

Clinicopathologic Characteristics of Early Gastric Cancer in Korea

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Abstract

Gastric cancer is the most common cause of cancer related death in Korea. Early gastric cancer (EGC), confined to mucosa or submucosa, regardless of lymph node metastasis, is known to have a favorable prognosis. From 1976 to 1995, four thousand nine hundred and twenty eight gastric cancer patients underwent operation at the Severance Hospital, Yonsei University, College of Medicine, Seoul, Korea. Of these, 1,117 patients (22.6%) were diagnosed as EGC and underwent curative operation. Clinicopathologic characteristics were reviewed and survival data was analyzed. The proportion of EGC has increased during the last two decades, from 14.9% during 1976–1985 to 25.8% for 1986–1995. EGC has a wide age distribution range from the thirties to the sixties, with highest incidence in the sixties. The male to female ratio is 1.8 : 1, without any significant change in last two decades. Most lesions are located in the lower third of stomach (52.3%), and the lesser curvature (52.2%) was the most frequent site in the transverse axis. Macroscopically, the depressed type was the most common (66.1%) followed by the elevated, flat and mixed types, in that order. Tumor confined to the mucosa layer was seen in 52.5%, and lymph node involvement in 11.7%. The depth of tumor invasion correlated with tumor size and regional lymph node involvement. On histopathologic examination, signet ring cell type accounted for 29.6% of all EGCs. Overall 5-year survival rate was 92.7% and the presence of lymph node metastasis significantly affected survival (84.6% versus 96.2%) ($p < 0.05$). In conclusion, the proportion of EGC, in terms of the gastric cancers operated upon, has been increasing in Korea over the last two decades. The introduction of active diagnostic approaches and diagnostic modalities could improve early diagnosis and the cure rate of gastric cancer in Korea.

Key Words: Early gastric cancer, clinicopathologic characteristics, survival

INTRODUCTION

Although, the incidence of gastric cancer is declining,^{1,2} gastric cancer remains one of the most common causes of cancer-related death, with a reported overall 5-year survival rate that is rarely in excess of 15% in most Western countries, and this despite continuous efforts to improve diagnostic and therapeutic modalities.^{3,4} In contrast, the prognosis of patients with early gastric cancer (EGC), defined as carcinoma confined to the mucosa or submucosa, with or without lymph node metastasis, is generally excellent with reported 5-year survival rates of 90–

95%.⁵ Numerous studies in Japan as well as in Western countries have reported an increase in the incidence of EGC over the years. The increase is ascribed to improved diagnostic procedures, particularly the introduction of the video endoscope combined with targeted biopsy.^{6,7}

The Japanese Society of Gastroenterological Endoscopy first defined EGC in 1962.⁵ The need for such a definition was based on the observation that gastric cancer of this type has a favorable prognosis. Over a 90 percent 5-year survival rate has repeatedly been reported in Japan and the Western countries. Consequently, mass screening of the asymptomatic population for EGC has been proposed in Japan, Chile⁸ and Venezuela.⁹

Most of the clinicopathologic reviews of EGC contain many conflicting results in terms of prognostic factors and observed survival rates. These discrepancies may be partly explained by several confounding variables, such as, multiple patients' pool from different hospitals, different surgical techniques and the different histologic definitions employed. By reviewing the retrospective data in a single institution

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over a longer period of time we present chronological changes and more consistent results. This study was undertaken in order to evaluate the chronological changes of the clinicopathologic characteristics and prognostic factors of EGC in Korea.

MATERIALS AND METHODS

From 1976 to 1995, 4,928 patients with gastric cancer were operated upon at Severance Hospital, Yonsei University, College of Medicine, Seoul, Korea. Of these, 1,117 (22.6%) patients were diagnosed as EGC and underwent curative surgical operations.

Clinicopathologic variables such as age, sex, location and size of the primary tumors, macroscopic characteristics, depth of tumor invasion, and presence of lymph node metastasis were analyzed. Macroscopic classification was made according to the criteria of the Japanese Society for Gastroenterological Endoscopy & the Japanese Research Society for Gastric Cancer.¹⁰ Histopathological examination of the primary lesions was performed using step sections in order to determine the depth of cancer invasion. Histological examination of the resected lymph nodes was also performed. The histological type and epithelium of origin were classified according to the Japanese Research Society Committee (1981), and are divided into papillary, tubular/well differentiated, and tubular/moderately differentiated adenocarcinoma (together these are considered as differentiated types and correspond to the intestinal type according to Lauren's classification¹¹), poorly differentiated and signet ring cell adenocarcinoma (corresponding to the undifferentiated or diffuse types according to Lauren's classification) and mucinous adenocarcinoma.

Patients were seen every 3 to 2 months for the first 2 years and then once a year after curative resection. Follow-up evaluations included gastroscopy, abdominal ultrasonography and/or abdominal CT scan, chest radiograph, hematological and biochemical tests including tumor markers, and clinical examinations.

The overall survival rate and the survival rate according to histologic differentiation, depth of invasion and presence of lymph node metastasis were compared. Length of survival was measured from the date of surgery to the time of death. Immediate postoperative mortality (less than one month) was excluded. Comparison of clinicopathologic factors was

performed with the Chi-square test. The Kaplan Meier method was used for calculating the overall survival rate. Comparisons of survival curves were based on the Log rank test. A probability value of less than 0.05 was considered to be statistically significant.

RESULTS

Incidence and demographic data of EGC

There were 4,928 gastric cancer patients that underwent curative gastric resection at Severance hospital, Yonsei University College of Medicine between 1976 and 1995. Among them, 1,117 patients (22.6%) were EGC. During the last two decades, there has been an increase in the absolute as well as the relative incidence of EGCs among gastric cancers resected, from 13 cases (7.1%) in the year 1976 to 1977 to 252 cases (29.1%) in the year 1994 to 1995 (Fig. 1).

Overall, the relative proportion of EGC has also increased from 10% in 1970s to almost 30% in the 1990s (Fig. 1).

The male to female gender ratio of EGC patients has remained unchanged through the years. Overall, the male to female ratio is approximately 1.8 : 1. Although statistically not significant, females account for relatively high proportions of EGC among those

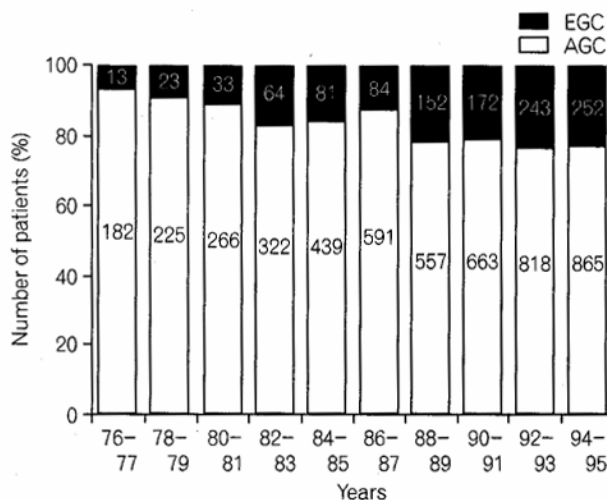


Fig. 1. Chronological changes in distribution of early gastric cancer and total gastric cancer plotted in 2 year interval (1976-1995).

Table 1. Dermographic Data of 903 EGC patients (1986–1995)

Age (years)	1986–1987	1988–1989	1990–1991	1992–1993	1994–1995	Total
	M/F	M/F	M/F	M/F	M/F	M/F
< 30	2/2	1/3	1/1	1/1	4/1	9/8
30–49	18/11	30/26	41/23	52/36	54/22	195/118
50–69	24/12	42/39	68/28	95/46	95/59	330/184
70 <	3/1	4/3	9/3	11/4	13/8	40/19
Total	73	154	174	246	256	903

M/F, male/female.

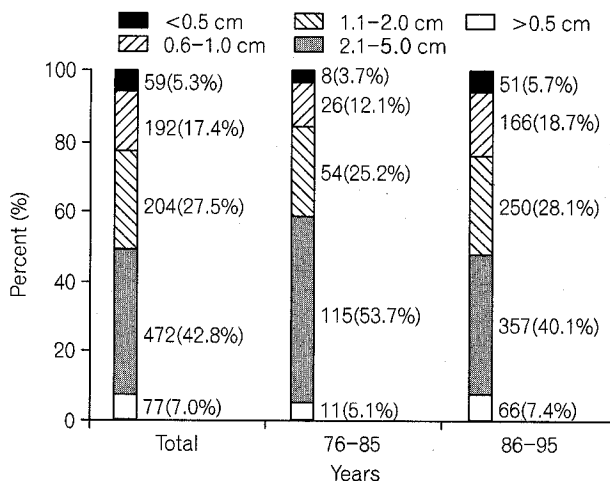


Fig. 2. Chronological changes in size of the lesions of EGC operated from 1976 to 1995.

younger than 30 years of age (Table 1).

Morphologic characteristics of EGC

Tumor size distribution changes were examined by comparing 1986–1996 data with that of 1976–1986. The proportion of EGC with smaller lesions, especially less than 1.0 cm (i.e. small and minute gastric cancer), have been increasingly diagnosed, from 15.5% during 1976–1985 to 24.3% during 1986–1995 ($p < 0.05$) (Fig. 2). While more than 50 percent of EGCs were in the size range 2–3 cm in the earlier decade (53.7%), 40.1% were in this range during 1986–1995 ($p > 0.05$). The proportions of tumors larger than 5 cm did not shown a significant change during the last two decades. Likewise, the number of minute gastric cancers (tumor less than 5 mm in

diameter) has increased from 8 cases to 51 cases and small gastric cancers from 25 to 166 cases over the same time periods (Fig. 2).

The topographic distributions of EGC were categorized as the A (antrum), M (middle) and C (cardia) region. A region was the most common site throughout the study periods. However, the relative proportion of lesions in the A area showed a tendency to decrease from 62% in the early period (1986–1990) to 49% in the late period (1991–1995). EGC was found to occur most frequently on the lesser curvature followed by the posterior wall, and this trend was similar for both periods ($p < 0.05$; lesser curvature against others) (Fig. 3).

Macroscopically, the depressed type was the most common (66.2%), followed by the elevated type (15.6%), the flat type (10.1%) and the mixed type (8.1%) in order (please refer to the figure legends for the classifications of morphologic type) (Fig. 4). The proportions of elevated and flat types showed a tendency to reduce, from 15.4% in the earlier decade to 25.7% in the recent decade, while the proportion of the depressed type showed a tendency for decrease only ($p > 0.05$) (Fig. 4).

Histopathologic characteristics

Histologically, the signet ring cell type showed a tendency to reduce from 33.1% in 1976–1985 to 28.8% in 1986–1995, while the papillary and the tubular/well differentiated or moderately differentiated types showed a slight increase from 32.6% to 45.1% during the same period. According to the Japanese criteria, differentiated type EGC accounted for 43% and undifferentiated type 57%. However,

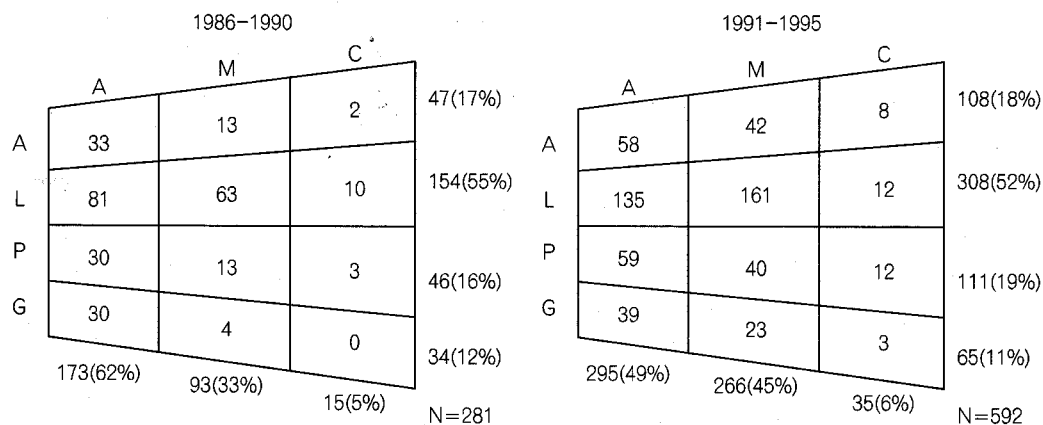


Fig. 3. Chronological changes of topographic location of EGC (1986-1995).

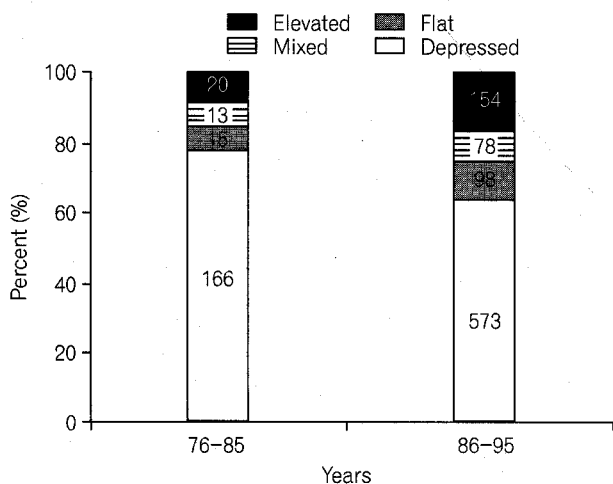


Fig. 4. Chronological changes in macroscopic types of EGC. Elevated: I, IIa, IIa+IIb; Mixed: IIa+IIc, IIc+IIa, IIa+III; Flat: IIb, IIb+IIc, IIb+IIa, Depressed: IIc, IIc+III, III+IIc, III.

there was no statistically significant change during the study periods (Table 2).

Tumor invasion depth correlated well with lesion size. As the size of the EGC lesions increased, the risk of SM invasion increased accordingly. The EGC lesions with sizes smaller than 1 cm in diameter had an M/SM ratio of 1.75, and lesions greater than 5.0 cm had an M/SM ratio of 0.76, and these correlations were statistically significant ($p < 0.05$) (Table 3).

The overall lymph node metastasis rate was 13%. Tumors less than 1.0 cm had a 6% lymph node metastasis rate, while tumors larger than 3.0 cm had an 18% lymph node metastasis rate (Table 4). Lymph node metastases were seen in 2.9% of cases when the

Table 2. Chronological Trend in Histologic Types of EGC

Histology	1976-1985	1986-1995	Total
Papillary	0 (0.0)	6 (0.7)	6 (0.6)
Tubular	WD 28 (16.0)	167 (19.1)	195 (18.6)
	MD 29 (16.6)	221 (25.3)	250 (23.8)
	PD 56 (32.0)	216 (24.7)	272 (25.9)
Mucinous	4 (2.3)	12 (1.4)	16 (1.5)
Signet ring cell	58 (33.1)	252 (28.8)	310 (29.6)
Total	175 (100.0)	874 (100.0)	1049 (100.0)

WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

Table 3. Depth of Tumor Invasion in Relation to Tumor Size (1986-1995)

Size (cm)	M cancer	SM cancer	Total	M/SM
≤ 0.5	26	11	37	2.36
$0.5 < \leq 1.0$	74	46	120	1.61
$1.0 < \leq 2.0$	75	100	175	0.75
$2.0 < \leq 3.0$	59	69	128	0.86
$3.0 < \leq 4.0$	35	33	68	1.06
$4.0 < \leq 5.0$	19	21	40	0.90
$5.0 <$	17	26	43	0.76
Total	305	306	611	1.00

M cancer, cancer confined to mucosa layer; SM cancer, cancer confined to submucosa layer.

tumor was confined to the mucosa. In contrast, a lymph node metastasis rate of 21.5% was seen when the tumor invaded the submucosa, and these differ-

Table 4. Lymph Node Involvement in Relation to Tumor Size (1986–1995)

Size (cm in diameter)	Number	LN positive	LN negative	LN +/- Total
≤0.5	51	2	49	0.04
0.5 < ≤1.0	166	12	154	0.07
1.0 < ≤2.0	250	29	221	0.12
2.0 < ≤3.0	192	27	165	0.14
3.0 < ≤4.0	106	18	88	0.17
4.0 < ≤5.0	57	9	48	0.16
5.0 <	66	14	52	0.20
Total	888	111	777	0.13

LN positive, presence of lymph node involvement; LN negative, absence of lymph node involvement.

Table 5. Relationship of Presence of Lymph Node Metastasis with Depth of Tumor Invasion

	Lymph node positive (%)	Lymph node negative (%)
Mucosa*	9 (2.9)	298 (97.1)
Submucosa*	66 (21.5)	241 (78.5)

* $p < 0.05$.

Table 6. Chronological Changes of Multiplicity of EGC

Years	1976–1985	1986–1995	Total
Multiple	3 (1.4)	40{3}(4.4)	43 (3.8)
Single	211 (98.6)	863 (95.6)	1074 (96.2)
Total	214 (100.0)	903 (100.0)	1117 (100.0)

{ }, denotes the triple lesions.

ences were statistically significant ($p < 0.05$) (Table 5). Multiple carcinomas were found in about 3.8% of the 1,117 EGC patients operated upon. The incidence of multiple EGC showed a tendency to increase from 1.4% in 1976–1985 to 4.4% in 1986–1995 (Table 6).

Survival rate

749 patients with EGC were eligible for the survival analysis. The overall 5-year survival rate

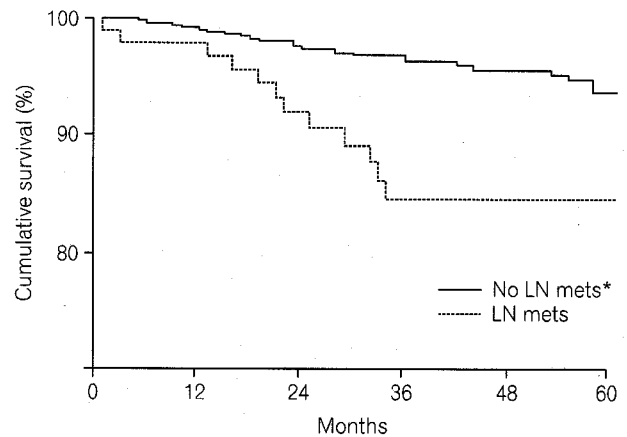


Fig. 5. Survival rate according to lymph node metastasis. * $p < 0.05$ (Log Rank Test).

(5YRSR) was 92.7%. Presence of submucosal invasion did not influence survival (93.7% of 5YRSR in mucosal cancer *vs* 92.1% in submucosal cancer). Likewise, histologic differentiation did not affect the survival rate (93.6% of the differentiated type *vs* 92.2% of the undifferentiated type). On the other hand, when lymph node metastasis was present, the 5 YRSR fell to 84.6%, while the 5YRSR was 96.2% without lymph node involvement and this difference was statistically significant (Fig. 5).

DISCUSSION

EGC was recognized as early as 1938 by Saeki who reported that patients with gastric cancer confined to the submucosa had a five year survival in excess of 90%.¹² Several mass screenings of asymptomatic individuals have been attempted in several countries,^{5,8,9} little prospective evidence exists that the availability of such mass screening reduces mortality from gastric cancer.¹³ Regarding survival discrepancies between Japan and Western countries, a variety of reasons have been offered, including differences in operative techniques, population characteristics and the natural history of the disease.¹³

The proportions of EGC operated upon in Korea has progressively increased over the last two decades as is demonstrated in this study. In Japan, patients with EGC account for 25–60 percent of operations carried out for gastric carcinoma.^{14,15} Despite the fall in the incidence of gastric cancer worldwide, it re-

mains the most common cause of death from malignancy in Korea, for example, it was responsible for 11,102 deaths in 1998. The prevalence rate of gastric cancer in Korea is 72.03 cases for every 100,000 males and 38.67 cases for every 100,000 females.^{16,17}

In our study the proportion of EGC among resected gastric cancer patients has steadily increased over the last two decades and approached 30% in 1995. Notably, the proportions of smaller lesions of less than 10 mm, have significantly increased from 15.5% to 24.3%. This increase may be explained by an improvement in diagnostic skills or the advent of various diagnostic modalities, including the widespread use of the video image endoscope with adequate biopsy, including large particle biopsy, chromoscopy, and endoscopic ultrasonography (EUS).^{6,7} As has been reported by other studies,^{18,19} a predominance of males among EGC cases was observed. The male to female ratio of EGC patients showed a similar trend to AGC, with a male to female ratio about a mean of 1.97. Our series shows similar proportions of gender to previous reports, however, in younger gastric cancer patients (younger than 30 years old), the male to female ratio approaches 1.0. Although this data was not statistically significant, it does suggest a different pathogenetic mechanism in this subset of the age population. Many authors,^{20,21} especially Japanese, report a high prevalence peak in the fifth to sixth decade and our results support this observation.

The observed increases - both relative and absolute in the incidence of proximally located gastric cancer have been reported worldwide.^{22,23} The prognosis of proximally located tumors in general is poor. Although, no definite explanation exists, this has been related to the presence of a thinner muscularis mucosae in the fundic region and the presence of firmly packed glands, which might prevent lateral growth.²⁴ In this study, the proportion of antral cancer showed a tendency to decrease with time but this was without statistical significance. This observation suggests that there is a possibility of encountering EGCs with different biological behaviors and characteristics in the near future if this trend continues.

The incidence of the diffuse type, however, varies less over time or may even have gradually increased.^{25,23} Increasing number of patients with diffuse type of tumors would pose some challenging diagnostic and therapeutic problems. In contrast to

the intestinal type, no precursor lesion of the diffuse type of gastric cancer has been identified, implying that endoscopic surveillance of patients at risk for developing this tumor is not feasible.²⁶ In EGC, the intestinal type predominates, and accounts for more than half of patients in the majority of clinical reports. Comparison with the Japanese experience is difficult, as the Lauren classification is not frequently quoted. In Japan, tumors are classified according to the Japanese Research Society Committee²⁷ and are divided into papillary, tubular/well differentiated, and tubular/moderately differentiated adenocarcinoma (which together are considered differentiated), poorly differentiated and signet ring adenocarcinoma (undifferentiated), and mucinous adenocarcinoma. Taken together, the differentiated type account for around 60% and the undifferentiated for 40%.^{19,28,29} Our reports show a somewhat lower frequency of the differentiated type of EGC at 43% and of the undifferentiated type 57%. The possible explanation for this discrepancy could be due to different pathophysiologic mechanisms of gastric carcinogenesis in the two countries. A higher prevalence of *Helicobacter pylori* infection or the predilection for salty and spicy dietary foods in Korea predisposes this observation. The low number of differentiated types of EGC's in Korea could lead to different EGC behaviors involving more frequent lymph node involvement. It has been reported that the degree of differentiation is closely related to the depth of invasion in gastric cancer, with poorer differentiation evident in submucosal and advanced cancers than mucosal lesions.³⁰

Some features of EGCs may influence the prognosis. Mucosal tumors were reported to have better survival than submucosal tumors. Lymph node metastasis in EGCs is rated to occur with a frequency between 10–20% in most reports. A significant positive correlation was noted between depth of tumor invasion and lymph node metastasis in several previous reports.^{30,31} In a retrospective report, lymph node metastasis was the only significant prognostic factor affecting survival in Korea.³² In this report it was reported that the overall lymph node metastasis rate was 15.7%, which is slightly higher than the 13% frequency of our study. Itoh et al.³³ on the other hand reported a similar survival rate at 10 years in both node positive and negative patients. Lymph node involvement in our study showed significant differences in the 5-year survival rate confirming

earlier reports. Maehara et al.³⁰ reported that the independent risk factors for nodal metastases are a large tumor, invasion of the vasa lymphatica and involvement of the submucosa. In our series, the high risk of lymph node metastases seemed to be dependent on submucosal invasion statistically.

The prognostic factors affecting the 5-year survival rate of EGC have been well-reported in the literature, and the prognosis of carcinomas confined to the mucosa without lymph node metastasis is reported to be better. This survival advantage is maintained to at least the 10 year level.^{29,33} Information on other prognostic factors is more variable. There is some controversy on the role of the degree of differentiation. Some showed no benefit, while others reported differences.^{29,34,35} In our series, there was no survival difference according to the histologic differentiation. Tumor size and depth of tumor invasion did not affect survival rates. The 5-year survival rate of 92.7% all EGC patients operated upon in our study is in accordance with previous reports.^{18,19}

The concept of multiple synchronous gastric cancers is well recognized. The reported prevalence of synchronous cancers is between 2 to 14% in the European literature, and closely echoes the Japanese experience of 5–13%. In addition to double tumors, triple and quadruple tumors have also been reported.³⁶ It has been found that the frequency of multiple tumors is more common in EGC than AGC,^{36,37} and this has been taken to imply that progressive carcinoma may represent a convergence of multiple primary foci. In our series, the incidence of multiple synchronous cancers was 1.4% in earlier decade, to 4.4% in the recent decade. The presence of multiple synchronous tumors suggests that EGC represents a field change of the gastric mucosa as a whole, indicating a higher risk of developing further tumors in the rest of the stomach.

In conclusion, the proportion of EGC has steadily increased during the last two decades. The depth of tumor invasion is correlated with the tumor size and regional lymph node involvement. On histopathologic examination, differentiated type EGC accounted for 43%, and the undifferentiated type for 57%. The overall 5-year survival rate was 92.6% and the presence of lymph node metastasis significantly affected the survival. Various new approaches including computer analysis of video-images of suspicious mucosal abnormalities, gene analysis of the biopsy speci-

mens, as well as mass screening for the risk groups will continue to increase the proportion of EGCs in resected gastric cancers in the near future.

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