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Gastric Carcinoma Confined to the *Muscularis Propria*: How Can We Detect, Evaluate, and Cure Intermediate-Stage Carcinoma of the Stomach?

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OBJECTIVE: The most important surgical strategy for advanced gastric cancer is its detection at the curative stage. The aim of this study was to characterize the curable intermediate-stage gastric carcinomas.

METHODS: Of 1120 consecutive patients who underwent gastric resection for primary gastric cancer from 1979 through 1996, 94 patients were histologically diagnosed as having cancer confined to the muscularis propria (mp cancer), analyzed clinicopathologically, and compared with patients with early and serosal cancers.

RESULTS: The operative incidence of mp cancer was around 8% among cases of gastrectomy, and the ratio of mp cancer to advanced cancer began to increase in 1991. Mp cancer was at a statistically intermediate stage, between early and serosal cancers in terms of symptoms, surgical curability (96%), size and histology of the tumor, and the rate of lymph node metastasis (46%). Preoperative assessments of tumor depth were unclear using radiology and endoscopy; however, 35% of 31 cases studied were diagnosed precisely by endoscopic ultrasonography (EUS). Accuracy of lymph node metastasis diagnosis was the same (65%) by preoperative EUS and by surgeon; however, sensitivity of the surgeon's assessment was higher (69% *vs* 38%) and specificity of EUS was higher (83% *vs* 39%). The 5-yr survival rate was 85%, which was significantly better than that of serosal cancer and similar to that of early cancer. Patient outcome was not affected by lymph node metastasis or macroscopic type of tumor.

CONCLUSIONS: Mp cancer should be considered an intermediate-stage cancer. Surgery with level 2 lymph node dissection should provide a cure rate similar to that for early cancer. (Am J Gastroenterol 1999;94:2251–2255. © 1999 by Am. Coll. of Gastroenterology)

INTRODUCTION

The standard treatment for gastric cancer is gastrectomy with lymph node dissection (1). The extent of surgery should depend on preoperative and intraoperative assessments of tumor invasion and nodal metastasis. The lower the stage of a tumor, the more likely that surgery will cure the cancer. Although early gastric cancer has been recognized as curable by surgical treatment, advanced cancer has a poor prognosis (2).

Advanced gastric cancer confined to the muscularis propria (mp cancer) is considered to be an intermediate-stage carcinoma, between early and more advanced cancer from both the pathological and clinical viewpoints of the primary tumor stage (pT categories) (3, 4). However, the clinical aspects of mp cancer are not completely understood because of its rarity and a history of poor clinical surveillance.

The aim of this study was to characterize curable advanced carcinoma according to T stage by obtaining clinicopathological findings of mp cancer based on a large series of patients who underwent standard surgery followed by thorough pathological evaluation.

MATERIALS AND METHODS

From 1979 through 1996, 1120 consecutive patients underwent gastric resection for primary gastric carcinoma in the First Department of Surgery, Kyushu University Hospital. Records of specific preoperative studies, intraoperative findings, postoperative pathological staging, clinical management, and follow-up data were prospectively recorded.

The surgically resected stomach was opened and fixed in 10% buffered formalin as preparation for histological diagnosis. The entire tumor and surrounding gastric wall of mp cancer and early cancer were serially sectioned to exclude understaging of serosal cancer (2). By these procedures, 94 patients (8.4%) were histologically diagnosed as having mp cancer and became the subject group of this study. The clinicopathological and prognostic data of these patients were compared with those of the remaining 1026 patients, of whom 611 had early cancer and 415 had serosal cancer.

Pathological diagnosis and classifications were evaluated according to the General Rules for the Gastric Cancer Study in Surgery and Pathology of Japan (5). Each tumor was macroscopically classified into Borrmann type cancer (6) or

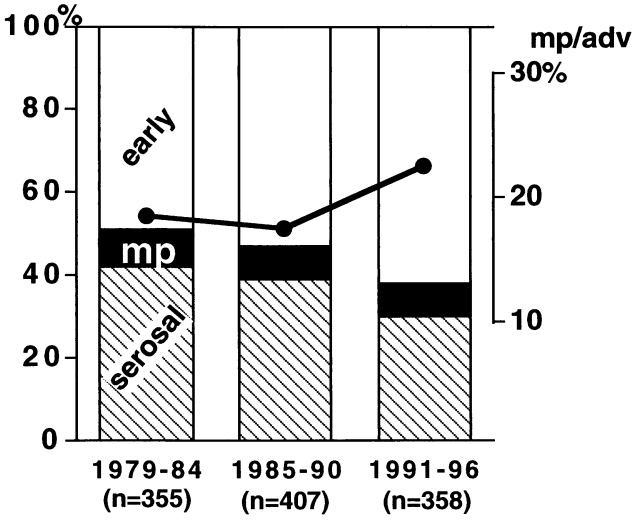

Figure 1. Chronological changes in the rate of patients with early, muscularis propria (mp), and serosal gastric cancer. The ratio of the number of patients with mp cancer to those with advanced cancer including mp and serosal cancers (mp/adv) increased over the last 5 yr.

simulating early cancer (7). Borrmann type cancer includes polypoid, ulcerating circumscribed, ulcerating infiltrative, and diffusely infiltrative tumors; simulating early cancer includes tumors grossly resembling early gastric cancer but histologically confirmed to show invasion beyond the submucosa.

Discrete variables were compared using the χ^2 test and Fisher's exact probability test, as appropriate, and continuous variables were compared using the Mann-Whitney U test. The follow-up study was performed using census-register certificates or outpatient records. The mean period of follow-up was 37 months, ranging from 1 to 193 months. Survival curves were calculated by the Kaplan-Meier method. Differences in survival curves were measured using the log-rank test. Statistical significance was assumed for p values <0.05.

RESULTS

The operative incidence of mp cancer was around 8% during the period of the study (Fig. 1). The number of early cancer patients gradually increased over time, whereas the number of advanced cancer patients decreased; however, the frequency of mp cancer among advanced cancers was 18% during 1979–84, 17% during 1985–90, and 22% during 1991–96.

The clinicopathological data of early cancer, mp cancer, and serosal cancer are summarized in Table 1. The mean age of patients with mp cancer was 61.6 yr, and the male:female ratio was 2.9:1. Age and gender distribution did not differ among the three groups.

Sixty of the 94 patients with mp cancer presented with some symptoms, whereas 34 were asymptomatic (Fig. 2). The symptomatic patients (63%) complained of epigastric pain (29%), general fatigue (9%), abdominal discomfort (8%), appetite loss (5%), nausea or vomiting (3%), abdominal fullness (2%), or other (7%). The mean duration of symptoms in patients with mp cancer was 3.2 months, which was between the 2.4 months and 3.8 months in those with early cancer and serosal cancer, respectively (Table 1). Among the asymptomatic group, detection of mp cancer was made by a mass screening program in 22 asymptomatic patients or by gastrointestinal screening during the treatment of other diseases in 12 patients.

All mp cancer patients preoperatively underwent both double-contrast barium meal radiography and endoscopy with biopsy. Radiological and endoscopic diagnosis of early cancer was made in 31 (35%) and 37 patients (39%), respectively, whereas advanced cancer was diagnosed in 63 (67%) and 57 patients (61%), respectively.

Distal or proximal gastrectomy was performed in 74 patients with mp cancer, and total gastrectomy was performed in the remaining 20 mp cancer patients. Both procedures were combined with at least level 2 lymph node dissection (D2). Splenectomy or distal pancreatectomy was added in nine patients. Operative mortality, defined as death within 30 days of surgery, was 1%. Postoperative recovery was uneventful in all but one patient, who died of myocardial infarction soon after surgery.

Surgical curability, defined as macroscopically complete removal of the tumor with no peritoneal spread, liver metastasis, or level 3 lymph node metastasis, was obtained in 90 patients (96%). In four patients, the resection was estimated to be absolutely or relatively noncurative because of $\geq$level 3 lymph node metastasis in three patients and hepatic metastasis in 1 patient.

The mp cancer was in the distal third of the stomach in 38 patients, the middle in 43, and proximal in 12. The mean diameter of mp cancer was 4.5 cm, and one tumor measuring 21 cm in diameter was widespread, reaching beyond the trisection boundaries of the stomach. Tumors were macroscopically classified into Borrmann type cancer in 58 patients and early-simulating advanced cancer in 36 patients.

Histologically, mp cancers were well differentiated adenocarcinoma in 29 patients, moderately differentiated in 28, and poorly differentiated in 37. Although the distribution showed no significant difference between the three groups, depth of invasion, increase in tumor size, and decrease in histological differentiation were correlated.

Lymph node metastasis was identified histologically in 39 (46%) of 85 patients studied, comprising level 1 metastasis in 27 patients, level 2 in 10, and level 3 in two. Patients with mp cancer had a significantly higher rate of positive metastasis than those with early cancer and a significantly lower rate than those with serosal cancer. On the TNM classification, all patients showed M0 cancer, but one with M1 cancer died on day 412 postoperatively. Five-year survival rates of T2M0 patients with N0, N1, and N2 cancers were

Table 1. Clinicopathological Data and Comparisons Between Patients With Early, mp, and Serosal Cancer

	Early Cancer (n = 611)	*p* Value	mp Cancer (n = 94)	*p* Value	Serosal Cancer (n = 415)
Age, yr (mean ± SD)	61.2 ± 11.5	NS	61.6 ± 12.0	NS	59.8 ± 12.6
Gender (male:female)	427:185	NS	70:24	NS	273:142
Presenting features					
Asymptomatic	327 (54%)	<0.01	34 (36%)	<0.01	58 (14%)
Symptomatic	278 (46%)		60 (64%)		352 (86%)
Duration (mean ± SD)	2.4 ± 4.0 mo	<0.01	3.2 ± 3.5 mo	NS	3.8 ± 5.5 mo
Unknown	6				5
Type of operation					
Total gastrectomy	93 (15%)	NS	20 (21%)	<0.01	201 (48%)
Distal gastrectomy	500 (82%)		73 (78%)		214 (52%)
Proximal gastrectomy	11 (2%)		1 (1%)		
Partial gastrectomy	7 (1%)				
Operative mortality	2/611 (0.3%)	NS	1/94 (1%)	NS	3/415 (0.7%)
Surgical curability	609/611 (99%)	<0.01	90/94 (96%)	<0.01	304/415 (73%)
Site of tumor					
Upper third	62 (10%)	NS	12 (13%)	NS	79 (19%)
Middle third	319 (52%)		43 (46%)		171 (41%)
Lower third	230 (38%)		38 (40%)		141 (34%)
Entire stomach			1 (1%)		24 (6%)
Size of tumor (mean ± SD)	3.1 ± 2.2 cm	<0.01	4.5 ± 2.5 cm	<0.01	7.5 ± 3.6 cm
Histological type					
Well diff.	309 (51%)	<0.01	29 (31%)	<0.01	70 (17%)
Moderately diff.	99 (16%)		28 (30%)		92 (22%)
Poorly diff.	203 (33%)		37 (39%)		247 (60%)
Other					6 (1%)
Lymph node metastasis					
	(n = 537)		(n = 85)		(n = 371)
Positive	35 (7%)	<0.01	39 (46%)	<0.01	277 (75%)
Negative	502 (93%)		46 (54%)		94 (25%)
5-yr prognosis	93.1%	NS	85.0%	<0.01	57.0%

diff = differentiated adenocarcinoma; NS = no significant difference; mo = months.

92%, 96%, and 53%, respectively. No significant differences were seen.

Recently, 31 patients with mp cancer underwent endoscopic ultrasonography (EUS). Analysis of tumor depth by EUS was correct in 11 patients (35%), but eight patients were overstaged as having serosal cancer, and 12 patients were understaged as having early cancer. There were three patients with mucinous adenocarcinoma, as described by Songur *et al*. (8), all of whom were evaluated correctly as having mp cancer. Nodal metastasis was estimated to be positive in eight patients and negative in 23 by EUS. Preoperative EUS and intraoperative findings of nodal status are shown in Table 2. Sensitivities of the diagnosis of nodal metastasis by EUS and intraoperative findings were 38% and 69%, respectively, specificities were 83% and 61%, respectively, and both showed 65% accuracy. The intraoperative assessment of nodal metastasis was superior to preoperative EUS by kappa coefficient of correlation for a two-way table ($\kappa = 0.31$ *vs* $\kappa = 0.22$).

The 5-yr postsurgery survival rate of patients with mp cancer was 85.0%, which is significantly higher than that of serosal cancer and not significantly different from that of early cancer (Fig. 3). The mp cancer coocurred with coronary artery disease in six patients (with 100% of 5-yr survival rate), with chronic obstructive pulmonary disease in six (with 80% survival), with diabetes mellitus in eight (with 53% survival), and with the habit of smoking in 53 patients (with 84% survival). Incidence or prognosis related to these factors in patients with mp cancer was not significantly different from that with early cancer or serosal cancer. The 5-yr survival rates of patients with mp cancer with and without lymph node metastasis were 82% and 92%, respectively ($p = 0.47$), and those of patients with tumors macroscopically of Borrmann type and of tumors simulating early cancer were 79% and 95%, respectively ($p = 0.36$).

DISCUSSION

The findings of this study prove that gastric mp cancer is an intermediate stage between early and more advanced serosal cancer. According to the depth of invasion, there were statistically significant differences in the clinical presentation, surgical curability, size, and histology of the tumor, and in the rate of lymph node metastasis. However, the prognosis of mp cancer was superior to that of serosal cancer and was similar to that of early cancer. The recent increase in the surgical incidence of mp cancer was probably

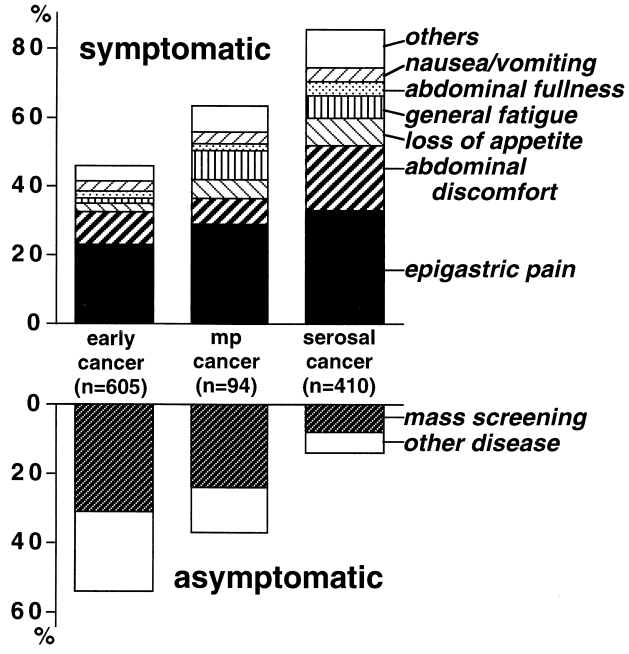

Figure 2. Presenting features in patients with early, mp, or serosal cancer. The deeper the tumor invasion, the higher the rate of symptomatic patients. More than half of the asymptomatic patients were diagnosed as having gastric cancer by mass screening.

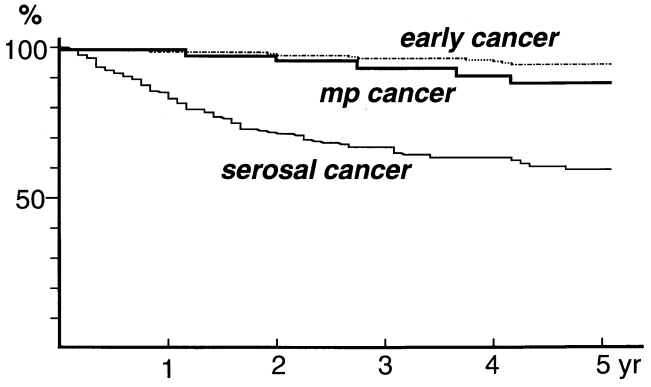

Figure 3. Cumulative survival curves of patients with early, mp, and serosal cancer. The difference in 5-yr survival rates was significant ($p < 0.01$) between patients with serosal cancer and those with mp cancer, but not ($p = 0.24$) between those with mp cancer and those with early cancer.

related to our improved clinical efforts to detect curable advanced cancer.

The issue of patient presentation has not been addressed previously because the symptoms of gastric cancer were assumed to be nonspecific (9). This study shows that paying attention to initial symptoms can provide an important contribution toward earlier detection of gastric cancer. In gastric cancer, the depth of invasion, number of symptoms related to a lesion, and time period of symptoms were correlated.

Gastric cancer is not unique to the Japanese population (10). However, the rate of its detection is high in Japan due to the prevalence of upper gastrointestinal screening not only for symptomatic patients but also for asymptomatic patients seeking medical advice for other diseases. Although a mass screening program might be impractical in Western countries, given the lower incidence of gastric cancer (11), it should be beneficial in Japan for early detection of intermediate-stage cancers, such as those described in this study.

Previous studies showed 5-yr postsurgery survival rates for patients with mp cancer varying from 60% to 82%, with a nodal metastasis incidence from 45% to 52%, both of which are similar to the present series. We found a 5-yr survival rate of 85% in patients with mp cancer, which was significantly better than that of serosal cancer and was similar to that of early cancer. The superior patient outcome was attained irrespective of lymph node metastasis or macroscopic type, a tendency also previously reported in early cancer (2). Yoshikawa and Maruyama (3) showed that liver metastasis was the most frequent mode of fatal recurrence of mp cancer after surgery.

Endoscopy and radiology, as well as computed tomography (CT) do not offer sufficient information for preoperative staging of advanced gastric cancer (12, 13), which is important for making surgical decisions concerning the extent of gastrectomy and nodal dissection. EUS is now expected to diagnose the depth of tumor invasion and lymph node status (13, 14). EUS diagnoses of gastric cancer were reported to have merits for echogenic mucinous tumor (8), as shown in this series, but shortcomings for ulcerated tumor (15). Moreover, the evaluation of nodal metastasis by EUS would still have to be limited to the perigastric region and depend on the size of the lymph nodes. EUS alone can not be used to evaluate nodal status without biopsy, and EUS criteria to differentiate benign and malignant nodes are not yet well defined (16). All these factors may have contributed to the low diagnostic sensitivity of EUS demonstrated in this study. Further technological improvements in EUS are needed to attain better diagnostic reliability.

Concerning surgery for gastric cancer, there has been controversy recently concerning the efficacy of D1 or D2

Table 2. Comparisons of Histological, EUS, and Intraoperative Findings of Regional Lymph Node Metastasis

Histological Finding	EUS Diagnosis			Intraoperative Diagnosis		
	Positive	Negative	Total	Positive	Negative	Total
Positive	5	8	13	9	4	13
Negative	3	15	18	7	11	18
Total	8	23	31	16	15	31

EUS = endoscopic ultrasonography.

dissection and the adequacy of minimal or extended gastric resection (1, 17). Gastrectomy with D2 dissection for mp cancer proved to be appropriate and sufficient in this study. Without a device to diagnose the precise level of the mural and nodal involvement, the surgical approach must rely on the comprehensive and combined assessments by radiology, endoscopy with biopsy, EUS, and intraoperative findings.

CONCLUSIONS

In summary, mp cancer, which remains classified as advanced cancer, should be regarded clinicopathologically as an intermediate-stage carcinoma, between early and serosal cancers. Patients with mp cancer should undergo surgery with D2 dissection, as is common for advanced cancer, they would then have a greater chance of cure, comparable to that for early cancer. Continuous efforts to detect mp cancer should lead to a better outcome for patients with advanced gastric cancer.

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