Early Gastric Cancer

Twenty-eight–Year Experience

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A retrospective study of early gastric cancer (60 patients) was performed to evaluate its diagnosis and treatment. Ninety-five per cent of patients presented with nonspecific gastrointestinal symptoms and 53.3% had been treated for presumed benign disease for up to 48 months before diagnosis. Fiberoptic endoscopy detected these lesions more accurately than radiologic examination. The disease-free 5-year survival rate after resection was 76.4%. Survival showed no significant correlation with sex, tumor site, macroscopic appearance, extent of gastric resection, or histopathologic type. Tumors larger than 1.5 cm in diameter, invasion of submucosa, or lymph node metastasis resulted in significantly lower survival rates. Three of eight patients with nodal metastasis survived 5 or more years, including one who had second-echelon deposits. A high index of suspicion may permit more frequent detection. Extended lymphadenectomy (R2) is recommended to achieve the highest possible cure rate.

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GASTRIC CARCINOMA IS still one of the ten major causes of death due to cancer in the United States, even though its incidence decreased during the last three decades. Substantial interest has arisen in recent years in the diagnosis and management of early gastric cancer because very high cure rates can be achieved in this as compared with advanced stages of this disease.[1–4] In the early 1960s, the Japanese Gastroenterological Endoscopy Society defined early gastric cancer as carcinoma limited to the gastric mucosa and submucosa, regardless of the presence or absence of lymph node metastases.[4] The Japanese Research Society for Gastric Cancer provided a macroscopic classification of early gastric cancer in 1981.[5] Three types were described: type I, protruded lesions; type II, superficial lesions that may be flat (IIa), minimally elevated (IIb), or minimally depressed (IIc); and type III, excavated or depressed lesions.

In a recent report from the Tokyo Women's Medical College of 1019 patients with early gastric cancer resected for cure between 1965 and 1982, 5-, 10-, and 15-year survival rates of 95%, 90%, and 85%, respectively, were observed.[6] The improvement in survival is attributed to early diagnosis by the use of mass screening programs, increasingly sophisticated equipment such as the panendoscope and enlargement fiberscope, and advanced techniques including dye-spraying endoscopy and spectrophotometric color analysis of gastric mucosa. With these methods the incidence of gastric cancer diagnosed at this early stage has increased in Japan from 5% to more than 30% during the past 15 years, with 2400 cases reported in 1980.[7]

Although the numbers are less impressive, reports of early gastric cancer have appeared in the western literature.[8–11] These reports have corroborated the Japanese findings of a high cure rate of gastric cancer when diagnosed and treated before infiltration of the muscularis propria. Vigorous efforts therefore have been initiated toward the early detection of these tumors worldwide. In the United States approximately 23,000 cases of gastric cancer are reported annually but the incidence of early gastric cancer detection is only 3% to 6%, or approximately 1400 cases per year.[12] Mass screening of this population is difficult to justify on economic grounds but evidence suggests that greater clinical suspicion and meticulous repeated diagnostic evaluation, especially by endoscopic examination of selected patients, may increase the rate of detection of these early lesions.

The purpose of the present study was to review the experience of patients treated for early gastric cancer at our center to determine whether there is a specific pattern of clinical, laboratory, radiographic, or endoscopic features that could distinguish them from patients with benign gastric disease. Accuracy of our diagnostic methods, rea-

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sons for diagnostic delay, and the outcome of treatment also were analyzed.

Methods

Patients with early gastric cancer were identified from two databases of gastric cancer at the Memorial Sloan-Kettering Cancer Center: one was a retrospective collection of curatively treated gastric carcinomas (1960 to 1984) and the other was a prospectively maintained database started in 1985. Sixty patients were found to meet the histologic criteria for early gastric cancer. These patients' medical records were reviewed to ascertain the type and duration of symptoms, clinical, laboratory, radiographic, and endoscopic findings, type of gastric resection, tumor size, location, histologic differentiation, depth of gastric wall invasion, lymph node status, and follow-up information, including recurrence and survival. The tumors were also categorized by their macroscopic appearance according to the Japanese Research Society for Gastric Cancer.[5] Survival distributions were computed using the method of Kaplan and Meier[13] and univariate analyses of survival comparing patient subgroups were performed using the log rank statistic.

Results

Of the 60 patients who had early gastric cancer during the 28-year period of the study, 10 were treated during the first half and 50 during the second half of this period. There were 35 men and 25 women; the male to female ratio was 1.4:1. They consisted of 51 whites, 5 Asians, 2 blacks, 1 Hispanic, and 1 Indian. Seventeen of the patients were born abroad and immigrated to the United States; the length of residence in the United States ranged from 21 to 62 years. The mean age at diagnosis was 62 years, with a range of 44 to 89 years.

Associated Diseases

Gastric cancer was a second primary malignant tumor diagnosed in 10 of the 60 patients, occurring 2 to 20 years after treatment of the first primary tumor. The sites of the first malignant tumor included the rectum in three patients, uterine cervix in two patients, and, in one patient each, the lung, breast, skin, larynx, and renal pelvis. None of these patients had evidence of their first malignancy at the time the diagnosis of early gastric carcinoma was made.

Fifteen patients (25%) had pre-existing conditions that may be implicated in the development of gastric carcinoma; the conditions were documented 2 to 27 years before the diagnosis of gastric cancer was made. Twelve patients had long-standing peptic ulcer disease; two of these patients underwent subtotal gastrectomy 17 years earlier. In three patients, two of whom had Barrett's esophagus and one had pernicious anemia, gastric cancer was detected by yearly surveillance studies.

Presenting Features

Fifty-seven of the sixty patients (95%) underwent diagnostic studies for upper gastrointestinal symptoms. Epigastric pain and dyspepsia were the most common complaints. Weight loss in 13 patients ranged from 6 to 23 kg during a 2- to 10-month period. Forty-two per cent of the patients sought medical attention within 2 months of onset of their symptoms. The remaining 58% endured their symptoms from 3 to 72 months before seeking medical consultation. Seventy-two per cent of patients had no physical findings referable to their gastric lesions. The most frequent physical finding was epigastric tenderness, present in 10% of the patients. Anemia was the most common laboratory abnormality; it was found in 21.6% of the patients.

Methods of Diagnosis

The diagnostic methods and the sequence in which they were used differed according to the time period in which the patient was treated and whether the patient first consulted a gastroenterologist or a physician of some other specialty. Fiberoptic gastroscopy was not commonly performed in the 1960 to 1970 period.

A diagnosis of cancer was obtained in all 12 patients who underwent endoscopy as their first diagnostic procedure. An average of four to six biopsies were taken to obtain the diagnosis. A computed tomogram (CT) was obtained as the first diagnostic procedure in one patient. Although thickened rugal folds were reported on CT, the definitive diagnosis of cancer was obtained later by endoscopy in this patient.

An upper gastrointestinal barium examination was the first study performed in 47 patients. Double-contrast examination with thin barium was not used routinely, except during the last 10 years. Malignancy was diagnosed in eight (17%) of these studies. Of the remaining 39 studies, 28 (59.6%) were reported as benign disease and 11 (23.4%) were equivocal. Six patients with reported benign disease underwent repeat radiographic examinations for persistent symptoms 2 to 12 months after their initial procedure; these radiographs were likewise considered to be consistent with benign ulcer disease. Endoscopy was performed subsequently on 37 of these 39 patients. A diagnosis of cancer was obtained by biopsy or cytology in 30 patients (81.1%), and of gastritis or peptic ulcer disease in seven patients. Repeat endoscopy was performed on these seven patients at 2- to 12-month intervals, resulting in the diagnosis of cancer in five. One of the seven patients underwent three endoscopic procedures during a period of 6 months, and

another had six endoscopic procedures during a period of 18 months, before the definitive diagnosis was obtained. The remaining 2 of the 39 patients were brought to the operating room with presumed peptic ulcer disease, without benefit of preoperative endoscopy.

In total 32 of the 60 patients (53.3%) were diagnosed erroneously as having benign ulcer disease and/or gastritis and were treated with antacids and H2-receptor antagonists at the time of their initial presentation. The diagnostic delay ranged from 2 to 48 months (mean, 14.3 months) in these patients. Twenty-nine of these patients were treated for presumed benign disease on the basis of their radiographic findings. Endoscopic procedures subsequently were performed in this group of patients only when their symptoms proved refractory to medical therapy. Two of the seven patients who required multiple endoscopic procedures actually exhibited healing of the ulcer with improved symptoms at the time of repeat evaluation.

Surgical Treatment

The surgical procedure performed was based on the location and extent of the lesion in all instances. Distal subtotal gastrectomy was performed in 42 patients, esophagogastrectomy in 8 patients, proximal subtotal gastrectomy in 4 patients, total gastrectomy in 4 patients, and wedge excision of polyps in 2 patients. The latter procedure was performed before the popular use of fiberoptic endoscopy in two patients who had small gastric polyps visualized by upper gastrointestinal barium examination. Concomitant procedures included 8 splenectomies, 4 cholecystectomies, and 1 distal pancreatectomy. Six of the splenectomies and the pancreatectomy were performed as *en bloc* resections for tumors close to these organs. Two splenectomies were performed as a result of intraoperative injury. All four patients who underwent cholecystectomy had symptomatic biliary disease and preoperative evidence of cholelithiasis.

The extent of the lymphadenectomy performed reflected the opinion and judgment of the surgeon and varied considerably during the 28-year period of the study. Lymphadenectomy was classified as R1 if dissection included only the first echelon or immediately adjacent nodes, R2 if the second echelon of draining nodes was included, such as those along the left gastric, celiac, and common hepatic artery. Review of the operative reports indicated that two patients showed gross nodal metastases, which prompted the performance of wide lymphadenectomy. An R1 lymphadenectomy was performed in 40 patients and an R2 lymphadenectomy in 18; no lymph node dissection was performed in the two patients who underwent wedge polypectomy.

Fourteen complications occurred in 13 patients: pneumonia in 3, myocardial infarction in 2, anastomotic leak in 2, wound disruption in 2, wound infection in 2, small bowel obstruction in 1, and intra-abdominal abscess in 1. These complications resolved with medical treatment; no surgical intervention was required except in one patient who underwent operative repair of wound disruption. The anastomotic leaks were treated conservatively with bowel rest and parenteral nutrition. The intra-abdominal abscess was drained percutaneously with CT guidance.

Pathology

All tumors were adenocarcinomas and ranged in size from microscopic foci to 7 cm in diameter. Thirty arose in stomachs with a background of coexisting pathologic changes: chronic ulcer in 18, chronic gastritis in 7, intestinal metaplasia in 4, and mucosal atrophy in 1. Thirty-nine (65%) of the tumors were intramucosal; 21 (35%) extended into the submucosa. By macroscopic classification, there were 16 (26.7%) type I, 12 (20%) type II, and 32 (53.3%) type III lesions.

The type I protruded lesions were intramucosal in 12 (75%) and penetrated the submucosa in four patients (25%). The 12 type II superficial lesions were equally divided between the intramucosal and submucosal categories. Twenty-one (65.6%) of the type III excavated lesions were intramucosal and 11 (34.3%) invaded the submucosa.

The type II superficial lesions were generally smaller in size than either the type I protruded or type III excavated lesions; the mean diameters were 1.9, 2.4, and 2.5 cm, respectively. Twenty-seven (45%) cancers were located in the body of the stomach, 22 (36.7%) in the pyloric antrum, eight (13.3%) at the cardioesophageal junction, and three (5%) in the fundus. Protruded and excavated lesions were found more commonly in the antrum and body while the superficial lesions were located mainly in the body of the stomach. Most of the lesions were either grade 1 well differentiated (58.4%) or grade 2 moderately differentiated (33.3%) tumors with an even distribution among the three macroscopic types of cancer. Fifty-two (86.7%) of the tumors were of the intestinal type and eight (13.3%) of the diffuse type based on the histopathologic classification of Lauren.[14]

All surgical margins were microscopically negative. Metastatic deposits in lymph nodes were histopathologically confirmed in 8 (13.3%) of the 60 patients (Table 1). In five of these patients the deposit consisted only of a microscopic focus (less than 1 mm in diameter). Macroscopic replacement of lymph nodes was found in three patients, including one who had both microscopic and macroscopic deposits. Six of the eight patients had metastatic involvement of the first-echelon (N1) lymph nodes only; included in this group were all three patients with macroscopic deposits. Two of the patients had metastases in second-echelon (N2) lymph nodes; these were micro-

TABLE 1. *Early Gastric Cancer with Lymph Node Metastasis, Pathologic Features, Treatment, and Outcome*

Lymph Node Stage	Macroscopic Type	Depth of Invasion	Size (cm)	Lymphadenectomy	Outcome
N1	III	Mucosa	4.0	R2	NED 105 m
N1	I	Mucosa	7.0	R1	DOD 10 m
N1	III	Mucosa and submucosa	1.8	R1	DOD 45 m
N1	III	Mucosa and submucosa	4.8	R1	NED 77 m
N1	IIa	Mucosa and submucosa	2.0	R1	DOD 21 m
N2	III	Mucosa	1.4	R2	NED 60 m
N2	IIa	Mucosa and submucosa	1.8	R2	DOD 11 m
N2	III	Mucosa and submucosa	7.0	R2	DOD 12 m

DOD, dead of gastric cancer disease; m, months; NED, no evidence of disease.

N1, metastasis in lymph nodes within 3 cm of the tumor; N2, metastasis in lymph nodes farther than 3 cm from the tumor, such as those along the celiac, common hepatic, or splenic arteries.

R1 and R2 refer to lymphadenectomy with removal of the first or the first plus the second echelons of regional lymph nodes.

scopic deposits in the celiac node of a patient with a lesser curvature lesion and in a mediastinal paraesophageal node of a patient with a tumor in the cardioesophageal junction.

Five of the eight patients with nodal metastases had excavated lesions, two had superficial lesions, and one had a protruded lesion (Table 1). Three of the eight lesions were intramucosal; five invaded the submucosa. Five of the eight tumors were of the intestinal variety: one of protruded type, one superficial type, and three excavated type. Three were of the diffuse variety: two of excavated type and one superficial type.

Adjuvant Therapy

Only one patient, who had microscopic evidence of metastatic disease in the first-echelon (N1) lymph nodes, received adjuvant postoperative chemotherapy. This patient developed lung metastases 45 months after surgery and subsequently died of his disease.

Recurrence

Ten of the sixty patients (16.7%) developed either local or systemic recurrence of disease at a mean interval of 26 months after surgery. One half of these patients had lymph node metastases at the time of surgery. Eight of the ten patients who recurred had tumors that invaded the submucosa. With regard to histologic grade, three of the ten patients had well-differentiated (grade 1) tumors, six had moderately well-differentiated (grade 2) tumors, and one had a poorly differentiated (grade 3) tumor. The mean survival of this group was 2.7 months after detection of recurrence.

Survival

None of the patients died within 30 days of the operation or at any time during their postsurgical hospital stay. Survival data was available in all 60 patients. Follow-up times ranged from 11 to 270 months (mean, 57 months) from the date of resection. The Kaplan–Meier estimates of 5- and 10-year disease-free survival rates were both 76.4% (Fig. 1). Ten patients (16.7%) died of recurrent gastric cancer; nine died of other causes. The remaining 41 patients are alive without evidence of tumor recurrence.

Comparison analysis of the survival distributions showed that there was no significant difference in the disease-free survival of patients based on sex, the location of the cancer within the stomach, macroscopic appearance, extent of gastric resection, scope of regional lymphadenectomy, or the Lauren histopathologic type. There was, however, a significant difference in survival according to tumor size, depth of invasion, and the presence or absence of lymph node metastases.

Figure 2 shows the difference in the survival distribution according to the size of the tumor ($p < 0.05$). The 5-year disease-free survival for the 18 patients with tumors measuring less than 1.5 cm was 100% compared with 67.5% for the 42 patients with tumors larger than 1.5 cm. Only one of eighteen patients with a tumor less than 1.5 cm had lymph node metastases at the time of surgery. This patient, who had a type III excavated tumor with second-echelon (N2) nodal involvement, is without evidence of disease 60 months after resection with R2 lymphadenectomy. Fifteen of eighteen patients with small tumors had intestinal type and three had diffuse type lesions.

The difference in survival distribution according to the depth of invasion ($p < 0.0005$) is shown in Figure 3. Intramucosal lesions in 39 patients resulted in a 92.6% 5-year disease-free survival rate, in contrast to 48.8% for tumors that invaded the submucosa in 21 patients.

The presence or absence of lymph node metastasis had a significant influence on disease-free survival ($p < 0.00005$), as shown in Figure 4. Only three of the eight patients with positive lymph nodes, as compared with 45 of 52 (87%) for patients with negative lymph nodes, survived free of disease after 5 years. The three survivors

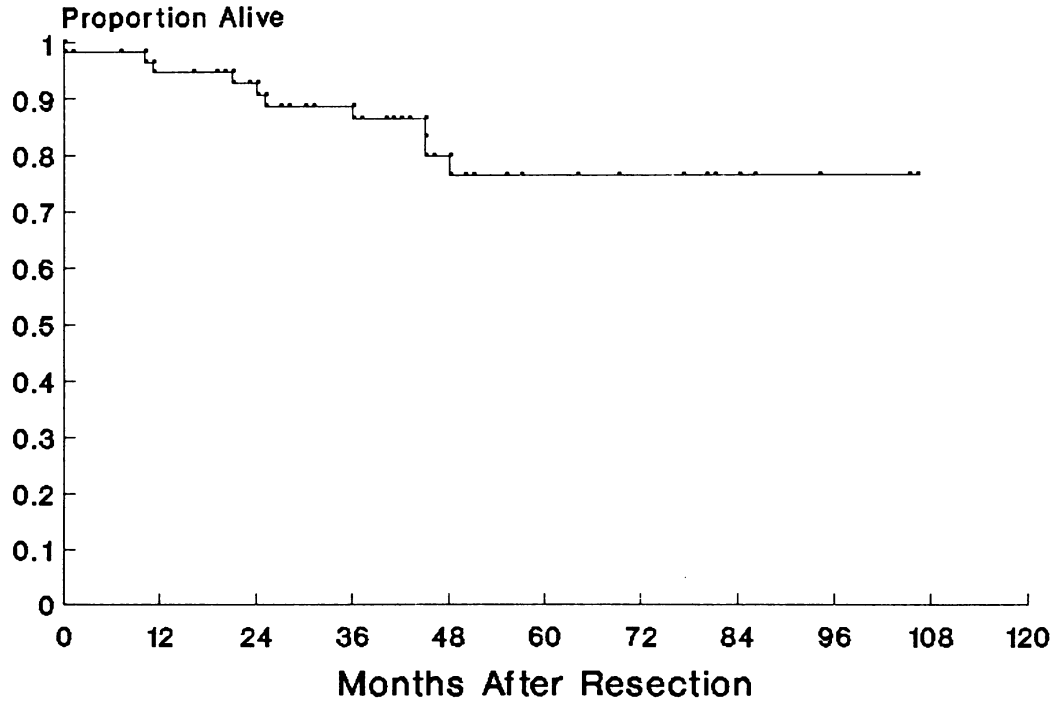

FIG. 1. Disease-free survival distribution of early gastric cancer patients who underwent resection with curative intent at MSKCC 1960–1988 (Kaplan–Meier plot).

consisted of two who had first-echelon (N1) and one who had second-echelon (N2) deposits. Of the two survivors who had N1 disease, one underwent an R2 lymphadenectomy for a diffuse-type, moderately differentiated, excavated tumor that was confined to the mucosa; the other underwent an R1 lymphadenectomy for an intestinal-type, well-differentiated, submucosal excavated tumor that had one microscopic focus of metastatic disease. The surviving patient who had N2 disease underwent an R2 lymphadenectomy for a diffuse-type, well-differentiated, intramucosal excavated lesion (Table 1).

Discussion

Early gastric cancer has been identified as a distinct clinical entity with a high surgical cure rate when com-

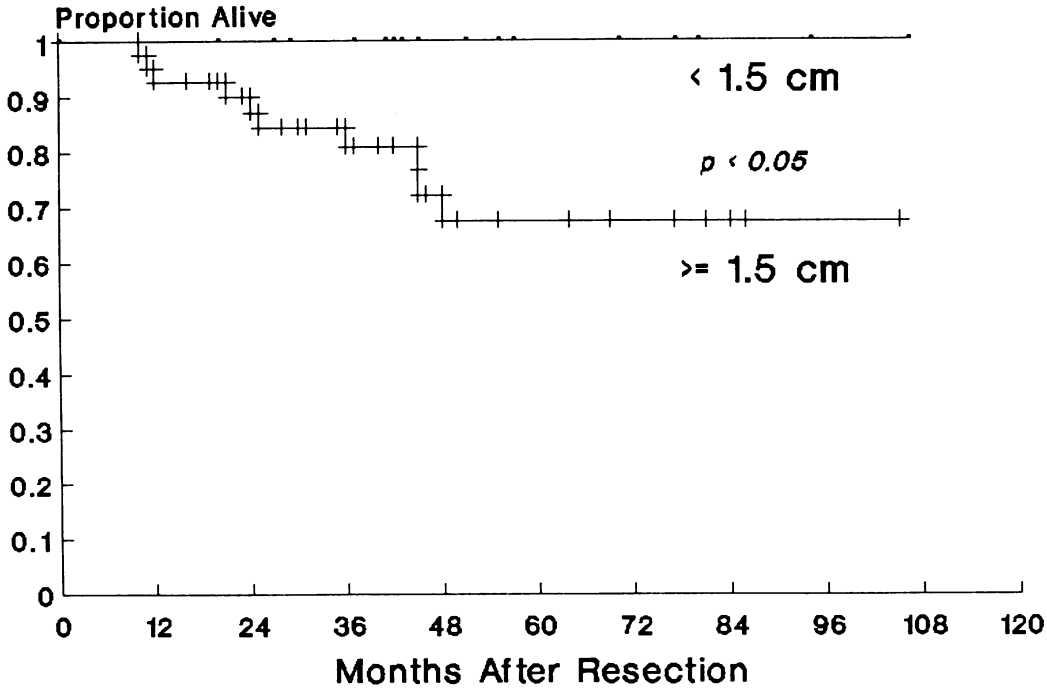

FIG. 2. Postoperative disease-free survival distribution of early gastric cancer patients according to tumor size (diameter in centimeters) (Kaplan–Meier plots).

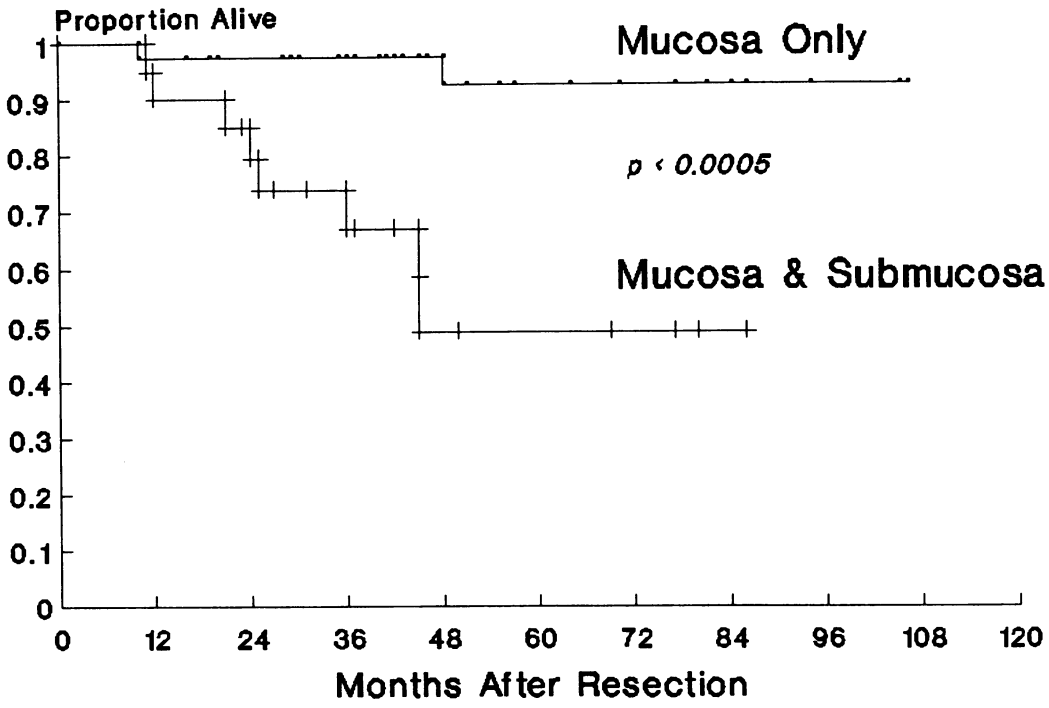

FIG. 3. Postoperative disease-free survival distribution of early gastric cancer patients according to depth of invasion (Kaplan–Meier plots).

pared with advanced gastric cancer. Our experience with these 60 patients treated in New York supports this concept and argues for more aggressive efforts to detect these lesions. Despite declining numbers of gastric cancer cases in this country, the incidence of these early lesions has been increasing in our institution and others since the advent of the fiberoptic gastroscope with capabilities for punch biopsy and brush cytology. Japanese studies suggest that advanced gastric cancer is preceded by the early lesion by about 5 to 10 years. Therefore hope for improved sur-

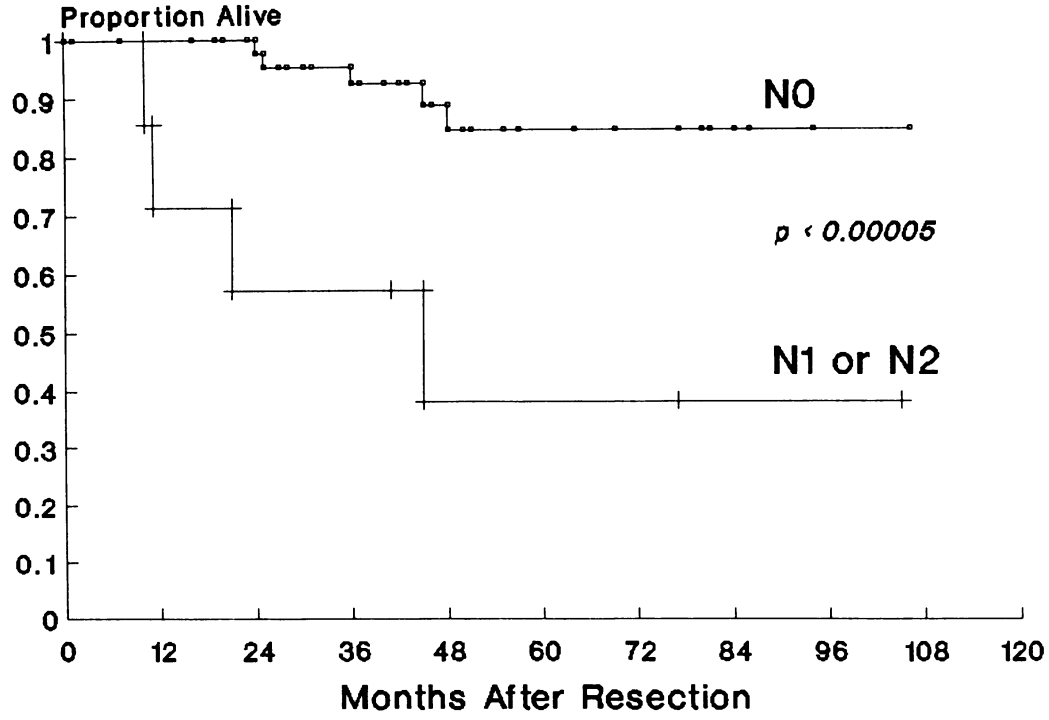

FIG. 4. Postoperative disease-free survival distribution of early gastric cancer patients according to lymph node status. N0, lymph nodes free of metastasis. N1 or N2, metastasis in first or second echelon of regional lymph nodes (Kaplan–Meier plots).

vival in this disease lies in our ability to detect and treat these lesions at an early stage. Because mass screening for this disease is not practical in the United States, other methods of early detection must be sought.

It is evident from this series that a prerequisite for the discovery of an early gastric lesion is the presence of symptoms referable to the upper gastrointestinal tract, *i.e.*, epigastric pain or dyspepsia, because 95% of our patients presented in this manner. Such nonspecific symptoms, particularly during the sixth or seventh decade of life, should not be regarded routinely as benign, non-neoplastic disease and, if persistent, should warrant investigation. In fact more than one third of the patients in this series had pre-existing benign gastric disease that prompted surveillance studies; these studies led to early diagnosis of their cancer. Therefore select screening of high-risk patients, including those with symptoms referable to the upper gastrointestinal tract, and careful follow-up evaluation of patients with seemingly benign gastric disease should improve the detection rate of early gastric cancer.

The diagnostic accuracy of radiographic evaluation was 17% and endoscopic evaluation was 86% in this series. The low yield of radiologic diagnosis is due to the fact that double-contrast thin barium examination was not used routinely. Endoscopy is the procedure of choice and should be performed on all patients in whom the diagnosis of gastric cancer is suspected. Not all early cancers are fluoroscopically visible and minute lesions can be missed even by double-contrast radiography. Malignancy associated with what appeared to be chronic gastric ulcer was prevalent in this series. This observation emphasizes the importance of repeated endoscopy and multiple biopsy specimens in the management of patients with benign gastric lesions, especially because the radiographic and endoscopic appearances of some early gastric cancers may mimic those of benign disease. It is worth remembering that as has been reported by others[15] and also observed in our study, ulcerating gastric carcinomas as well as benign gastric ulcers may heal with the administration of antacids and H2-receptor antagonists.

In our series early gastric cancer assumed many variations in the site, macroscopic appearance, size, and degree of histologic differentiation. However a high incidence of type III excavated lesions was noted and nearly one half of all tumors in our patients were located in the body of the stomach. These two phenomena have been reported in the Japanese literature.[16] Significant prognostic variables found to favor survival in these patients included small tumor size, lack of submucosal invasion, and negative lymph node status. Depth of invasion has been shown to be of the highest prognostic significance, followed by lymph node metastases, in many Japanese and Western studies. Because the small (diameter measuring less than 2 cm), protruded (type I) intramucosal lesions rarely have lymph node metastases, endoscopic resection by cautery snare has been advocated, particularly for elderly patients.[17]

The extent of lymphadenectomy remains a controversial issue in the management of early gastric cancer. In Japan the standard treatment policy for all potentially curable patients with gastric carcinoma is radical resection, including extensive lymphadenectomy. This policy is applied to early as well as advanced gastric cancer; substantial increases in survival time have been reported.[18–20] Approximately 90% of early gastric cancers are reported to be node negative.[10,21] The 5-year disease-free survival rate of node-negative patients was 86.7% in our series. However about 10% of patients in most series of early gastric cancer have shown lymph node metastasis,[10,21] and this was encountered in 8 of 60 patients in our study. Three of these eight patients survived after resection with lymphadenectomy. Two of these eight patients had metastatic deposits in second-echelon (N2) nodes. The risk of lymph node involvement was slightly greater with tumors showing submucosal invasion (23.8%) than with intramucosal lesions (7.7%). Because of the possibility of N2 metastasis, even with accurate knowledge of the depth of invasion (Table 1), selective performance of simple or R1 gastrectomy for mucosal lesions and extended lymphadenectomy (R2) for tumors showing submucosal invasion is not justified. We think an aggressive surgical approach including extended lymphadenectomy should be used for all early gastric cancers if there is potential for cure. The only exception may be the small protruded (type I) intramucosal lesion that can be removed by endoscopic cautery snare, particularly in frail patients. The benefit of extended lymphadenectomy as applied to all stages of curable gastric cancer must be proved by prospective randomized clinical trial. However the surgeon who treats an early gastric cancer needs to consider that even though the cure rate is high, up to 10% of these tumors have lymph node metastases and that such metastases may be present in a second-echelon lymph node. At least for this reason, extended lymphadenectomy (R2) should be performed for these highly curable patients.

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