.6%		58.5%	
Likelihood ratio of a positive test	2.47		1.89	
Likelihood ratio of a negative test	0.17		0.07	

N+ cases with metastasis of dissected lymph nodes or those confirmed by postoperative image studies; *N−* cases without lymph node metastasis

Table 4 Relation between each grade of lymphatic tumor emboli and the frequency of lymph node metastasis

	Frequency of patients with lymph node metastasis	Percentage of metastatic lymph nodes among dissected lymph nodes
D2-40 immunostain[a]		
LY0	3/33 (9.1%)	0.3 ± 1.0%
LY1	9/23 (39.1%)	0.9 ± 1.7%
LY2	9/11 (81.8%)	3.9 ± 5.4%
LY3	8/8 (100.0%)	6.5 ± 6.4%
Conventional methods[b]		
ly0	1/24 (4.2%)	0.1 ± 0.6%
ly1	17/38 (44.7%)	1.6 ± 3.4%
ly2	8/10 (80.0%)	3.3 ± 3.5%
ly3	3/3 (100.0%)	11.5 ± 7.3%

[a] LY0, LY1, LY2, and LY3: 0, 1–2, 3–9 and 10 or more lymphatic tumor emboli detected by D2-40 immunostain

[b] ly0, ly1, ly2 and ly3: absent, low, moderate, and high frequency of lymphatic tumor emboli detected by conventional hematoxylin-eosin and elastica van Gieson staining

grade (Table 4). When LY grade was compared with ly grade, a progressive increase in LY grade was associated with a stepwise decrease in the number of cases. As for ly grade, however, ly1 was by far the most common grade, accounting for over 50% of all cases. Moreover, about 35% of the 38 cases classified as ly1 were LY0 (i.e., no LY detected) on D2-40 immunostaining. Likewise, LY2 and LY3 included eight ly1 cases and three ly1 cases, respectively (Table 5).

Discussion

The Guidelines for the Treatment of Carcinoma of the Esophagus [6] consider m1 and m2 superficial carcinomas of the esophagus an absolute indication for endoscopic resection. In our study, no m1 or m2 cases were positive for LY or N, confirming the validity of these treatment guidelines. The Guidelines consider m3 and sm1 cases a relative indication for endoscopic resection, but we found high rates of both LY and N in m3 cases (LY, 54%; N, 27%) as well as in sm1 cases (LY, 70%; N, 47%). Our results thus reconfirm the vital importance of lymph-node imaging studies, both before and after endoscopic

Table 5 Number of patients with lymphatic tumor emboli detected by D2-40 immunostain and conventional methods

	ly0	ly1	ly2	ly3	Total
LY0	17	13	3	0	33
LY1	6	14	3	0	23
LY2	1	8	2	0	11
LY3	0	3	2	3	8
Total	24	38	10	3	75

resection. In m3, all LY− cases were N−, indicating that the assessment of LY is an important determinant of the postoperative treatment policy. When sm1 cases were classified as to whether the depth of invasion was ≤200 μm or >200 μm in accordance with the criteria for the invasion depth of endoscopically resected specimens, the frequencies of both LY and N were significantly higher in the >200 μm group. On the other hand, some sm1 cancers with an invasion depth of ≤200 μm were positive for LY or N, but N was not positive if LY was negative. Therefore LY was considered useful for predicting N. One sm1 case was LY− and N+, but the tumor had an invasion depth of >200 μm. These findings indicate that it is risky to assess the probability of N solely on the basis of LY when the depth of tumor invasion is >200 μm.

When the ability to detect N was compared between LY and ly, LY was superior to ly in terms of specificity, accuracy, positive predictive value, and false positive rate. In particular, the false positive rate was about 15 percentage points lower for LY. The three cases that were LY−, but N+ (one sm1 case and two sm2 cases) were false negative cases. The reason for false negative results may be that the tissue blocks were sliced at 5-mm intervals; consequently, all tissue was not continuously assessed. It is possible that LY may have existed between separate slices of tissue. Mori et al. used D2-40 immunostaining to detect lymphatic tumor emboli at the invasion front [20]. They found that 6 (13%) of 46 cases were N + despite being LY−. In contrast, with our technique only 3 (4%) of 75 cases were N+ but LY−, suggesting that false negative cases can be reduced by examining thinner slices of whole tissue samples. Because specimens of endoscopically resected tissue are prepared at intervals of about 2 mm in clinical practice, the LY detection rate would be even higher, further reducing false negative cases.

Various imaging techniques (CT, MRI, EUS] fluorodeoxyglucose positron emission tomography [FDG-PET]) are used to preoperatively assess lymph-node metastasis [21–23]. On imaging studies, metastatic lymph nodes are evaluated on the basis of normal lymph node size, and a diameter of 5 mm or greater is usually used as the criterion for positive nodes. Lymph node micrometastasis frequently occurs in esophageal cancer. Studies examining the size of metastatic lymph nodes in esophageal cancer have reported that 37.2% of all metastatic lymph nodes were less than 5 mm in diameter [24]. Consequently, small metastatic lymph nodes cannot be detected. This is an important limitation of the diagnosis of lymph-node metastasis on imaging studies. In patients considered candidates for endoscopic mucosal resection (EMR), the inability to detect lymph node micrometastases is a major problem. Endoscopic mucosal resection can produce good treatment outcomes in patients who have node-negative superficial esophageal cancer, but follow-up therapy is required for any lymph-node metastasis. Although follow-up treatment such as open surgery and chemoradiotherapy can produce good outcomes after EMR, these procedures are highly invasive, and the indications should be strictly evaluated. Our technique for LY can evaluate the probability of lymph-node metastasis irrespective of node size. Our results suggest that LY can be used to identify lymph node micrometastases unable to be detected on imaging studies.

We propose that LY is classified into four grades (LY0, LY1, LY2, LY3) on the basis of the number of lymphatic tumor emboli. When this classification is used, an increase in the LY grade is accompanied by a linear rise in the frequency of N (N+ rate). The LY grade can thus be used to predict the risk of N. LY1 was already associated with N+ in 40% of cases. The N+ rate further increased to greater than 80% for LY2 and 100% for LY3. On the basis of LY grade, LY2 and LY3 cases are likely to require treatment for metastatic lymph nodes. Thus LY grade can effectively contribute to determining the treatment policy.

Like LY, an increase in ly grade was associated with a rise in the N+ rate. The N+ rate was 100% in ly3 cases, similar to LY3. However, there were 8 LY3 cases and only 3 ly3 cases. This finding implies that on assessment by conventional staining five patients who were N+ would probably have been followed up with no further treatment after endoscopic resection. Another limitation of conventional staining techniques is that the evaluation of ly grade depends on the judgment of the pathologist and thus lacks objectivity. The LY2 cases in the present study had an N+ rate of 81.8%, indicating the need for additional treatment. The N+ rate was also high for ly2 cases (80%), but the criteria defining ly2 are ambiguous, similar to ly3. Doubt remains about whether follow-up treatment can be recommended with confidence for ly2 and ly3 cases. In contrast, LY2 and LY3 cases can be more objectively defined, permitting a more convincing argument for follow-up therapy.

A direct comparison of LY grade with ly grade clearly demonstrated other limitations of ly. As the LY grade increased, the number of cases decreased in a stepwise fashion, whereas with ly grade the most frequent category by far was ly1, accounting for 38 cases. Of these cases, 13

were classified as LY0, suggesting that retraction artifacts were responsible for the classification of these cases as ly1. On the other hand, eight ly1 cases were LY2 and three ly1 cases were LY3, indicating that conventional staining techniques could not detect many lymphatic tumor emboli.

In conclusion, only LY and V significantly correlated with N on regression analysis. The LY factor was superior to ly in terms of specificity, accuracy, positive predictive value, and false positive rate. The classification of LY into four grades on the basis of the number of LY allows the risk of N+ to be evaluated more objectively than previously possible. In particular, LY2 and LY3 cases had extremely high N+ rates of 80% and 100%, respectively. When mucosal cancer (m1, m2, and m3) is diagnosed on EMR in patients with SSCCE, the risk of N is low if LY is negative, and EMR alone can provide good treatment outcomes. If LY is positive, however, additional treatments should be considered owing to the risk of N. Submucosal cancers with an invasion depth of $\leq$200 μm from the lower margin of the muscularis mucosae have a low risk of N if the number of LY is 0; EMR alone can provide good treatment outcomes in such patients.

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Macroscopic estimation of submucosal invasion—stomach

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KEYWORDS:
Gastric cancer;
Invasion depth;
Macroscopic type;
Paris endoscopic classification

Accurate endoscopic determination of invasion depth for gastric cancer is essential in making the proper decisions for planning treatment strategy. The use of endoscopic resection such as endoscopic submucosal dissection has become more widespread in treating early gastric cancer, particularly in Asia. As a result, differential endoscopic diagnosis between mucosal and submucosal depth of invasion has become increasingly important in determining the indications for endoscopic resection. Endoscopy is the primary modality for diagnosing gastric cancer. Correlations between macroscopic type and invasion depth for early gastric cancer have been reported in the Paris endoscopic classification of superficial neoplastic lesions; thus, the proper use of macroscopic classification is helpful in determining invasion depth.

Accurate endoscopic determination of invasion depth for gastric cancer is essential in making the proper decisions for planning treatment. Endoscopic resection preserves the stomach, improves patient quality of life compared with surgery, and is accepted in many countries as a less invasive method for local resection of gastric cancers that have a negligible risk of lymph node metastasis.[1–4] Remarkable progress has been made during the past decade in the development and refinement of endoscopic resection methods from endoscopic mucosal resection to endoscopic submucosal dissection, as well as in an expansion of the indications for endoscopic resection.[5–16] Consequently, accurate differential endoscopic diagnosis between mucosa (M) and submucosa (SM) invasion depth of early gastric cancer has become more important in determining the indications for such procedures. Endoscopic ultrasonography (EUS) is a modality for determining invasion depth. In particular, EUS using a miniprobe (20 MHz) has demonstrated a high diagnostic accuracy for early gastric cancer between M and SM.[17–19] There was no significant difference, however, in the diagnostic accuracy between EUS using a miniprobe and endoscopy in a blind comparison study.[20] Consequently, endoscopy, which is the primary modality for diagnosing gastric cancer, can also be helpful in determining invasion depth, but such a determination is subjective in nature; hence, a need exists for objective criteria.

Classification of macroscopic types of gastric cancer was first introduced in Japan.[21] Many endoscopists, especially in Western countries, consider the Japanese classification system too complex for practical clinical use. With the recent increased incidence of early lesions in the gastrointestinal tract, especially neoplasia in Barrett's esophagus, however, there is a greater interest on the part of Western endoscopists for improving detection and standardizing classification of such neoplastic lesions. Uniform classification of macroscopic types was accomplished in the Paris Workshop. Correlations between macroscopic type and invasion depth for superficial esophageal squamous cell carcinoma, early gastric, and early colorectal adenocarcinomas have subsequently been reported, as well as a more recent evaluation of macroscopic types for early Barrett's neoplasia and early esophagogastric junction adenocarcinomas.[22–24] Macroscopic classification, therefore, is a relatively objective criteria and its proper use is helpful in the determination of invasion depth.

In this chapter, we describe the endoscopic estimation of invasion depth for gastric cancer by considering macroscopic type.

Macroscopic Classification (Figure 1)

The Paris endoscopic classification defined macroscopic types as polypoid (0-I) and nonpolypoid (0-II and 0-III) types. The polypoid (0-I) type is subdivided into protruded

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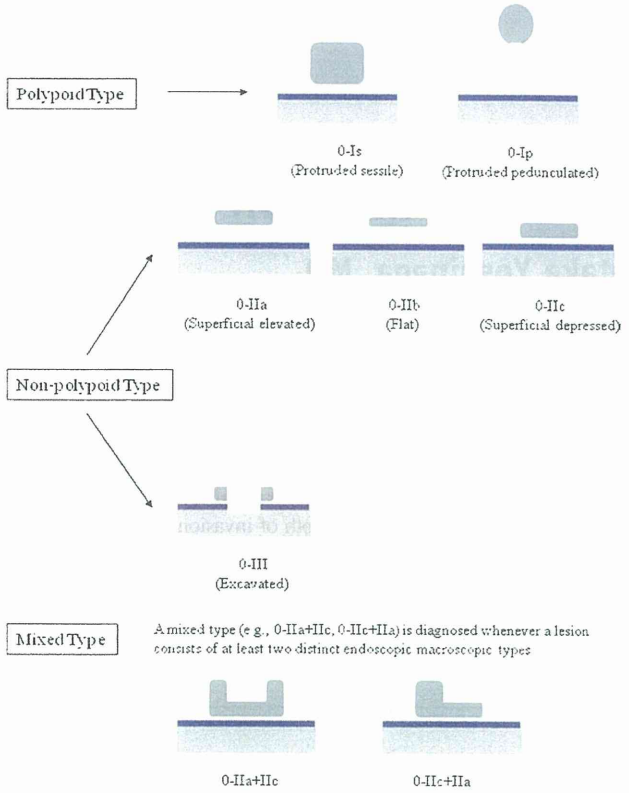

Figure 1 Classification of macroscopic types of early gastric cancer. (Color figure is available online at www.techgiendoscopy.com.)

sessile (0-Is) and protruded pedunculated (0-Ip) subtypes. The nonpolypoid type is subdivided into superficial elevated (0-IIa), flat (0-IIb), superficial depressed (0-IIc), and excavated (0-III) subtypes. A mixed type (eg, 0-IIa + IIc, 0-IIc + IIa) is diagnosed whenever a lesion consists of at least 2 distinct macroscopic types.[22]

Correlations between macroscopic type and invasion depth

Table 1 indicates the correlations between macroscopic type and invasion depth for early gastric cancer that had been reported in the Paris endoscopic classification of superficial neoplastic lesions.[22] The most common type of early gastric cancer is 0-IIc, followed by 0-IIa, 0-IIa + IIc, and 0-I types. Generally speaking, nonpolypoid type without mixed type (0-IIa, 0-IIb, or 0-IIc) lesions had a lower risk for SM invasion compared with polypoid type (0-I) and 0-IIa + IIc mixed type lesions. We describe the endoscopic estimation of invasion depth for gastric cancer according to each macroscopic type in the next section.

Table 1 Correlations between macroscopic type and invasion depth of early gastric cancer

	Invasion depth	
	Mucosal	Submucosal
Macroscopic type		
0-I (n = 66)	43% (28)	57% (38)
0-IIa (n = 356)	71% (254)	29% (102)
0-IIb (n = 10)	80% (8)	20% (2)
0-IIc (n = 1488)	63% (931)	37% (557)
0-IIc + IIa (n = 19)	53% (10)	47% (9)
0-IIa + IIc (n = 132)	35% (46)	65% (86)
0-IIc + III (n = 15)	60% (9)	40% (6)
Total (n = 2086)	62% (1286)	38% (800)

Cases

0-I type

- Tumor size correlates with the depth of invasion. Lesions ≤ 2 cm usually indicate M lesions (Figure 2).
- Lesions between 2 and 3 cm have approximately a 50% possibility of SM invasion. Sessile subtype lesions have an increased possibility of SM invasion (Figure 3) in contrast to pedunculated subtype lesions, which have a lower risk for SM invasion.
- Lesions > 3 cm have a greater possibility of SM (or deeper) invasion (Figure 4).

0-IIa type

- The depth of invasion is usually M because tumor size does not correlate with the depth of invasion (Figure 5).
- Lesions with a central depression or an uneven surface are associated with SM invasion (Figure 6).

0-IIc type

The following endoscopic findings suggest SM invasion:

- Thickening of the gastric wall at the depression (Figures 7 and 8);
- Rigidity of the gastric wall at the depression (Figure 7);
- Disappearance of the mucosal surface pattern at the depression (Figure 7);
- Extensive redness of the depression (Figure 8);
- Depression with submucosal tumor-like surrounding elevation (Figure 8);
- Large nodule in the depression (uneven surface; Figure 9); and
- Swelling of converging folds (Figure 10).
- Lesions without any of the above findings are probably M lesions (Figures 11 and 12). M lesions are generally smaller than SM lesions.

For lesions with an ulcer finding, it is difficult to estimate the invasion depth because of fibrosis resulting in rigidity. M lesions with an ulcer finding usually do not have thickening of the gastric wall, submucosal tumor-like surrounding elevation, or a large nodule in the depression (Figure 13). In contrast, SM lesions with an ulcer finding show thickening of the gastric wall (Figure 14).

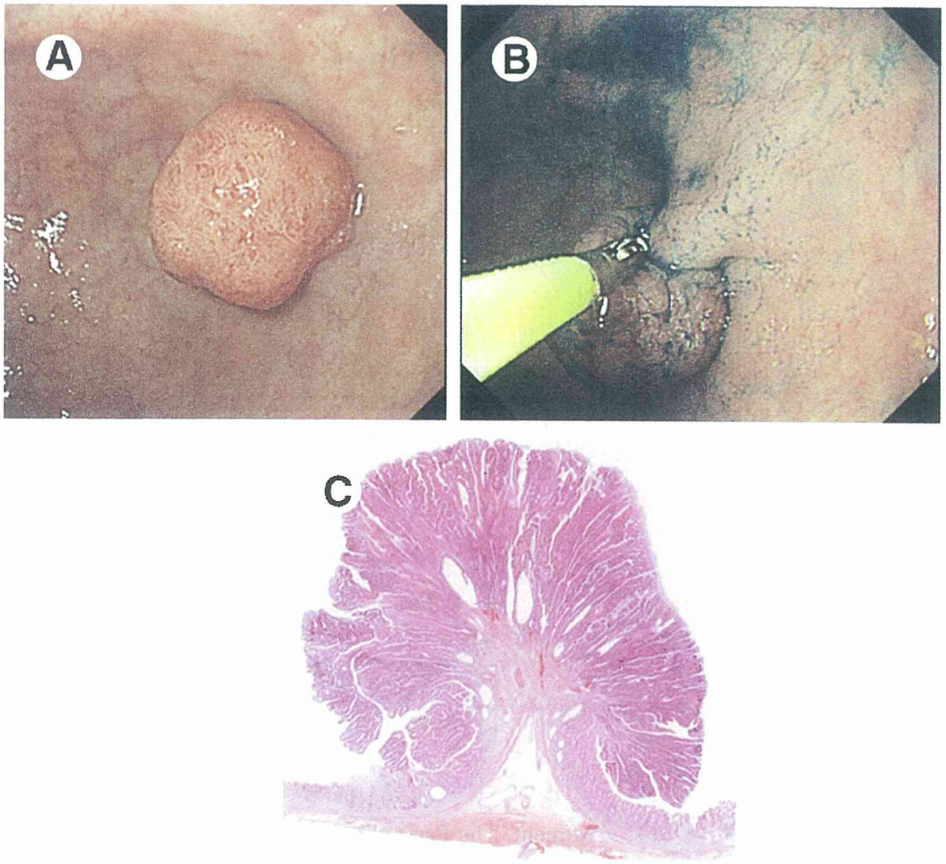

Figure 2 (A and B) Endoscopic images reveal a polypoid type (0-I) lesion, 1.5 cm in size, with subpedunculation on the lesser curvature of the gastric antrum. (C) Histology of the resected specimen indicates a well-differentiated adenocarcinoma confined to the mucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

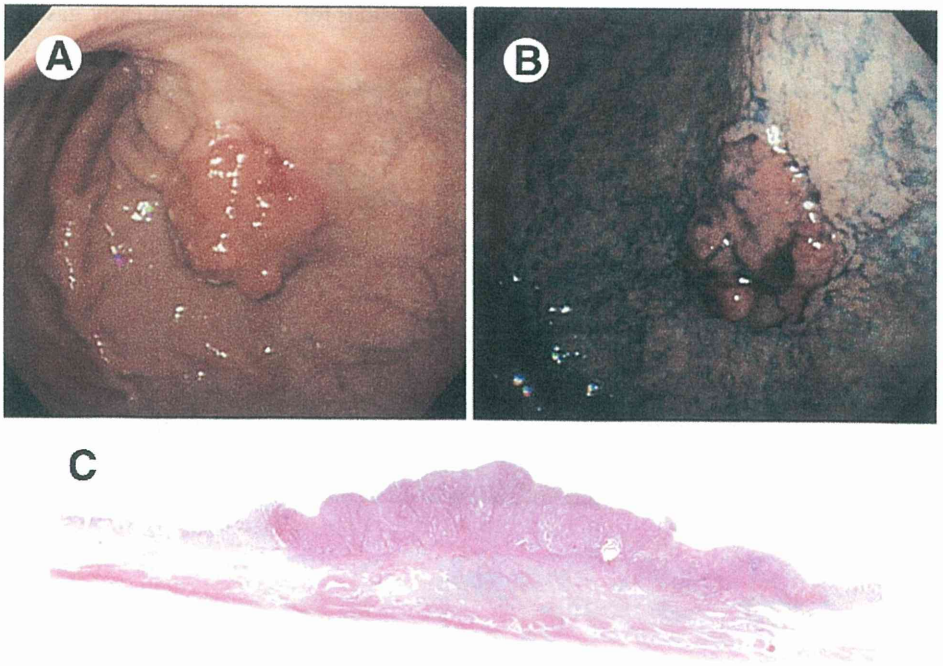

Figure 3 (A and B) Endoscopic images reveal a polypoid type (0-I) lesion, 2.5 cm in size, with a sessile finding on the posterior wall of the upper gastric body. (C) Histology of the resected specimen indicates a well- and poorly differentiated adenocarcinoma that had invaded the submucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

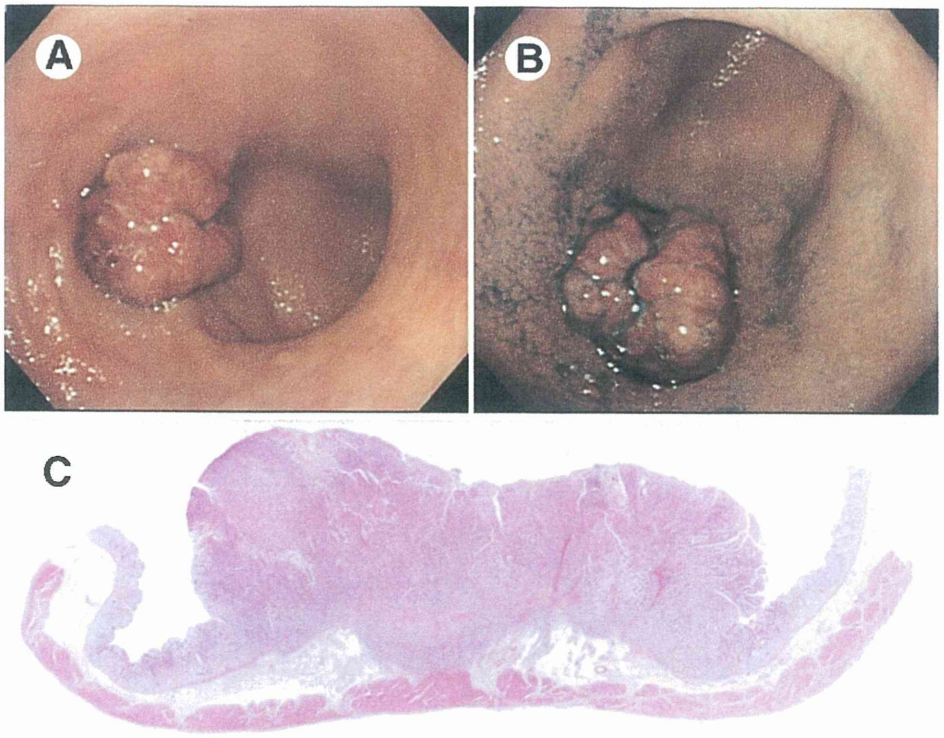

Figure 4 (A and B) Endoscopic images reveal a polypoid type (0-I) lesion, 3.5 cm in size, with a sessile finding on the greater curvature of the lower gastric body. (C) Histology of the resected specimen indicates a moderately to poorly differentiated adenocarcinoma that had invaded the submucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

0-IIa + IIc type

- Mixed types, in particular 0-IIa + IIc types, are generally associated with SM invasion (Figure 15).
- When the IIc components are less prominent, the lesions are usually M (Figure 16).

Conclusions

Accurate endoscopic estimation of invasion depth for gastric cancer is essential in making the proper decisions for treatment. The Paris classification provides a relatively objective method for the endoscopic diagnosis of early gastric cancer macroscopic types while simultaneously estimating invasion depth. Endoscopic prediction of invasion depth, however, is not always accurate, even with the proper use of macroscopic classification and EUS. Thus, further improvement in determining depth of invasion is necessary.[20,25] As a result, we are now creating a simple scoring system model to more accurately and objectively estimate the invasion depth of early gastric cancer.[26]

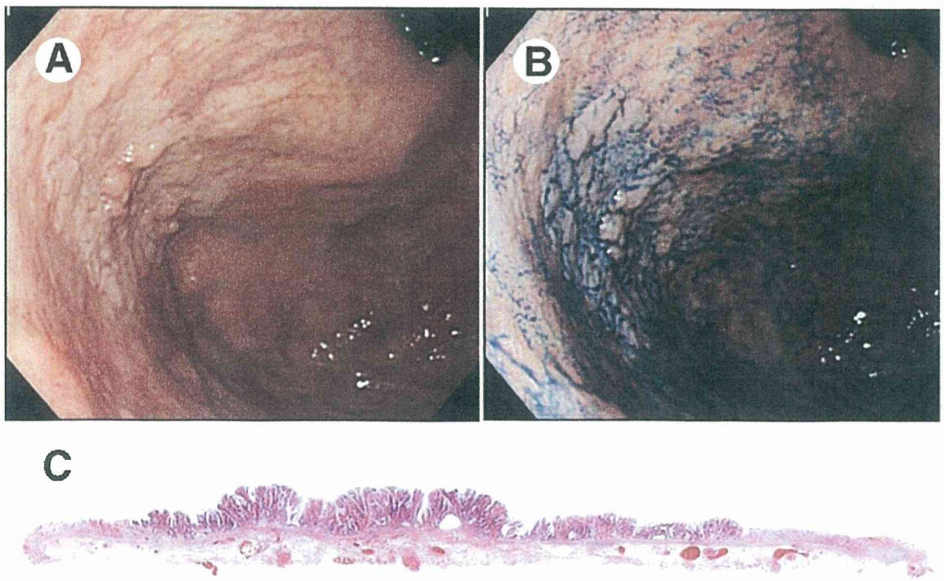

Figure 5 (A and B) Endoscopic images reveal a superficial elevated type (0-IIa) lesion, 4 cm in size, on the posterior wall of the upper gastric body. (C) Histology of the resected specimen indicates a well-differentiated adenocarcinoma confined to the mucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

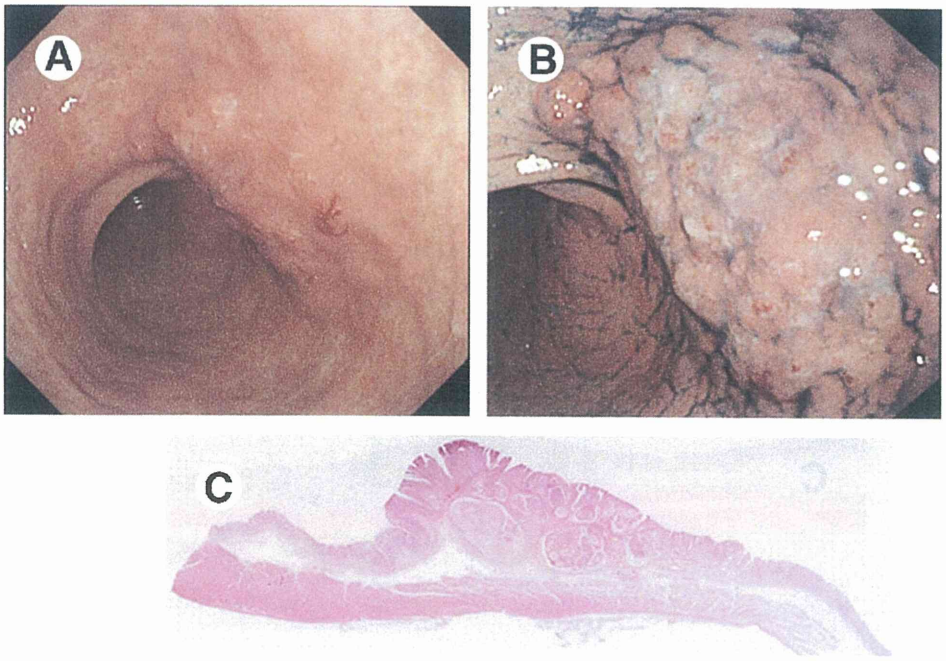

Figure 6 (A and B) Endoscopic images reveal a superficial elevated type (0-IIa) lesion with an uneven surface, 4 cm in size, on the posterior wall of the gastric antrum. (C) Histology of the resected specimen indicates a well- and moderately differentiated adenocarcinoma that had invaded the submucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

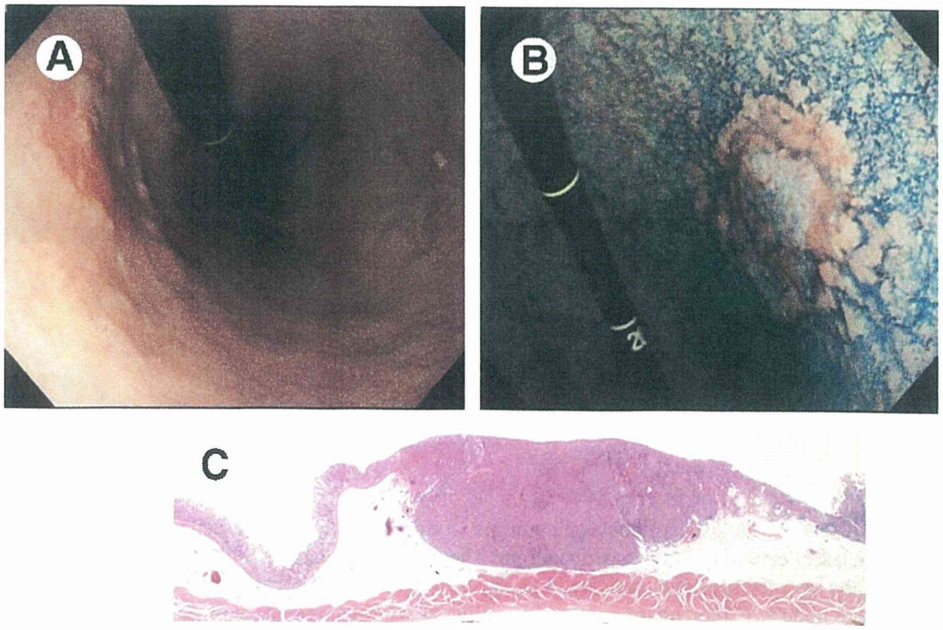

Figure 7 (A and B) Endoscopic images reveal a superficial depressed type (0-IIc) lesion with a thickening of the gastric wall, 3 cm in size, on the posterior wall of the lower gastric body. Chromoendoscopy using indigo carmine dye indicates the disappearance of the mucosal surface pattern at the depression. (C) Histology of the resected specimen indicates a poorly differentiated adenocarcinoma that had invaded the submucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

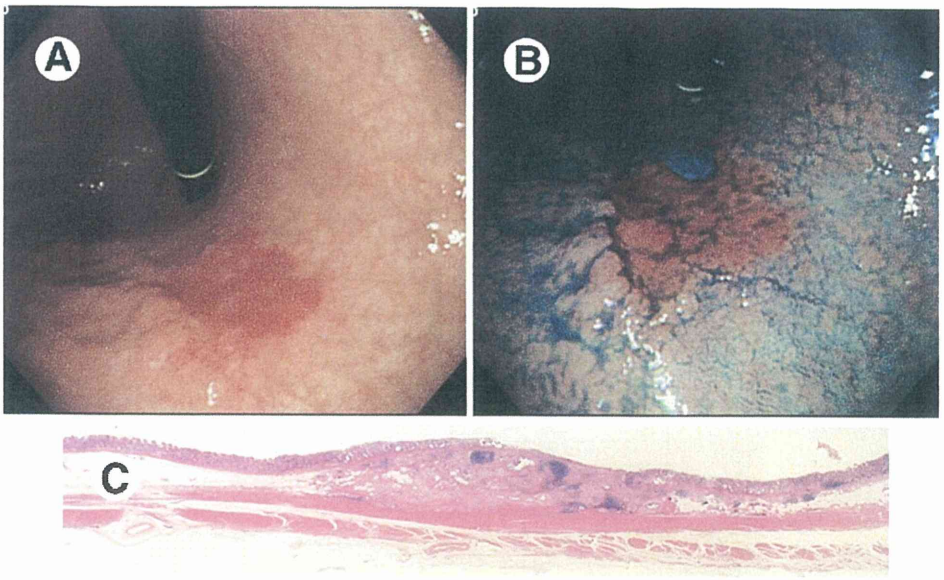

Figure 8 (A and B) Endoscopic images reveal an extensively reddish superficial depressed type (0-IIc) lesion, 3 cm in size, on the anterior wall of the middle gastric body. The tumor has a thickening of the gastric wall and submucosal tumor-like surrounding elevation on the anterior wall side. (C) Histology of the resected specimen indicates a well-differentiated adenocarcinoma that had invaded the superficial level of the muscularis propria on the anterior wall side. (Color figure is available online at www.techgiendoscopy.com.)

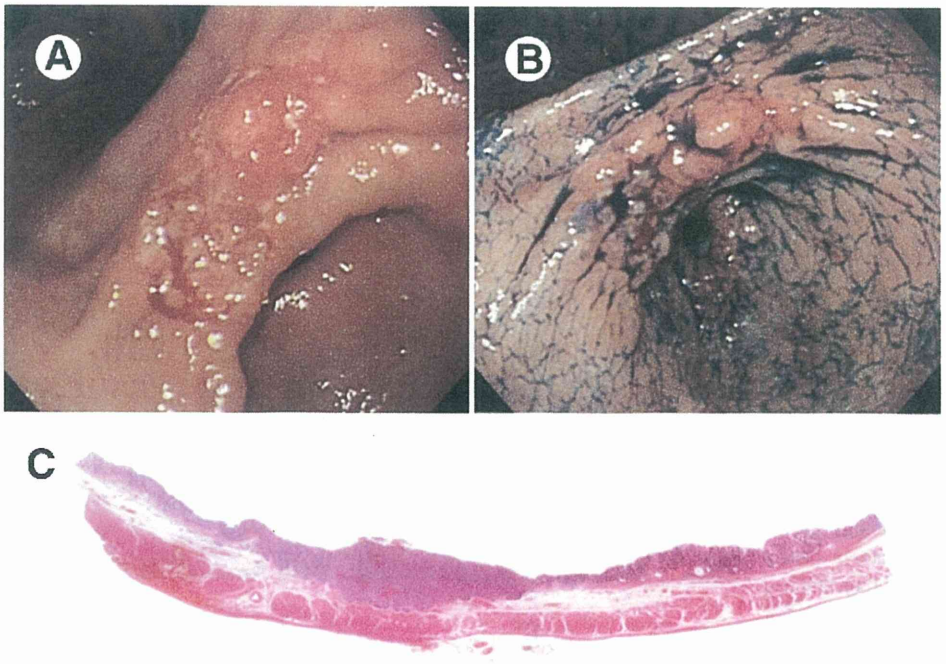

Figure 9 (A and B) Endoscopic images reveal a superficial depressed with elevation type (0-IIc + IIa) lesion, 4 cm in size, on the lesser curvature of the gastric antrum. The tumor has a large nodule in the depression on the posterior wall side. (C) Histology of the resected specimen indicates a poorly differentiated adenocarcinoma that had invaded the submucosal layer at the area of the large nodule. (Color figure is available online at www.techgiendoscopy.com.)

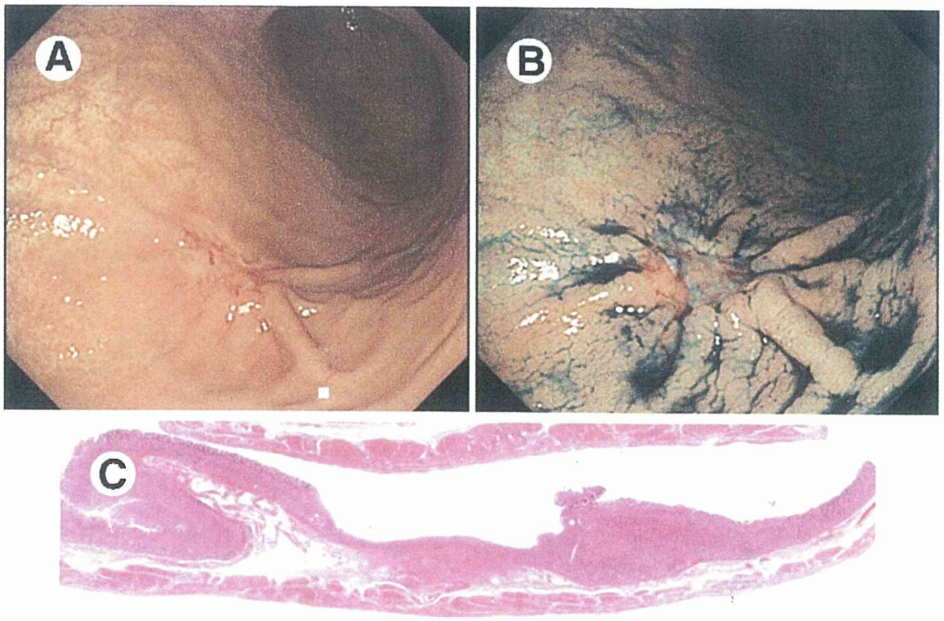

Figure 10 (A and B) Endoscopic images reveal a superficial depressed (0-IIc) type lesion with swelling of the converging folds, 2 cm in size, on the greater curvature of the middle gastric body. (C) Histology of the resected specimen indicates a poorly differentiated adenocarcinoma and signet ring cell carcinoma that had invaded the submucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

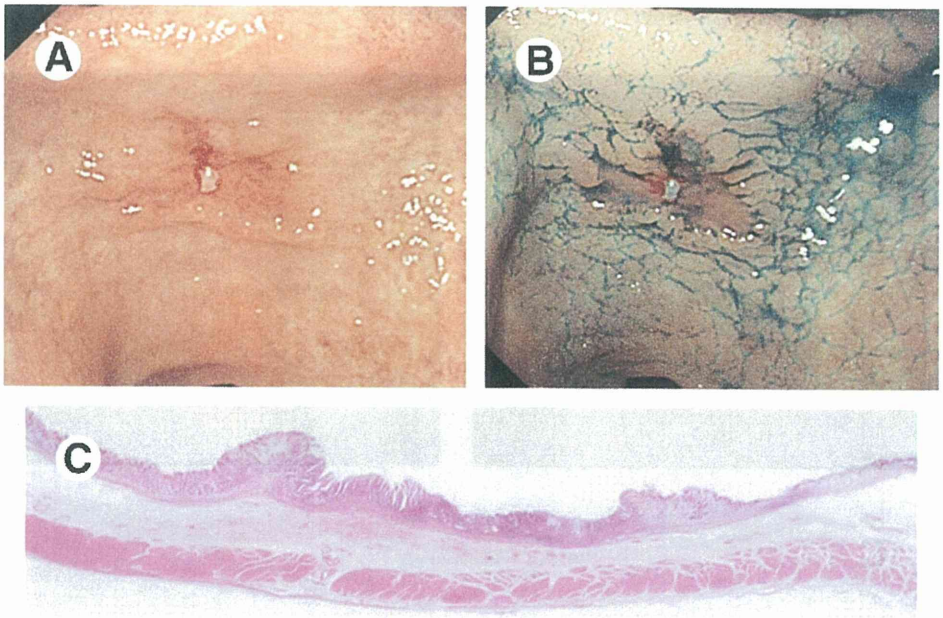

Figure 11 (A and B) Endoscopic images reveal a superficial depressed (0-IIc) type lesion without any endoscopic findings that suggest submucosal invasion, 1.5 cm in size, on the lesser curvature of the gastric antrum. (C) Histology of the resected specimen indicates a well-differentiated adenocarcinoma confined to the mucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

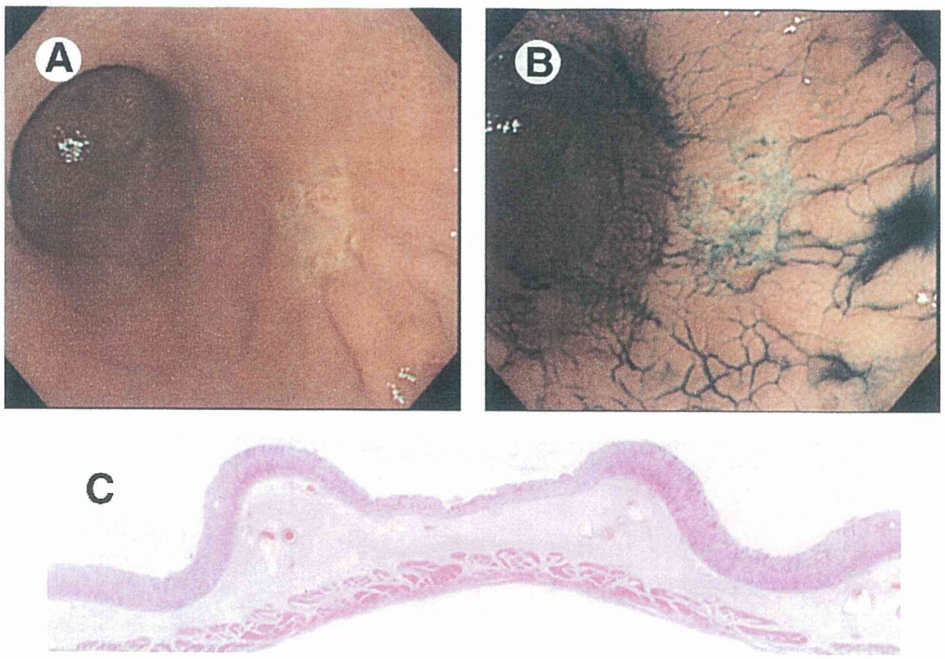

Figure 12 (A and B) Endoscopic images reveal a superficial depressed (0-IIc) type lesion without any endoscopic findings that suggest submucosal invasion, 1.5 cm in size, on the posterior wall of the lower gastric body. (C) Histology of the resected specimen indicates a signet ring cell and poorly differentiated adenocarcinoma confined to the mucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

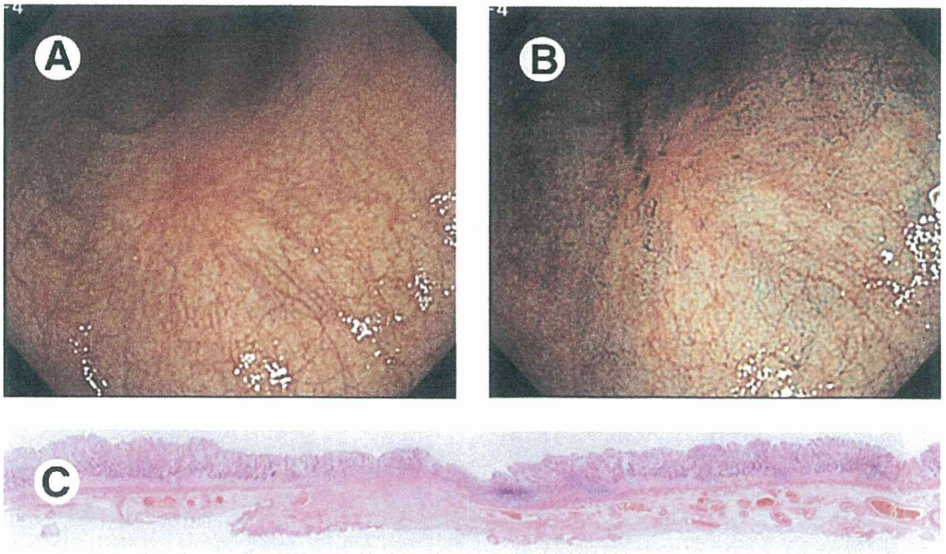

Figure 13 (A and B) Endoscopic images reveal a superficial depressed (0-IIc) type lesion with ulcer scar, 1 cm in size, on the lesser curvature of the middle gastric body. (C) Histology of the resected specimen indicates a well-differentiated adenocarcinoma confined to the mucosal layer with ulcer fibrosis in the submucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

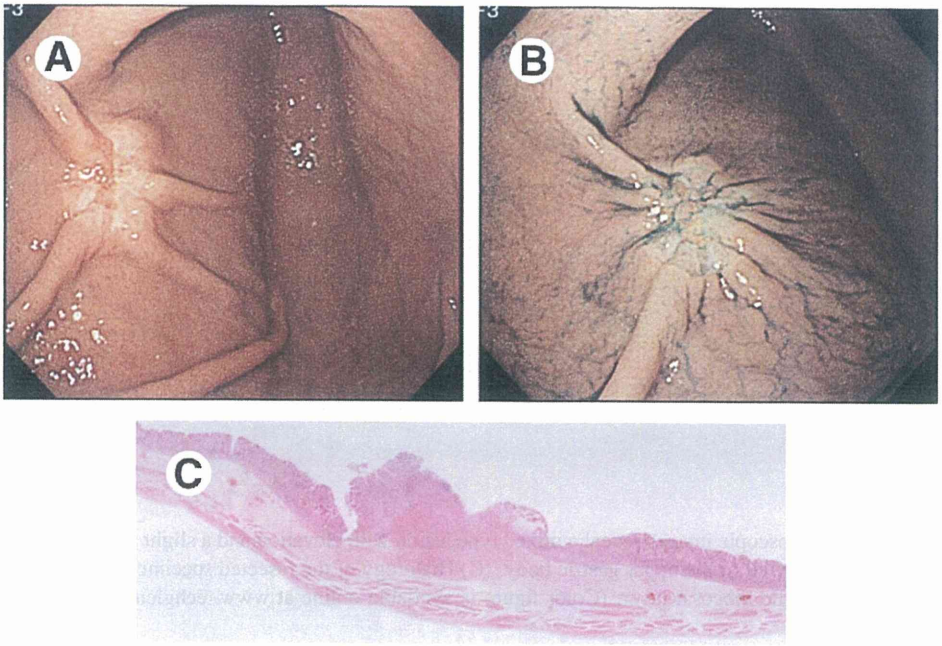

Figure 14 (A and B) Endoscopic images reveal a superficial depressed (0-IIc) type lesion with ulcer scar, 1.5 cm in size, on the greater curvature of the lower gastric body. The tumor has a thickening of the gastric wall. (C) Histology of the resected specimen indicates a signet ring cell and poorly differentiated adenocarcinoma that had invaded the submucosal layer as well as ulcer fibrosis in the submucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

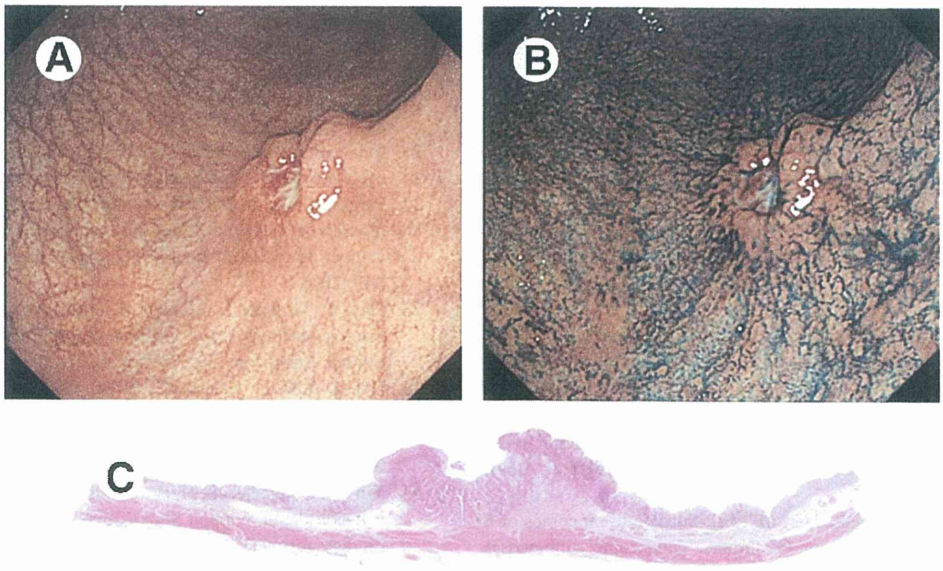

Figure 15 (A and B) Endoscopic images reveal a mixed type lesion with surrounding elevation and a central depression (0-IIa + IIc), 2 cm in size, on the greater curvature of the lower gastric body. (C) Histology of the resected specimen indicates a well- and poorly differentiated adenocarcinoma that had invaded the superficial level of the muscularis propria. (Color figure is available online at www.techgiendoscopy.com.)

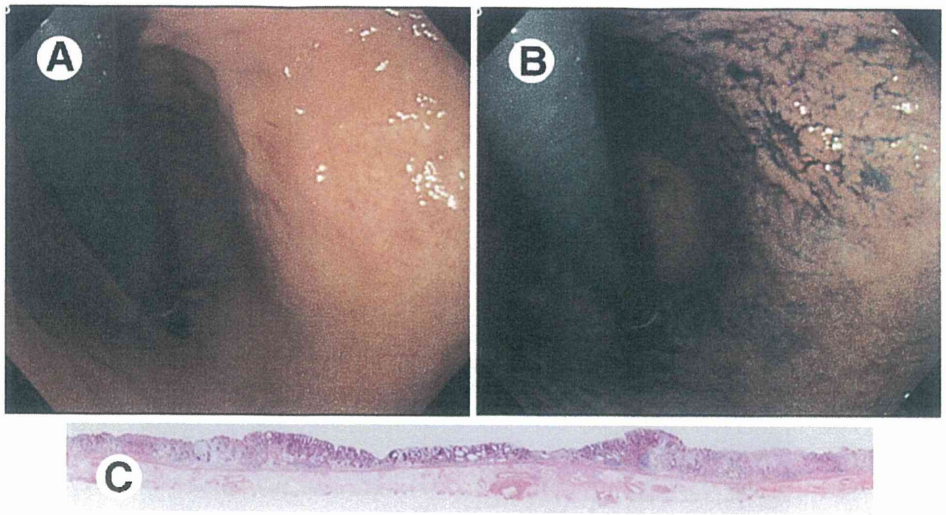

Figure 16 (A and B) Endoscopic images reveal a mixed type lesion with elevation and a slight central depression (0-IIa + IIc), 1 cm in size, on the posterior wall of the upper gastric body. (C) Histology of the resected specimen indicates a well-differentiated adenocarcinoma confined to the mucosal layer. (Color figure is available online at www.techgiendoscopy.com.)

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SPECIAL ARTICLE

Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry

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Abstract The Japanese Gastric Cancer Association (JGCA) started a new nationwide gastric cancer registry in 2008. Approximately 50 data items, including surgical procedures, pathological diagnoses, and survival outcomes, for 12004 patients with primary gastric cancer treated in 2001 were collected retrospectively from 187 participating hospitals. Data were entered into the JGCA database according to the JGCA *Classification of gastric carcinoma, 13th edition* and the International Union Against Cancer (UICC) *TNM Classification of malignant tumors, 5th edition* by using an electronic data collecting system. Finally, data of 11261 patients with gastric resection were analyzed. The 5-year follow-up rate was 83.5%. The direct death rate was 0.6%. TNM 5-year survival rates (5YSRs)/JGCA 5YSRs were 91.8/91.9% for stage IA, 84.6/85.1% for stage IB, 70.5/73.1% for stage II, 46.6/51.0% for stage IIIA, 29.9/33.4% for stage IIIB, and 16.6/15.8% for stage IV. The proportion of patients more than 80 years old was 7.0%, and their 5YSR was 48.7%. Compared to the JGCA archived data, though the follow-up rate needs to be improved, these data suggest that the postoperative results of patients with primary gastric carcinoma have improved in those with advanced disease and in the aged population in Japan.

All the authors belong to the Registration Committee of the Japanese Gastric Cancer Association.

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Keywords Gastric cancer · Registry · Survival rate · Japan

Introduction

From 1998, the Japanese Gastric Cancer Association (JGCA) began conducting a nationwide gastric cancer registration project by using electronic data collecting systems. Detailed survival analyses of 8851 patients with primary gastric cancer treated in 1991 were reported in 2006 [1]. However, this nationwide registry was suspended because of several issues such as the operation of the Act Concerning Protection of Personal Information, revision of the JGCA classification for gastric cancer, and rapid changes in the information technology (IT) environment at the member hospitals. After a period of 10 years in which the program was inactive, the registration committee of the JGCA started a new registration program to collect anonymized data simply, correctly, and quickly, in 2008 [2, 3]. Based on this program, we investigated the survival outcomes of patients with primary gastric cancer treated in 2001.

Subjects, materials, and methods

In the 2008 JGCA nationwide registration program, approximately 50 data items, including surgical procedures, pathological diagnoses, and prognoses, for patients with primary gastric carcinoma surgically treated in 2001 were collected retrospectively in 2008 by using custom-made software. This software could be downloaded from the JGCA website. The JGCA member hospitals could participate in this project voluntarily.

The registration data of this system are listed in Table 1. Definition and documentation of the items were based on the Japanese (JGCA) *Classification of gastric carcinoma, 13th edition* [4, 5] and the International Union Against Cancer (UICC) *TNM Classification of malignant tumors, 5th edition* [6]. These two classifications were not compatible with each other and items could not be converted automatically. The JGCA T-category was identical to the TNM classification. On the other hand, in the JGCA classification, peritoneal metastasis and liver metastasis were individually recorded as P- and H-categories, both of which could be translated into the M-category in the TNM classification. Intraoperative peritoneal washing cytology (CY) was an independent category in the JGCA classification. The JGCA N-category was defined by the anatomical extension of lymph node metastasis in association with the location of the primary tumor, while the TNM N-category was defined by number of metastatic regional lymph nodes. Items that are compatible in the JGCA classification and the TNM classification, and items that are not compatible are listed in Table 2 for convenience.

After the patients' data were entered with the data entry software, the patients' names and other personal information were removed from the exporting data set for privacy protection. A compact disk containing the linkable anonymous data was then mailed to the JGCA data center, located at Niigata University Medical and Dental Hospital. The accumulated data of the patients were reviewed and analyzed by the JGCA registration committee. One- to 5-year survival rates (5YSRs) were calculated for various subsets of prognostic factors by the Kaplan–Meier method. Deaths of any cause observed during 5 postoperative years were counted as events in the survival analysis. SPSS Ver. 15 software (SPSS, Chicago, IL, USA) was used for

Table 1 Registration data

Category	Item
Personal information	Name of hospital, serial no., case no., ID no.[a], age, sex
Follow-up	Date of follow-up, survival situation, causes of death
Surgery	Date of operation, approach, operative procedure, LN dissection (D), organs resected together with stomach, type of reconstruction
Pathology	Anatomical subsite, macroscopic type, size of tumor, histological type, depth of tumor invasion, ly, v, number of dissected LNs, number of metastatic LNs, N, PM/DM, CY
JGCA final diagnosis	Depth of tumor invasion, adjacent structure involved, fN, H, P, M, curability, stage
UICC TNM categories	T, N, M, stage

LN lymph node, *ly* lymphatic invasion, *v* venous invasion, *N* extent of LN metastasis (JGCA), *PM/DM* involvement of proximal and distal margin, *CY* peritoneal cytology, *fN* extent of LN metastasis (final diagnosis), *H* liver metastasis, *P* peritoneal metastasis, *M* distant metastasis, *JGCA* Japanese Gastric Cancer Association, *UICC* International Union Against Cancer

[a] ID no. was not exported to the registration data set

Table 2 Compatibility to convert JGCA classification to TNM classification

Category	JGCA 13th ed.	TNM 5th ed.	Compatibility
T	1–4	0–4	Compatible
N	0	0	Identical
	1–3	1–3	Incompatible
M[a]	0	0	Compatible
	1	1	Compatible
H	0	None	
	1	M1	Compatible
P	0	None	
	1	M1	Compatible
CY	0	None	
	1	None	
Stage	IA	IA	Identical
	IB, II, IIIA, IIIB, IV	IB, II, IIIA, IIIB, IV	Incompatible
Lymphatic invasion	ly0	L0	Identical
	ly1–3	L1	Compatible
Venous invasion	v0	v0	Identical
	v1–3	v1	Compatible
	None	v2	
Histological typing	Differentiated type	G1–2	Compatible
	Undifferentiated type	G3–4	Compatible
Residual tumor	Resection A–C	R0–2	Incompatible

[a] JGCA M-category is defined as distant metastases other than peritoneal, liver, or cytological metastases

statistical analyses. This nationwide registration program was approved by the ethics committee of the JGCA.

Results

The data were collected from 187 participating hospitals across the country. The geographical distribution of the registered patients among Japan's 47 prefectures is illustrated in Fig. 1. More than 1000 patients per year were registered in the prefectures of Tokyo and Osaka; on the other hand, the number of registered patients was less than 100 in 15 prefectures. The hospital volumes in the participating hospitals are indicated in Fig. 2. The median hospital volume was 66 patients per year.

Data of 13067 patients who had undergone surgery in 2001 for primary gastric tumors were eventually accumulated. Of these, 88 patients with benign tumor or non-epithelial tumor were excluded from the analysis. Ninety-four patients who received endoscopic mucosal resection were also excluded. Data of 881 patients lacked essential items. Consequently, data of the remaining 12004 patients were used for the final analysis.

The results are shown in Tables 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, and 28; data in these Tables are for the total number of patients, survival rates by year, standard error of 5YSR, direct death within 30 postoperative days, numbers lost to follow-up within 5 years, 5-year survivors, and main causes of death (such as local and/or lymph node metastasis, peritoneal metastasis, liver metastasis, distant metastasis, recurrence at unknown site, other cancer and other

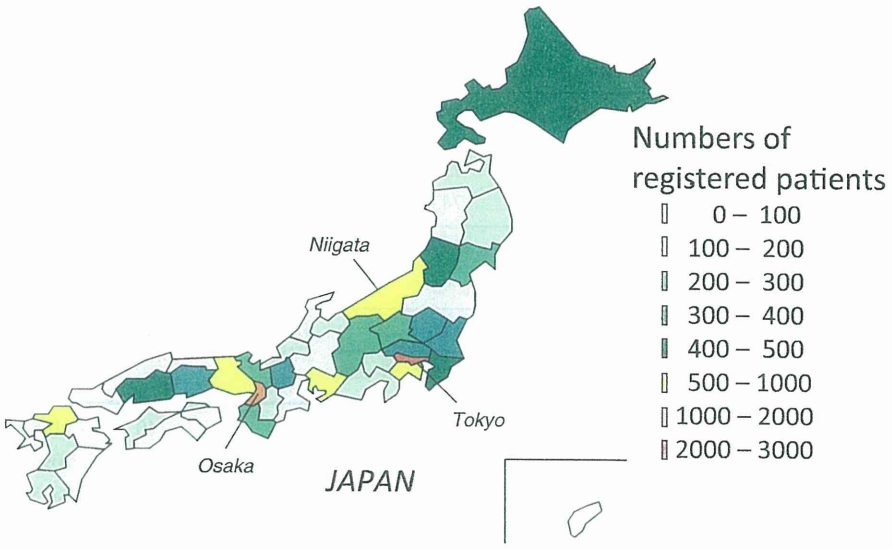

Fig. 1 Geographical distribution of the registered patients

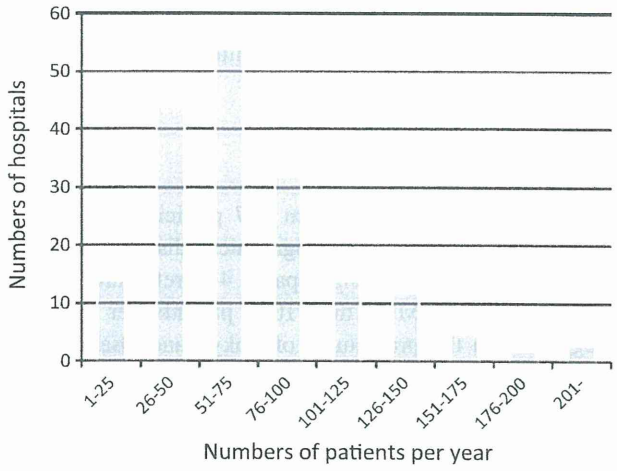

Fig. 2 Hospital volumes in the 187 participating hospitals

disease). Figures 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 show cumulative survival curves of patients stratified by essential categories.

The 5YSR in the 12004 patients with primary gastric cancer was 69.1% (Table 3; Fig. 3). Within 5 postoperative years, 1976 patients were lost to follow-up; the follow-up rate was 83.5%. Of the 12004 patients, 11261 underwent gastric resection; 350 were unresected; and in 393 the type of surgery was not specified. Accordingly, the resection rate was 97.0% (11261/11611). Sixty-three of the 11261 patients who had undergone gastrectomy died within 30 postoperative days; the direct death rate was 0.6% (Table 4; Fig. 4).

The most frequent cause of death in patients who had received gastrectomy was peritoneal metastasis (n = 1040), followed, in descending order, by other diseases (n = 501), liver metastasis (n = 357), recurrence at an

Table 3 Survival outcomes of primary cancer

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Primary cancer	12004	86.4	78.7	74.1	71.1	69.1	0.4	95	1976	6588	309	1266	374	183	349	162	530	267

SE standard error, *5YSR* 5-year survival rate, *DD* direct death, *Lost to follow up* lost to follow-up within 5 years, *Alive* 5-year survivors, *L* local recurrence and/or lymph node metastasis, *P* peritoneal metastasis, *H* liver metastasis, *M* distant metastasis, *R* recurrence at unknown site, *OC* other cancer, *OD* other disease, *UK* unknown

Table 4 Survival outcomes of resected cases and unresected cases

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Resected cases	11261	88.6	80.9	76.2	73.0	70.9	0.4	63	1877	6354	267	1040	357	161	298	155	501	251
Unresected cases	350	23.0	9.8	7.1	5.6	5.3	1.3	20	40	14	32	176	12	13	43	0	10	10

Table 5 Survival outcomes by sex

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Male	7828	88.4	80.7	75.6	72.3	70.0	0.5	47	1314	4348	190	646	299	112	205	138	403	173
Female	3419	88.9	81.1	77.5	74.6	73.0	0.8	16	562	1997	76	392	58	49	93	17	97	78

Table 6 Survival outcomes by age

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
<40	257	89.9	82.0	80.3	79.4	78.4	2.7	0	40	165	3	30	2	8	4	1	0	4
40–59	3232	92.5	86.6	83.1	80.6	79.3	0.7	12	516	2095	60	274	58	48	66	13	54	48
60–79	6924	87.9	80.1	74.9	71.6	69.2	0.6	37	1129	3818	186	651	259	91	182	135	322	151
≧80	788	78.5	64.3	58.6	53.1	48.7	2.0	14	178	256	18	84	35	13	29	6	123	46

Table 7 Survival outcomes by tumor location

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
U	2399	86.0	76.7	71.3	67.5	65.3	1.0	13	370	1258	69	237	107	49	75	32	134	68
M	4351	92.2	87.1	83.3	80.8	78.9	0.6	23	760	2741	65	260	90	43	84	65	161	82
L	3936	89.4	81.4	77.1	74.2	71.9	0.7	21	685	2230	108	309	141	52	99	55	176	81
Whole	532	63.7	44.7	33.7	25.8	23.4	2.0	6	56	104	23	230	17	17	34	3	28	20

U upper third, *M* middle third, *L* lower third of stomach

Table 8 Survival outcomes by macroscopic type

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Type 0	6085	97.5	95.7	93.7	91.8	90.3	0.4	12	1143	4401	20	45	23	23	32	100	217	81
Type 1	318	79.1	66.7	61.7	56.5	54.6	2.9	4	49	136	12	18	28	7	14	7	36	11
Type 2	1419	84.8	73.0	66.5	62.5	59.7	1.4	11	220	669	58	127	126	29	59	10	81	40
Type 3	2151	76.5	60.8	52.4	47.8	45.1	1.1	21	306	760	119	425	152	62	124	25	112	66
Type 4	779	62.1	41.9	30.0	23.4	20.4	1.5	10	65	133	37	363	11	31	54	7	35	43
Type 5	340	86.8	74.3	67.4	62.6	59.5	2.8	4	48	166	13	49	16	7	15	4	15	7

Table 9 Survival outcomes by histological diagnosis

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
pap	364	85.8	75.1	70.4	67.5	65.1	2.6	3	64	185	11	27	23	6	13	8	23	4
tub1	2752	95.2	91.1	87.9	85.3	83.5	0.7	5	519	1818	30	55	42	16	36	51	137	48
tub2	2997	89.2	81.4	76.3	73.1	70.6	0.9	20	537	1651	64	207	156	46	74	45	160	57
por1	1476	82.5	72.4	67.8	64.9	63.7	1.3	14	238	737	53	174	82	30	40	14	69	39
por2	1903	81.4	69.7	63.4	59.5	56.6	1.2	15	244	886	75	401	34	44	86	19	59	55
sig	1325	93.2	88.0	84.5	81.2	79.4	1.2	4	217	855	17	108	2	14	32	12	30	38
muc	231	81.5	68.8	60.4	53.7	51.2	3.4	1	24	100	9	54	5	1	10	3	19	6
Adenosquamous carcinoma	6	50.0	33.3	33.3	16.7	16.7	15.2	0	0	1	0	2	2	0	0	1	0	0
Squamous cell carcinoma	5	60.0	30.0	0.0	0.0	0.0	0.0	0	1	0	2	1	0	1	0	0	0	0
Miscellaneous carcinoma	45	65.2	53.1	48.1	45.6	45.6	7.7	0	4	18	2	8	7	2	2	0	1	1

Pap papillary adenocarcinoma, *tub1* tubular adenocarcinoma, well-differentiated type, *tub2* tubular adenocarcinoma, moderately differentiated type, *por1* poorly differentiated adenocarcinoma, solid type, *por2* poorly differentiated adenocarcinoma, non-solid type, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma

Table 10 Survival outcomes by histological differentiation

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Differentiated type	6113	91.7	85.4	81.2	78.3	76.1	0.6	28	1120	3654	105	289	221	68	123	104	320	109
Undifferentiated type	4935	84.9	75.4	70.1	66.6	64.6	0.7	34	723	2578	154	737	123	89	168	48	177	138
Other type	144	81.6	75.3	71.9	68.4	68.4	4.1	1	29	74	6	12	11	4	2	1	3	2

Table 11 Survival outcomes by venous invasion (v)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
v0	6453	95.4	91.5	88.6	86.2	84.5	0.5	23	1228	4304	54	258	59	36	70	101	260	83
v1	2601	84.5	72.7	66.6	62.2	59.7	1.0	17	352	1276	103	365	115	53	112	29	127	69
v2	1347	75.7	59.8	50.4	45.8	42.6	1.4	17	168	463	71	271	95	44	74	16	84	61
v3	539	59.4	44.5	35.7	32.2	30.8	2.1	5	69	128	30	123	85	23	34	4	21	22

Table 12 Survival outcomes by lymphatic invasion (ly)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
ly0	4783	97.2	95.3	93.3	91.4	89.9	0.5	11	956	3389	10	48	23	11	35	80	177	54
ly1	2604	92.4	86.1	81.1	77.7	75.1	0.9	13	398	1606	51	187	84	36	37	40	115	50
ly2	2047	80.7	65.8	58.4	53.3	50.5	1.2	22	271	834	102	346	134	53	103	17	123	64
ly3	1481	65.2	45.4	36.3	31.6	29.4	1.3	16	194	334	95	438	110	57	110	13	77	53

Table 13 Survival outcomes by depth of invasion

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
pT1(M)	3071	98.1	96.9	95.0	93.5	92.2	0.5	5	606	2248	7	4	4	1	7	53	98	43
pT1(SM)	2662	97.5	95.0	93.1	90.9	89.1	0.6	6	500	1898	11	16	19	11	16	51	109	31
pT2(MP)	1071	93.4	88.7	84.0	80.9	78.3	1.3	3	183	675	13	23	31	19	22	17	68	20
pT2(SS)	1695	87.0	74.7	67.6	63.2	60.6	1.2	17	262	817	67	148	122	48	65	20	99	47
pT3(SE)	2278	69.7	50.9	41.3	35.8	33.0	1.0	26	264	601	132	712	140	72	148	10	102	97
pT4(SI)	417	57.7	38.1	30.0	26.0	22.8	2.2	5	45	77	36	134	39	8	40	4	24	10

p pathological finding, *M* mucosa or muscularis musoca, *SM* submucosa, *MP* muscularis propria, *SS* subserosal, *SE* serosa, *SI* adjacent structures

Table 14 Survival outcomes by pT classification

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
pT1	5733	97.8	96.0	94.1	92.3	90.8	0.4	11	1106	4146	18	20	23	12	23	104	207	74
pT2	2766	89.5	80.1	74.0	70.1	67.5	0.9	20	445	1492	80	171	153	67	87	37	167	67
pT3	2278	69.7	50.9	41.3	35.8	33.0	1.0	26	264	601	132	712	140	72	148	10	102	97
pT4	417	57.7	38.1	30.0	26.0	22.8	2.2	5	45	77	36	134	39	8	40	4	24	10

Table 15 Survival outcomes by lymph node metastasis (pN)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
pN0	6508	97.0	94.7	92.5	90.6	89.0	0.4	22	1240	4616	18	95	38	16	44	109	248	84
pN1	2274	84.7	72.3	66.2	61.3	58.3	1.1	12	322	1074	78	309	139	46	99	23	118	66
pN2	1703	72.1	52.8	41.4	35.8	33.4	1.2	19	224	439	103	442	135	69	109	13	100	69
pN3	421	53.8	33.1	25.8	22.0	17.4	1.9	4	33	61	60	136	37	28	35	3	13	15