

Early Gastric Cancer

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Although common in Japan, early gastric cancer (EGC = gastric adenocarcinoma confined to the mucosa and submucosa of the stomach, with or without regional lymph node metastases) is thought to be an infrequent occurrence in the United States. However, a review of all "curative" resections for carcinoma of the gastric body and antrum at the University of Virginia between 1974 and 1982 revealed EGC in five of 31 patients (16%). The purpose of the present study was to compare EGC to more advanced gastric cancer (ADV; $n = 26$) to determine whether any presenting historical, laboratory, x-ray, or endoscopic features distinguished the two groups before surgery and to ascertain whether postoperative survival in the United States mimicked the Japanese experience. All surviving patients were contacted, all charts were abstracted, all pathologic specimens were re-examined, and all radiographs were reviewed blindly by an experienced radiologist. Statistical evaluation was accomplished using Kaplan-Meier plots, chi square analysis, and unpaired "t" tests, as appropriate. At presentation, patients with EGC were younger (44 ± 6 vs. 67 ± 2 years, $p < 0.01$) with higher admission albumin levels (4.1 ± 0.2 vs. 3.7 ± 0.1 mgm/dl, $p < 0.01$). Although not significantly different, admission hemoglobin tended to be higher (41 ± 2 vs. $35 \pm 2\%$), the incidence of weight loss tended to be less (40 vs. 65%), duration of symptoms tended to be longer (21 ± 11 vs. 8 ± 3 months), and tumor diameter tended to be smaller (1.7 ± 0.6 vs. 5.8 ± 0.7 cm) in EGC. No differences were apparent with respect to endoscopic or radiographic appearance, tumor location ($>70\%$ antrum), presence of regional lymph node metastases (EGC = 2/5; ADV = 20/26), or type of resection (subtotal gastrectomy in 4/5 EGC, in 19/26 ADV). On median 5-year follow-up, however, survival with EGC has been 100%. In contrast, the Kaplan-Meier estimate of 5-year survival in ADV is 15% (42% with muscularis invasion, 0% with serosal invasion, 12% with extra-gastric spread; $p < 0.01$ vs. EGC). One suture line recurrence in EGC was successfully treated by re-resection. No ADV patient with recurrence survives ($p < 0.01$). Thus, EGC behaves similarly in the United States and Japan; for example, prognosis is excellent even in the presence of lymph node metastases. Inability to distinguish EGC from ADV before surgery justifies an aggressive surgical approach to all patients with resectable gastric neoplasms.

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EARLY GASTRIC CANCER (EGC) is defined as adenocarcinoma confined to the mucosa or submucosa of the stomach with or without regional lymph nodes metastases.^{1,2} Although common in Japan, EGC is thought to be rare in the United States where the prognosis for gastric cancer is considered to be poor. However, a review of all cases of "curative" resections for gastric adenocarcinoma performed at the University of Virginia between 1974 and 1982 demonstrated a 16% incidence of EGC. The purpose of the present study was to review these cases in order to determine if any presenting historical, laboratory, x-ray, or endoscopic features distinguished patients with EGC from those with more advanced disease and to ascertain whether or not postoperative survival in the United States mimicked the Japanese experience.

Methods

All cases of gastric adenocarcinoma resected for "cure" (all gross tumor removed, no distant metastases noted) between 1974 and 1982 at the University of Virginia were reviewed. Adenocarcinoma of gastroesophageal junction with extension into the esophagus was excluded as no instance of EGC in this tumor location was found. Thirty-one patients met the inclusion criteria. Of these, five demonstrated EGC histologically; the remainder were designated as advanced gastric cancer (ADV). All charts were abstracted to ascertain the type and duration of symptoms, history of weight loss, admission hemogram, liver function tests, electrolyte levels, endoscopic appearance, type of gastric resection, and recurrence and survival rates. Endoscopic reports were available in four of five patients with EGC and in 23 of 26 patients with ADV. In addition, all pathologic specimens were reviewed by a senior experienced pathologist to determine depth of gastric wall invasion, tumor location, tumor diameter, and presence or absence of regional lymph node metastases.

Further, all available radiographs were reviewed by a senior experienced gastrointestinal radiologist unaware of

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the purpose of the study or of the clinical histories of the individual patients. He was asked to categorize the appearance of any lesions detected on the upper gastrointestinal series as either benign, malignant, or indeterminate. Lesions were also classified as ulcerative, polypoid, or infiltrating. Upper gastrointestinal series were available for review in four of five EGC patients and in 25 of 26 ADV patients.

Results are reported as mean \pm standard error. Statistical evaluation was accomplished using unpaired "t" tests, chi square analysis, and Kaplan-Meier plots, as appropriate.

Results

Length of Follow-up

Median length of follow-up in EGC is 62 months, ranging from 24 to 100 months after surgery. Median length of follow-up on all surviving patients with ADV has been 68 months, ranging from 39 to 96 months.

Age and Sex Ratios

At presentation, patients with EGC were, on average, 23 years younger than those with ADV: 44 ± 6 years (range 26–61 years) vs. 67 ± 2 years (range 37–83 years), a difference which was statistically significant ($p < 0.01$). Male:female ratios were 1:1.5 in patients with EGC vs. 2.5:1 for those with ADV.

Symptoms

Mean duration of symptoms tended to be longer in the EGC patients (21 ± 11 months) vs. patients with ADV (8 ± 3 months) (Table 1). The incidence and amount of weight lost and the incidence of hematemesis were greater in the ADV group than in the EGC group, whereas a principal complaint of epigastric pain was more common in EGC than in ADV. None of these differences were significant, however.

Admission Laboratory Assessment

There were no significant differences between EGC and ADV for virtually all of the admission laboratory data, although admission hematocrits tended to be higher in the EGC group ($41 \pm 2\%$ vs. $35 \pm 2\%$). The only significantly different parameter was the admission albumin level that was substantially higher in patients with EGC (4.1 ± 0.2 vs. 3.7 ± 0.1 mg/dl; $p < 0.01$).

Preoperative Evaluation

The preoperative diagnosis of carcinoma was established either endoscopically or radiographically in 80%

TABLE 1. Symptoms at Presentation

	EGC	ADV	"p" Value
Epigastric pain	4/5	8/26	NS
Nausea	1/5	10/26	NS
Anorexia	0	5/26	NS
Fatigue	0	5/26	NS
Hematemesis	0	3/26	NS
Weight loss	2/5	16/26	NS
Duration	21 ± 11 Months	8 ± 3 Months	NS

of the EGC group and in 77% of the advanced group. Routine upper gastrointestinal series were uniformly insensitive, however, even when interpreted by a senior experienced gastrointestinal radiologist. None of the radiographs in the EGC group were regarded as malignant: two of the four available for review were read as benign, the remainder as indeterminate. Even in the advanced group, only 60% of patients were felt to have an upper gastrointestinal series indicative of gastric adenocarcinoma; 12% were read as benign and 28% as indeterminate. Lesions were said to be infiltrating in the majority of instances in the ADV group (Table 2).

Endoscopy proved more sensitive in the diagnosis of gastric adenocarcinoma, but only when combined with biopsy. The endoscopist's impression in the EGC group was that two had benign disease, one was clearly malignant, and one was indeterminate. In patients with ADV, five of 23 were felt to be benign, 13 of 23 malignant, and six of 23 were considered indeterminate. Tissue obtained at endoscopy was positive for carcinoma in all four of the EGC group in whom biopsies were performed. However, biopsies were positive for carcinoma in only 15 of 23 ADV patients. Thus, no radiographic or endoscopic criteria reliably distinguished EGC from ADV.

Operative Approach

Subtotal gastrectomy was performed in four of five patients in the EGC group and in 19 of 26 in the ADV group. Total gastrectomy was performed in the remainder. There was no operative mortality in the EGC group. Three patients died in the ADV group within 30 days of operation, one from an arrhythmia and two from sepsis. These differences were not statistically significant.

TABLE 2. Radiologic Evaluation

	EGC	ADV	"p" Value
Benign	2/4	3/25	NS
Indeterminate	2/4	7/25	NS
Malignant	0/4	15/25	NS
Ulcerative	3/4	5/25	NS
Polypoid	1/4	1/25	NS
Infiltrating	0/4	9/25	NS

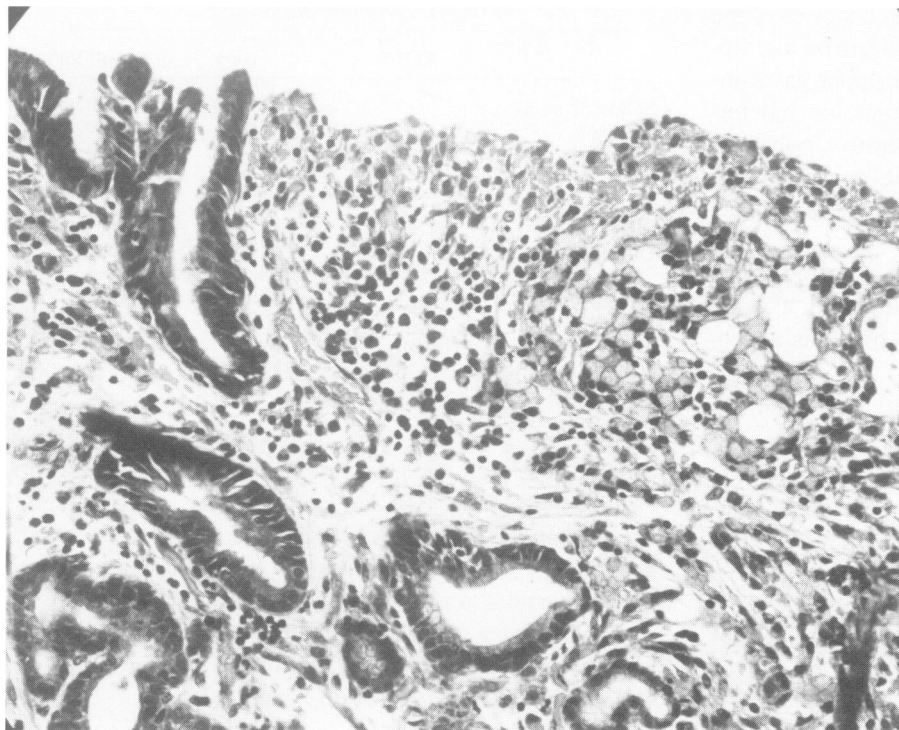


FIG. 1. Photomicrograph of early gastric cancer confined to the mucosa ($\times 250$).

Tumor Location and Size

More than 70% of both EGC and ADV tumors were antral in location. The EGC group had a predominance of lesser curvature lesions, whereas ADV cancers were evenly distributed between the lesser and greater curvature. EGC tumors tended to be smaller (1.7 ± 0.6 vs. 5.8 ± 0.7 cm in greatest diameter) although the difference was not significant. Three patients among the ADV group had microscopic evidence of tumor at the margin of resection; all developed recurrence by 4 months.

Histology

All tumors were adenocarcinomas. An example of EGC is shown in Figure 1, demonstrating foci of adenocarcinoma in areas of atrophic gastritis. Three patients with EGC had tumor confined to the mucosa while, in two, tumor extended into the submucosa. In the ADV group,

tumor extension to the muscularis propria was noted in eight, to the serosa in six, and into the perigastric tissue in 12.

Lymph Node Metastases

Metastases to regional lymph nodes were found in two of five patients with EGC and in 20 of 26 ADV, a difference which was not significant statistically. Positive nodes were found at all levels of tumor invasion, although the percentage of patients harboring lymph node metastases increased with increasing depth of invasion (Table 3).

Adjuvant Therapy

Thirty-eight per cent of the ADV group received post-operative chemotherapy and 15% received radiation therapy. In general, these treatments were begun after tumor recurrence and did not appear to improve survival. One patient in the EGC group received a partial course of chemotherapy; none received radiation therapy.

TABLE 3. Correlation of Positive Regional Lymph Nodes with Depth of Gastric Wall Invasion

Invasion	EGC		ADV	
	Number of	% (+) Nodes	Number of	% (+) Nodes
Mucosa	3	33%		
Submucosa	2	50%		
Muscularis propria			8	38%
Serosa			6	83%
Perigastric tissues			12	100%

Recurrence

Twenty of 26 ADV patients (73%) developed either local or systemic recurrence of disease at a mean interval of 17 ± 6 months after surgery. In contrast, only one patient in the EGC group developed recurrence ($p < 0.01$). This proved to be a suture line recurrence, found 2 years following the initial operation. The patient

was successfully treated by subsequent near-total gastrectomy and is alive without detectable disease 3 years following this procedure. In contrast, no patient who developed recurrence in ADV is alive ($p < 0.01$ vs. EGC), mean survival in this group being 5 ± 9 months following detection of recurrent tumor.

Survival

Median 5-year survival in the patient with EGC is 100% (Fig. 2). In contrast, the Kaplan-Meier estimate of 5-year survival in the ADV group is only 15% ($p < 0.01$). Estimated survival is clearly influenced by the depth of gastric wall invasion by tumor: 42% 5-year survival for tumor confined to the muscularis propria, 0% for tumor extending into the serosa, and 12% with tumor invasion of the perigastric tissue (Fig. 3).

Discussion

In 1962, the Japanese Gastroenterologic Endoscopy Society adopted the term "early gastric cancer" to signify the Society's belief that, when detected early, gastric adenocarcinoma could be cured.³ This belief was based on the survival statistics of the Japanese surgeon, Saeki, who demonstrated in 1938 that a subset of patients with gastric adenocarcinoma, those with tumor confined to the mucosa or submucosa, had a 91% 5-year survival, irrespective of the presence or absence of regional lymph node metastases. It is now clear that EGC is a distinctive malignancy, at least in terms of prognosis, and that it is identifiable in areas outside of Japan: the superficial spreading carcinomas of Stout⁴ and Friesen⁵ in the United States and the superficial carcinomas and surface gastric cancers reported from Britain^{6,7} are pathologically identical to EGC.

The relative proportion of EGC to all diagnosed gastric adenocarcinomas is a function of the diligence with which the diagnosis is sought. In Japan, the advent of mass screening examinations has resulted in an increase in incidence of EGC among resected gastric carcinomas from 16% in 1960 to 63% in 1974.⁸ The 16% incidence of EGC in the present series is comparable to the incidence reported by Machado from England,⁶ Miller from Western Europe,⁹ and Paulino from South America.¹⁰ It is also comparable to the 13% incidence of EGC found by Green in 213 gastric resections for adenocarcinoma at Columbia University.¹¹

In the United States, the prognosis for gastric adenocarcinoma is regarded as being uniformly grim. This belief has led some to adopt a posture of "therapeutic nihilism" with respect to the disease, while others feel bound to employ exhaustive (and costly) preoperative testing in order to identify "suitable" candidates for surgery. The present study suggests that both approaches are inappropriate. In the first instance, no distinctive historical, lab-

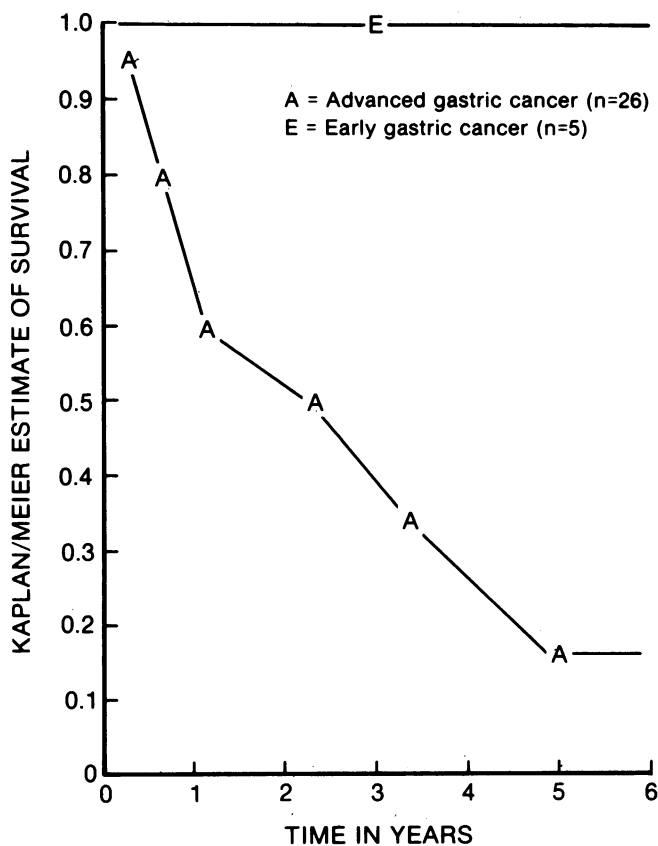


FIG. 2. Survival of early gastric cancer versus advanced gastric cancer patients.

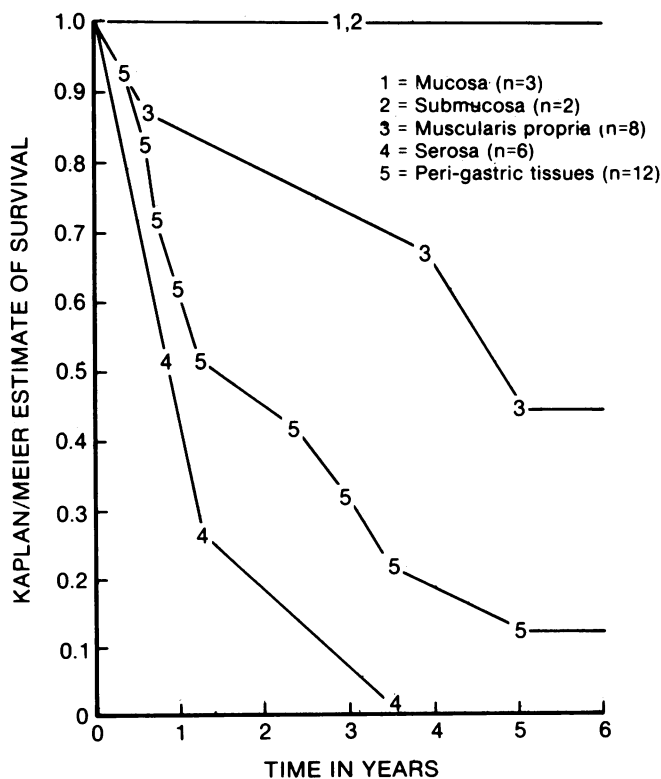


FIG. 3. Survival by depth of gastric invasion.

oratory, radiographic, or endoscopic features reliably distinguished the patients with early gastric cancer from those with more advanced disease. At presentation, only two significant differences were identified between these groups: age and admission albumin levels. Neither is specific. Furthermore, larger series report very similar age distribution between EGC and ADV; Johansen¹² noted a mean of 66 years in a series of 70 patients with EGC while Miller,⁹ in a review of 658 patients with EGC, found the disease most common in the sixth and seventh decades of life. In addition, symptoms of patients with EGC are vague, often consisting only of epigastric fullness or indigestion. The present study is in agreement with other reports that indicate that epigastric pain is, indeed, the most common presenting symptom in EGC, whereas significant weight loss, hematemesis, or melena suggest (but do not prove) the presence of more advanced carcinoma.^{11,13}

The diagnosis of gastric adenocarcinoma is most readily made by endoscopy when seven to ten biopsies are routinely obtained.¹⁴ However, endoscopic biopsies cannot distinguish early from more advanced gastric cancer. Routine upper gastrointestinal series, at least as performed in the United States, is also relatively insensitive, although the air-contrast techniques used in the mass screening examinations in Japan are reportedly more accurate.¹⁵ In the present series, neither the location, the appearance, nor the size of the lesions reliably distinguish EGC from ADV.

Adequate surgical resection is the mainstay of therapy, with subtotal gastrectomy the treatment of choice for EGC of the antrum and total gastrectomy reserved for lesions high in the fundus or for patients with recurrent disease.¹³ Adjuvant chemotherapy or radiation therapy do not appear to improve survival of patients with EGC, even in those with nodal metastases.¹⁶ Therefore, neither modality can be recommended. Recurrence rates of 3% have been noted by others in EGC with a mean disease-free interval of 3 years.^{16,17} Higher local recurrence rates (9%) have been reported for patients in whom the diagnosis of adenocarcinoma was not suspected before surgery.¹⁸ As a rule, recurrence tends to be local and can be treated successfully by repeat resection.

That "therapeutic nihilism" is also inappropriate is suggested by the superb survival statistics noted in the present (admittedly small) series, as well as those reported from Japan by Kishimoto (97% 5-year survival for intramucosal cancers, 96% for submucosal cancers).¹⁹ In Western European Countries and in the United States, survival rates in EGC are somewhat lower: 87% in Germany,²⁰ 71% in Britain,¹⁸ and 68% in New York.¹¹ Unlike other solid tumors of the gastrointestinal tract, depth of gastric wall invasion and not metastases to regional nodes

appears to be the primary determinate of prognosis in both EGC and ADV.

In summary, early gastric cancer behaves similarly in the United States and Japan; for example, prognosis is excellent even in the presence of regional lymph node metastases. Inability to distinguish early from advanced gastric cancer before surgery justifies an aggressive surgical approach to patients with resectable gastric neoplasms.

Acknowledgment

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