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Clinicopathologic Prognostic Features in Patients with Gastric Cancer Associated with Esophageal or Duodenal Invasion

Takashi Yokota, Yasou Kunii, Shin Teshima, Yasuo Yamada, Toshihiro Saito, Michinori Takahashi, Shu Kikuchi and Hidemi Yamauchi

Department of Surgery, Sendai National Hospital, Miyagino-ku, Sendai 983-8520, Japan

ABSTRACT

Background

We evaluated the influence of several clinicopathologic variables on 5-year survival of patients with gastric cancer associated with esophageal or duodenal invasion, and determined the significance of resection line involvement.

Patients and Methods

A review of the database for gastric adenocarcinoma at Sendai National Hospital between January 1985 and December 1995 identified 923 patients who underwent gastric cancer resection. Of these patients, 37 were reported to have tumour infiltration of the esophagus or duodenum on histological examination of the resected specimens. Univariate and multivariate analyses of patients with esophageal or duodenal invasion were performed to evaluate the prognostic significance of clinicopathologic features. Then the patients were divided into two groups based on the results of microscopic examination: a tumour wedge-positive group for resection margins of less than 5 mm in width and a tumour wedge-negative group for resection margins of more than 5 mm in width. There were 8 patients in the narrow (margin-positive) group and 29 patients in the wide margin (margin-negative) group, respectively.

Results

Univariate analysis revealed that the significant prognostic factors were nodal involvement ($p=0.0004$) and gross type ($p=0.0031$). Multivariate analysis of the esophagus or duodenum-invaded cancer cases, however, revealed that only nodal involvement was a significant prognostic factor. There were statistical correlations between these groups (margin-positive and margin-negative groups) and the Borrmann type of tumour and tumour size. The survival rate was worse in patients with tumour line involvement.

Conclusions

Multivariate analysis revealed that the prognosis of patients with esophageal or duodenal invasion was affected only by nodal involvement independently. The risk of surgical margin involvement was high in cases of a large Borrmann type-4 tumour and infiltrative carcinoma.

INTRODUCTION

Gastric cancer is still one of the leading causes of death in Japan. Numerous efforts have been made to identify prognostic variables in patients affected by cancer to predict outcome and to help define high-risk patients who may benefit from adjuvant therapy (29-35). In advanced gastric cancer, the most important prognostic factors are reported to be depth to cancer invasion and status of lymph nodal involvement (1, 14).

Esophageal invasion or duodenal invasion is common in patients with gastric cancer (11, 12, 16). Recurrence of resected gastric cancer at the esophageal or duodenal anastomosis is due to tumour remnants left behind in the resection margin (21). Although recurrence is not seen in every patient with histological marginal invasion, cases of recurrence after esophagojejunostomy or gastroduodenostomy are difficult to manage because the tumour has usually caused mediastinal involvement or invasion to organs such as the pancreas at the time of reexploration (24-27). What, if any, are the contributory factors to local recurrence? In this study, the prognostic factors in patients with esophageal or duodenal invading gastric cancer and variables associated with these factors were investigated by univariate and multivariate analyses. Theoretically, recurrence can be prevented by more extensive resection, including wider margins at the time of surgery. These considerations prompted us to evaluate the problem of the surgical margin in patients with gastric cancer associated with esophageal or duodenal invasion.

PATIENTS AND METHODS

Definitions

The resected neoplasms were classified according to the TNM system on the basis of data from the pathology and operative reports. Tumour: T1, tumour extending into the mucosa or the submucosa; T2, tumour extending into the muscularis propria or the subserosa; T3, tumour penetrating the serosa; T4, tumour penetrating through the serosa with direct invasion of continuous structures. Nodal involvement: positive or negative for metastases from the primary tumour. Metastases; MO, no distant metastases; M1, distant metastases present. The tumours were classified histologically into well-differentiated, moderately differentiated, and poorly differentiated adenocarcinoma according to the grade of glandular formation. Surgery was performed by the same team in each case. At operation, adequate proximal esophageal or distal

duodenal clearance was obtained. When cancer infiltration to the esophagus was detected preoperatively by X-ray or endoscopy, a left thoracotomy was also performed so that a sufficient surgical margin could be obtained. The surgical margin was defined as the distance from the microscopic edge of the primary lesion to the line of esophageal or duodenal transaction, as advocated by the Japanese Research Society for Gastric Cancer (10). After macroscopic examination, the specimens were fixed in 10% formalin, then sectioned and stained with hematoxylin and eosin. If cancer cells were within 5 mm of the cut edge of the proximal or distal margin, lesions were diagnosed as tumour wedge-positive. If no cancer cells were present within 5 mm of the cut edge, lesions were diagnosed as tumour wedge-negative. According to the minimal width of the surgical margin on microscopic examination, the patients were divided into two groups: a margin-positive group and a margin-negative group.

Methods

From January 1985 to December 1995, 923 patients with gastric cancer underwent gastric resection at Sendai National Hospital. The location of the tumour within the stomach influenced the type of operation performed. Patients with a tumour in the upper third or whole stomach underwent a total gastrectomy; patients with a tumour in the body of the stomach underwent a total or subtotal gastrectomy, depending on the tumour extension; and a subtotal gastrectomy was performed for patients with a distal or antral tumour. Data on age, gender, tumour size, macroscopic appearance, nodal involvement, histologic type, lymphatic invasion and vascular permeation were obtained for each patient. Data are expressed as median values ± standard error. Survival was calculated by the method of Kaplan-Meier and compared by the log rank test. Survival was calculated from the data of operation to the most recent date of follow-up examination or to the date of death. Other comparisons were made by the t test for unpaired data and the chi square test. Multivariate Cox's proportional hazard regression analysis was then performed to determine which variables were independent prognostic factors. The following independent variables were entered in the univariate analysis: gender, tumour size, gross type, nodal involvement, peritoneal involvement, histologic type, lymphatic invasion and vascular invasion. Statistical significance was defined as $p<0.05$.

The patients were examined regularly every month during the first two postoperative years and at six-month intervals thereafter. The choice of adjuvant chemotherapy was based on the clinical status of the patients. Patients with advanced cancer were prescribed 200 mg/day of oral 5-fluorouracil for as long as it could be tolerated.

Table 1. Prognostic significance by univariate analysis of various variables for patients with gastric cancer invading the esophagus or duodenum.

Variable	5-Year survival (%)	Log rank p value
Gender		0.0946
Male	32.0	
Female	13.5	
Size, diameter (cm)		0.3567
2-4.9	20.0	
>5	35.7	
Gross type		0.0031
Borrman type 2	68.6	
Borrman type 3	25.1	
Borrman type 4	0	
Borrman type 5	0	
Lymph node metastasis		0.0004
Negative	85.7	
Positive	10.0	
Peritonitis carcinomatosa		0.1074
Negative	32.7	
Positive	14.0	
Histologic type		0.4759
Intestinal type	32.5	
Diffuse type	30.0	
Lymphatic invasion		0.0503
Negative	68.6	
Positive	22.2	
Vascular invasion		0.3942
Negative	39.3	
Positive	27.3	

RESULTS

Thirty-seven patients were found to have tumour infiltration of the esophagus or duodenum on microscopic examination. These patients included 24 men and 13 women, with a mean age of 60.1 years (range, 31-84 years) at the time of surgery.

Prognostic significance by univariate and multivariate analyses

Univariate analysis was performed to evaluate significant relationship between clinicopathologic features and patient survival. Of the 8 clinical and pathologic variables entered in the analysis, two were found to have a significant influence on survival. Table 1 summarizes the results of the analysis. Unfavourable prognostic factors included Borrman type 3,4 and 5 and presence of lymph node metastasis. The 5-year survival rates of patients with Borrman type 2, 3, 4 and 5 were 68.6, 25.1, 0 and 0%, respectively. The presence of lymph node metastasis was associated with lower long-term survival rates: the 5-year survival rate of patients with nodal involvement was 10%, while that of patients without such nodal involvement was 85.7%. To account for the interrelationships among variables of 5-year survival, multivariate analysis was performed on several variables. Using Cox's proportional hazard regression model, only nodal involvement emerged as the independent statistically significant prognostic parameters associated with long-term survival (Table 2).

Surgical margin in patients with gastric cancer associated with esophageal or duodenal invasion

Of the 37 patients, 29 were placed in the margin-negative group. Histologically positive margins were found in the other 8 patients. Table 3 shows the gross type, tumour size, depth of tumour invasion, and the pathological findings in each group. The mean tumour size in the margin-positive group (11.3 cm) was significantly larger than that in the margin-negative group (6.8 cm) ($p=0.0065$). A significant difference was seen in the gross tumour appearance between the two groups; Borrmann type-4 tumours were more common in the margin positive group. Tumours penetrating the serosa with direct invasion of continuous structures were found more frequently in the margin-positive group than in the margin-negative group, although the difference was not significant ($p=0.0978$). There were no other differences, including nodal involvement, distant metastasis, or histological type, between the two groups.

Of these eight patients with histologically positive esophageal or duodenal margins, at the time of surgery, three had peritoneal dissemination, two had liver metastases, and two did not undergo full lymph node dissection because of extensive metastases. In most cases, the tumour was a poorly differentiated scirrhous adenocarcinoma accompanied by intense proliferation of fibrous connective tissue. It could not be determined whether or not the patients with

histologically involved margins would have eventually developed local recurrence, since they died soon after, due to distant metastases. Cumulative survival curves up to 70 months for both groups of patients are shown in Fig. 1. The survival curves or the two groups did not differ significantly.

Table 2. Multivariate analysis of significant prognostic factor for survival in patients with gastric cancer invading the esophagus or duodenum using Cox's proportional hazards regression model.

Variable	Relative risk	95% CI	p value
Gender (Female/Male)	0.999	0.243-4.108	0.9994
Tumour size	3.805	0.840-17.231	0.0828
Gross type	1.083	0.164-7.131	0.9340
Lymph node metastasis (positive/negative)	19.301	1.680-221.765	0.0175
Lymphatic invasion (positive/negative)	5.414	0.444-66.041	0.1857
Vascular permeation (positive/negative)	1.069	0.263-4.353	0.9258
Tumour location			0.2980
Upper/Whole	0.205	0.026-1.630	
Distal/Whole	0.350	0.033-3.757	
Peritonitis carcinomatosa (positive/negative)	6.341	0.755-53.220	0.0888

Table 3. Perioperative data of 37 patients with gastric cancer invading the esophagus or duodenum.

Variable	Margin positive (%)	Margin negative (%)	p Value
Number	8	29	
Age	60.9 ±6.0	61.0 ±2.1	p=0.9805
Gender			
Male	5 (62)	19 (66)	p=0.7948
Female	3 (38)	10 (34)	
Gross type			
Borrmann type 1	0 (0)	0 (0)	p=0.0023
Borrmann type 2	0 (0)	11 (38)	
Borrmann type 3	1 (13)	13 (45)	
Borrmann type 4	6 (74)	4 (14)	
Borrmann type 5	1 (13)	1 (3)	
Tumour size (cm)	11.3 ±2.2	6.8 ±0.5	p=0.0065
Depth of invasion[1]			
T1 (m, sm)	0 (0)	0 (0)	p=0.0978
T2 (mp, ss)	0 (0)	10 (34)	
T3 (se)	2 (25)	8 (28)	
T4 (si)	6 (75)	11 (38)	
Nodal involvement			
Negative	0 (0)	8 (29)	p=0.1779
Positive	7 (100)	20 (71)	
Unknown	1	1	
Distant metastasis			
M0	4 (50)	11 (38)	p=0.8345
M1	4 (50)	18 (62)	
Microscopic type			
Well-differentiated	0 (0)	7 (26)	p=0.2222
Moderately	3 (38)	10 (37)	
Poorly	5 (62)	10 (37)	
Unknown	0	2	

[1] Tumor extends into the mucosa (m), submucosa (sm), muscularis propria (mp) or subserosa (ss). Tumor penetrates the serosa (se). Tumor penetrates through the serosa with direct invasion of continuous structures (si).

DISCUSSION

The aim of the present study was to review at our institution the experience of gastric cancer associated with esophageal or duodenal invasion in order to determine the influence of several clinicopathologic variables on outcome. Nodal involvement and gross type were associated with survival of patients in univariate analysis, but the latter was not a significant factor in multivariate analysis. In the multivariate analysis, the statistically significant prognostic factor was nodal involvement. The results reported here are in agreement with previous reports that have analyzed various clinical, pathologic and therapeutic variables to identify prognostic indicators. In advanced gastric cancer, depth of invasion and status of lymph node metastasis have been reported to be prognostically important, and these factors are related to the staging of gastric cancer (1,14). In this study, there is only one gastric cancer case invading the muscularis propria of the stomach and statistical analysis including depth of invasion could not be performed.

The failure of surgical treatment to cure gastric cancer is caused by two factors: (a) the development of distant metastases, e.g., involvement of the regional lymph nodes of the stomach, peritoneal dissemination, or metastases to other organs; and (b) failure to remove the primary lesion with an adequate tumour-free margin around it. Failure of cure due to surgical margin involvement implies that the surgeon did not do all that was possible at the time of surgery. In this study, we examined the problem of the surgical margin in patients with gastric cancer associated with esophageal or duodenal invasion. The risk of tumour remnants being left behind in the resection margin during surgery was found to be related to the clinicopathological features of the patients. According to our data, the risk of surgical margin involvement depended mainly on the size of the primary tumour, its macroscopic appearance, and the depth of cancer invasion.

Marginal involvement was significantly more frequent among patients with a Borrmann type-4 tumour than with other types of gastric cancer. However, the differences between the various stages and histological types of cancer were not statistically significant. Borrmann type-4 gastric cancer reportedly has the ability to cause widespread intramural invasion of the esophagus as a squamous esophageal primary carcinoma (9,13,20). Surgeons have traditionally used palpation of the esophageal margin to determine the adequacy of the resection. Frozen section examination of the esophageal margin cannot determine the adequacy of resection accurately, since the microscopic spread of scirrhous carcinoma cells in Borrmann type-4 tumours can be either continuous with or discontinuous from the primary lesion, forming skip submucosal foci. The histologic techniques for diagnosis during surgery still consist of methods using dyes such as hematoxylin and eosin. In most cases, cells stained with hematoxylin and

eosin can be identified as malignant by standard cytologic criteria. In the case of scirrhous carcinoma of the stomach, however, the malignant cells are dispersed and resemble reactive inflammatory cells.

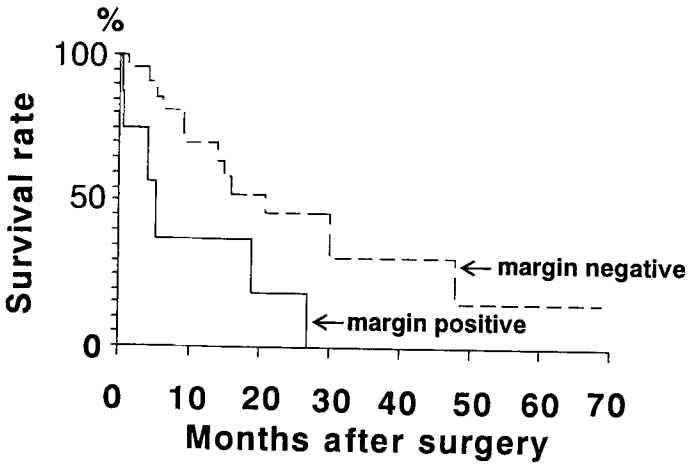

Figure 1. Cumulative survival curves for patients with and without histologically positive margins. The survival was worse in those with tumour line involvement, but it was not significantly.

Bozzetti et al. (2) reported that 11% of proximal margins were positive after resection for proximal gastric cancer. This was significantly higher compared to the 1.7% for those specimens resected for distal gastric cancer. According to Papachristou and Fortner, 25% of patients who undergo gastrectomy for gastric cancer eventually develop local recurrence (22). It is difficult to determine the true incidence of local recurrence since not all patients die from cancer following surgery and since some patients die with subclinical recurrence that is never discovered. Papachristou et al. (23) observed that positive margins affected only those patients with stage I or II disease, whereas patients with stage III or IV lesions were unaffected by a positive margin, dying of distant disease. In addition, 23% of their 51 patients with a tumour at the surgical margin lived long enough to have recurrence at anastomosis. Patients with early-stage disease live longer and have a greater chance of developing recurrence at anastomosis, thus explaining why local recurrence is more common in patients with early rather than advanced lesions. McNeer et al. (19) reported that most recurrences of gastric cancer occurred within 22 months after surgery and that residual stomach or gastric stump recurrences had a higher rate of late

occurrence than did hepatic or peritoneal lesions. Iwanga et al. (8) also reviewed the incidence of residual cancer in the gastric stump after radical surgery, and they found that the procedure had failed to control the disease in 5% of cases.

As we believe that resection offers the best cure or palliation for patients with gastric cancer, most of the operations were performed on patients with advanced disease, including those with nodal involvement, peritoneal dissemination, and liver metastases (3,17). Inevitably, in most of these patients, residual tumours were present in the abdomen after resection, and this would have increased the overall incidence of local recurrence (15,18,28). These residual tumours usually take some time to reach a sufficient size to compress the gastrointestinal tract, by which time widespread metastases are already evident. Anticancer drugs should be given to suppress the proliferation of residual tumour cells. In the current series, margin positivity was translated into a negative predictor of survival for gastric cancer associated with esophageal or duodenal invasion. Among the causes of failure of cure following an operation, surgeons are particularly responsible for local recurrence due to resection margin involvement (4-7). It is therefore important to identify both the causes and clinical associations of histologically positive surgical margins.

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Address correspondence to:
Takashi Yokota, M.D.
Department of Surgery, Sendai National Hospital
Miyagino-ku, Sendai 983-8520
Japan
E-mail address: yokoyoko@jun.ncvc.go.jp