



Original article

Involvement of three or more lymph nodes predicts poor prognosis in submucosal gastric carcinoma

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Abstract

Background. Multivariate analyses has shown that the status of lymph node metastasis and the depth of tumor penetration through the gastric wall are the most important prognostic factors in patients with advanced gastric carcinoma after curative operation. A clinicopathological study was carried out to clarify a simple and optimal prognostic indicator for early gastric cancer.

Methods. Retrospective analyses of 982 patients with early gastric cancer (562 with mucosal [M] and 420 with submucosal [SM] tumor) treated by gastrectomy with D2 lymph node dissection were performed.

Results. The incidence of lymph node metastasis from M and SM tumors was 2.5% (14/562) and 20.2% (85/420), respectively. There were no apparent prognostic indicators in patients with M tumors. In patients with SM tumors, the cancer-specific 5-year survival of those with lymph node metastasis was significantly lower than that of those without such metastasis (77.6% vs 98.2%; $P < 0.001$). An sharp decrease in survival was seen between patients with two positive nodes and those with three positive nodes, and the cancer-specific 5-year survival rate of patients with three or more metastatic lymph nodes was significantly lower than that of those with one or two nodes ($P < 0.001$; univariate analysis). Multivariate analysis revealed that the involvement of three or more lymph nodes was the sole independent prognostic determinant ($P = 0.016$); the level of nodal metastasis was not an independent prognostic factor ($P = 0.384$). All patients with N2 lymph node echelons (according to the Japanese Research Society for Gastric Cancer classification of the draining lymph nodes of the stomach) in the group with one or two positive nodes survived for more than 5 years.

Conclusion. The sole independent prognostic factor in SM gastric cancer is the involvement of three or more metastatic lymph nodes. We suggest that this simple prognostic indicator for the follow-up of early gastric cancer, and this could lead to potentially effective adjuvant chemotherapy.

Key words Early gastric carcinoma · Lymph node metastasis · Prognostic factor · Surgery · Adjuvant chemotherapy

Introduction

It is well known that the status of lymph node metastasis and the depth of penetration of the tumor through the gastric wall are the most important prognostic factors in patients with gastric carcinoma after curative operation [1–4]. A strong correlation has been demonstrated between survival rates and lymph node status (such as the number and the extent of positive lymph nodes) in patients with advanced cancer [5–10]. The staging of lymph node metastasis in gastric cancer has generally been determined by the extent of positive lymphatic stations. The Japanese Research Society for Gastric Cancer has classified the draining lymph nodes of the stomach and assigned 16 different lymphatic stations [11]. The nodes are then assigned to one of four echelons, as N1–N4, and this Japanese rule is considered to reflect the anatomical pathway of lymphatic spread. On the other hand, in the Union Internationale Contre le Cancer (UICC) tumor node metastasis (TNM) system, the method for evaluation of regional lymph node metastasis in gastric cancer, established in 1987 [12], was revised in 1997 and simply classified according to the number of metastatic lymph nodes (new TNM system) [13].

Recently, it has been noted that the Japanese lymph node staging system, based on the anatomic level of the invaded lymph nodes, yields less prognostic information than the new UICC lymph-node staging system, which is based on the number of invaded lymph nodes [14–16]. However, to examine lymph node status as a prognostic factor, it is necessary to analyze gastric carcinomas without serosal invasion in a large cohort study. In such a study, a clear prognostic predictor of lymph node status

could be determined, and this could lead to effective adjuvant chemotherapy for patients with early gastric cancer who have a high risk of recurrence. To establish a clear prognostic factor, it is imperative to elucidate which factor, i.e., the level (extent of anatomic location) or the degree (number of metastatic lymph nodes) of positive nodes, is closely related to prognosis in early gastric cancer patients with lymph node metastasis.

In the present study, we extensively analyzed the relationship between lymph node status and prognosis in approximately 1000 patients with early gastric cancer, and, in the light of our findings, we propose a simple and optimal prognostic indicator of early gastric cancer after curative operation.

Patients and methods

From 1980 to 1995, 2117 patients with no evidence of any other malignancy underwent gastric resection for primary gastric carcinoma at the Second Department of Surgery, Kumamoto University Hospital, and at the Department of Surgery, Kumamoto Regional Hospital. The results of specific preoperative studies, intraoperative findings, postoperative pathologic staging, clinical management, and follow-up data were registered prospectively, and informed consent was obtained from all patients.

Pathologic diagnosis and classifications were based on the *Japanese classification of gastric carcinoma* of the Japanese Research Society for Gastric Cancer [11]. The macroscopic features of each gastric cancer were classified in terms of type and size. The surgically resected stomach and dissected lymph nodes were fixed in 10% buffered formalin in preparation for histologic diagnosis with standard hematoxylin and eosin staining. The entire tumor and surrounding gastric wall were sliced to about 5-mm in width and sectioned to exclude advanced disease that had been clinically understaged. One single slice of each dissected lymph node, obtained by a cross-section through the hilus at the central portion, was examined. Using this method, 1051 patients (49.6%) were histologically diagnosed as having early gastric carcinoma. Lymph node stations, numbered 1–14 were palpated and evaluated during surgery. Lymph node stations were designated as group 1, 2, or 3 according to the extent from the primary tumor [11]. In all patients, group 1 and group 2 lymph nodes were removed (D1 and D2 gastrectomy, respectively). Gastrectomy with D2 lymph node dissection was performed in 982 patients (93.4% of the patients with early gastric cancer); these patients formed the subject group of this study. Tumors were classified macroscopically into two types: elevated or depressed. Histopathologically, papillary adenocarcinoma and tubular adenocarcinoma were

grouped together as differentiated-type adenocarcinoma, whereas poorly differentiated adenocarcinoma and signet-ring cell adenocarcinoma were regarded as undifferentiated-type adenocarcinoma. Multiple early carcinoma lesions were observed in 87 patients (8.9%). In these patients, the deepest or largest tumor was adopted as the representative lesion.

Statistical analyses were performed, using univariate analysis and multivariate analysis, to identify independent prognostic factors for survival in the submucosal (SM) cancer patients with lymph node metastasis. In the univariate analysis, cumulative survival rates were calculated using the Kaplan-Meier approach. In the multivariate analysis, independent prognostic factors for survival were determined using a Cox proportional hazards model. Follow-up data were obtained from census register certificates or outpatient records (range of follow-up, 60–240 months). The cumulative cancer-specific 5-year survival rate was calculated by the Kaplan-Meier method, and survival curve differences were measured with the log-rank and Breslow-Gehan-Wilcoxon tests. Statistical significance was assumed for *P* values of less than 0.05.

Results

Pathological examination showed that, of the 982 early gastric patients with D2 dissection, 562 had mucosal (M) tumors and 420 had submucosal (SM) tumors. The total number of dissected lymph nodes from D2 dissection for each patient with early gastric cancer was 32.8 ± 16.4 (mean \pm SD), with 21.8 ± 9.3 group 1 lymph nodes and 11.0 ± 7.9 group 2 lymph nodes. The proportion of patients with 15 or more dissected lymph nodes was 98.5%. The incidence of lymph node metastasis from M and SM tumors was 2.5% (14/562) and 20.2% (84/420), respectively (Table 1). The mean number of positive lymph nodes was 2.7 ± 2.8 . Detailed pathological analysis revealed that all M tumors with lymph node metastasis had an ulcer or ulcer scar in the lesions, even if these tumors were smaller than 1.5 cm in diameter, whereas no M tumors without an ulcer or ulcer scar had any lymph node metastasis. There was no relationship between lymph node status and prognosis in patients with M tumors. Of the 14 patients with M tumor involving lymph nodes, only 1 patient died of cancer, caused by hematogenous recurrence (Table 1).

In patients with SM tumors, the cancer-specific 5-year survival of those with lymph node metastasis was significantly lower than that of those without lymph node metastasis (77.6% vs 98.2%; *P* < 0.001) (Table 1). To determine the clinicopathological factors that significantly influenced the cancer-specific 5-year survival, we performed univariate analysis of the data for SM tumor

Table 1. Lymph node metastases and cancer deaths in patients with early gastric carcinoma treated by D2 gastrectomy

	No. of dissected lymph nodes	Cancer-specific 5-year survival rate (%)	Cancer death	Recurrence mode		
				Hematogenous	Lymphatic	Peritoneal
Mucosal tumors	562					
Node positive (%)	14 (2.5)	92.9*	1	1	0	0
Node negative (%)	548 (97.5)	98.9*	6	6	0	0
Submucosal tumors	420					
Node positive (%)	85 (20.2)	77.6**	19	14	3	2
Node negative (%)	335 (79.8)	98.2**	6	5	0	1

*Not significant; ** $P < 0.001$

Table 2. Univariate analysis of clinicopathological factors in submucosal gastric cancer patients with lymph node metastasis

	No. of patients	No. of deaths	Cancer-specific 5-year survival (%)	P value
Sex				
Male	51	12	76.5	0.716
Female	34	7	79.4	
Age (years)				
<60	28	7	75.0	0.678
≥ 60	57	12	78.9	
Tumor size (cm)				
<3	25	5	80.0	0.898
<5	40	9	77.5	
≥ 5	20	5	75.0	
Gross type				
Elevated	15	6	60.0	0.083
Depressed	70	13	81.4	
Histological type				
Differentiated	47	10	78.7	0.763
Undifferentiated	38	9	76.3	
Level of positive lymph node				
N1	65	11	83.1	0.022
N2	20	8	60.0	
No. of positive lymph nodes				
1 and 2	52	5	90.4	<0.001
≥ 3	33	14	57.6	

patients with lymph node involvement. Univariate analysis showed that the 5-year survival of SM cancer patients with lymph node involvement was significantly related to both the number and the level of metastatic lymph nodes ($P < 0.001$ and $P = 0.022$, respectively) (Table 2). To determine which of these lymph node status parameters was the best prognostic factor, we performed multivariate analysis. Surprisingly, the multivariate analysis revealed that the number of positive nodes was the sole significant prognostic determinant in patients with early gastric cancer that had invaded the SM ($P = 0.016$), while the nodal level was not a significant prognostic factor ($P = 0.384$) (Table 3). This is probably because all patients with N2 in the group with one or two positive nodes survived for more than 5 years.

A decreased survival rate was associated with an increased number of positive nodes in all of the subjects (Fig. 1). A sharply significant decrease in survival was seen between patients with two positive nodes and those with three positive nodes ($P = 0.041$), while there was little difference in the survival rate among those with none (98.1%), one (95.1%), and two positive nodes (85.7%), and among those with three (57.1%) and four or more (57.9%) positive nodes (Fig. 1). The cancer-specific 5-year survival rate of patients with three or more metastatic lymph nodes was significantly lower than that of those with one or two metastatic lymph nodes ($P < 0.001$) (Fig. 2). In addition, the 5-year survival rates according to the levels of lymph node metastasis were 98.1%, 85.1%, and 61.9% for N0, N1, and N2, respectively (Fig. 3).

Table 3. Multivariate analysis indicating independent prognostic factors in submucosal gastric cancer patients with lymph node metastasis

	Coefficient of variation	Standard error	Relative risk	P value
Level of positive lymph node N1 vs N2	-0.483	0.555	-0.871	0.384
No. of positive lymph nodes 1 and 2 vs ≥ 3	-1.433	0.598	-2.398	0.016

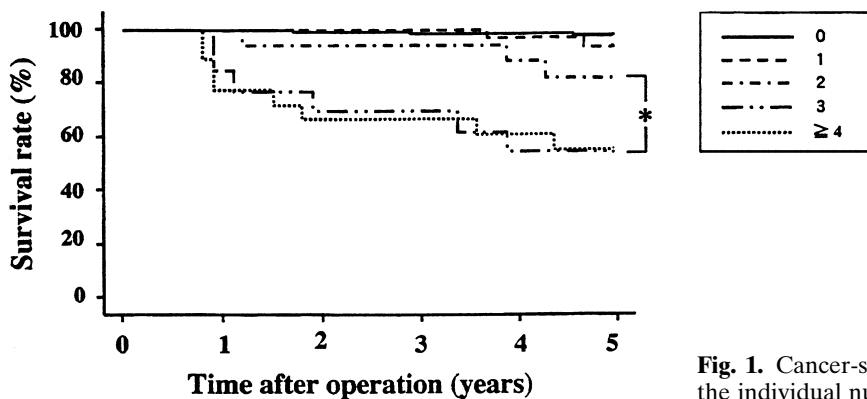


Fig. 1. Cancer-specific 5-year survival curves with regard to the individual number of positive lymph nodes * $P = 0.041$

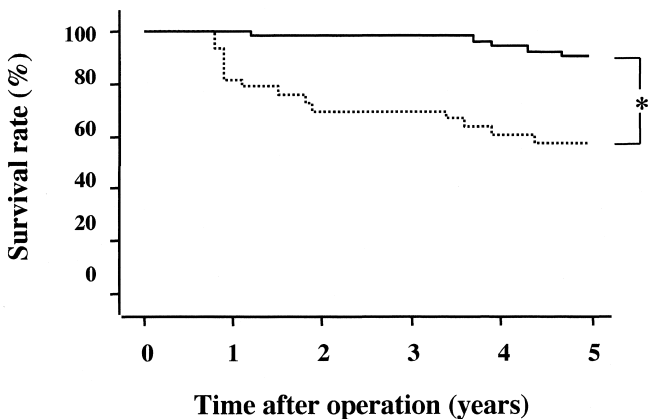


Fig. 2. Cancer-specific 5-year survival curves with regard to one and two positive lymph nodes (*continuous line*); and three or more positive lymph nodes (*dotted line*). * $P < 0.001$

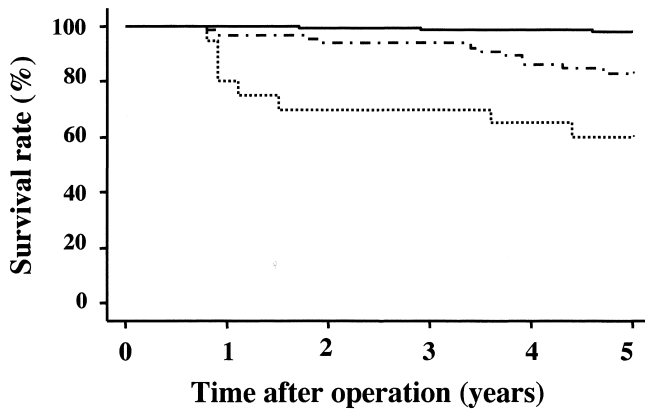


Fig 3. Cancer-specific 5-year survival curves with regard to the levels of positive lymph nodes. *Continuous line*, N0; *dashed/dotted line*, N1; *dotted line*, N2

Discussion

Patients with early gastric carcinoma generally have a good prognosis after adequate surgical resection, as evidenced by a 5-year survival rate of more than 90% worldwide [17,18]. Unfortunately, however, approximately 10% of those with early gastric cancer have recurrence. Therefore, it is very important to assess the probability of recurrence of early gastric carcinoma after a curative operation so that appropriate adjuvant

chemotherapy can be administered, so that appropriate follow-up is carried out to find recurrence of early status, and so that some prognostic information can be given to patients and their families. The oral administration of adjuvant chemotherapy has not yet been established as an effective treatment for gastric carcinoma, although recent studies have shown its effectiveness in Western countries [19].

Serosal invasion by the tumor and lymph node metastasis are well known to be the major risk factors

in the recurrence of gastric cancer [1–4]. Accordingly, in advanced gastric cancers, in which the two major risk factors coexist it may be difficult to determine a simple and clear independent risk factor for recurrence. Many authors have reported that the number of positive nodes was the most important prognostic determinant, followed by serosal invasion, and that the anatomic level of positive nodes was not a significant prognostic factor on multivariate analysis [14–16]. However, different numbers of positive nodes have been proposed as an indicator of prognosis. Therefore, in practice, a common number of positive lymph nodes that predicts a poor prognosis for gastric cancer has not yet been determined, and this uncertainty has led to inappropriate prognostic indicators for clinical use. Furthermore, some authors have reported that multivariate analyses showed independent prognostic factors to be the depth of serosal invasion and/or the anatomic level, as well as the number, of positive nodes [4,7,20,21]. These discordant results may be reflect the coexistence of two major risk factors, as mentioned above. Because the results of multivariate analysis in advanced gastric carcinoma are influenced by the sample size and by complex interactions among the variables, we believe this explains why multivariate analysis failed to show the optimal independent prognostic indicator, i.e., the clear-cut number of metastatic nodes. Therefore, in the present study, we analyzed the relationship between lymph node status and prognosis, to elucidate the optimal practical prognostic determinant for early gastric cancer. This retrospective study, in 982 patients treated by D2 operation, was conducted at two related institutes. From 1980 to 1995, we performed D2 lymph node dissection for patients with early gastric cancer, including that confined to the mucosa, in order to clarify the status of lymph node metastasis. Furthermore, because our two institutes employed the same D2 operation procedures, universal standard histological examinations, and a long follow-up system, such issues as variations in lymph node dissection procedures, the stage migration phenomenon, and insufficient long-term survival data, could be excluded.

It is well known that the depth of the tumor and the presence of lymph node metastasis has a strong positive correlation. Our recent study demonstrated that invasion of the submucosal layer was one of the major factors related to lymph node metastasis [22]. In that study [22] the submucosal carcinomas were classified into three groups according to depth of invasion, by dividing the SM layer into three groups according to depth of invasion, by dividing the SM layer into three equal parts: upper (SM1), middle (SM2), and lower (SM3). The three subgroups of SM had a strong positive correlation with the rate of lymph node metastasis ($P < 0.001$), with an incidence of 10%, 19%, and 33% in SM1, SM2, and SM3, respectively.

The present study revealed that lymph node metastasis influenced the prognosis and that not only a qualitative but also a quantitative evaluation of lymph node metastasis was important and useful for estimating the prognosis of patients with submucosal gastric carcinoma by univariate analysis. However, if the specific number of metastatic lymph nodes (i.e., three or more) proves to be a good prognostic factor, it will provide a simple and universally applicable assessment for patients with lymph node metastasis, because the level of lymph node dissection for gastric cancer varies among countries and/or institutes. Multivariate analysis in the present study clearly revealed that the involvement of three or more lymph nodes was the sole significant independent prognostic determinant ($P = 0.016$). The number of metastatic lymph nodes is a very good prognostic factor in breast cancer and colon cancer, according to the TNM classifications of breast and colon cancers [23–25]. Since 1997, in the new TNM classification for gastric cancer, the metastatic involvement of six or more lymph nodes has been distinguished from that of five or fewer nodes. The present large cohort study revealed that, when the number of metastatic lymph nodes was three or more, the cancer-specific 5-year survival rate was significantly ($P < 0.001$) lower than that in patients with one or two metastatic lymph nodes. The 5-year survival rate of the patients with more than four metastatic lymph nodes was similar to that of those with three metastatic lymph nodes. To our surprise, the multivariate analysis revealed that the nodal level was not a significant prognostic factor in the patients with submucosal gastric cancer. This is probably because all patients with N2 in the group with one or two positive nodes have survived for more than 5 years. These results should be reflected in a modification of the staging in the new TNM classification of early gastric cancer.

In conclusion, the involvement of three or more metastatic lymph nodes is the sole independent prognostic indicator in early gastric cancer that has invaded the submucosa, whereas the nodal level is not an independent prognostic indicator. This simple and useful prognostic determinant should contribute to the follow-up for submucosal gastric cancer, and should help in the selection of potentially effective adjuvant chemotherapy.

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