

# Factors related to lymph node metastasis and surgical strategy used to treat early gastric carcinoma

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## Abstract

**AIM:** The prognosis of early gastric carcinoma (EGC) is generally excellent after surgery. The presence or absence of lymph node metastasis in EGC is an important prognostic factor. The survival and recurrence rates of node-negative EGC are much better than those of node-positive EGC. This study examined the factors related to lymph node metastasis in EGC to determine the appropriate treatment for EGC.

**METHODS:** We investigated 748 patients with EGC who underwent surgery between January 1985 and December 1999 at the Division of Gastroenterologic Surgery, Department of Surgery, Chonnam National University Hospital. Several clinicopathologic factors were investigated to analyze their relationship to lymph node metastasis: age, sex, tumor location, tumor size, gross type, histologic type, depth of invasion, extent of lymph node dissection, type of operation, and DNA ploidy.

**RESULTS:** Lymph node metastases were found in 75 patients (10.0%). Univariate analysis showed that male sex, tumor size larger than 2.0 cm, submucosal invasion of tumor, histologic differentiation, and DNA ploidy pattern were risk factors for regional lymph node metastasis in EGC patients. However, a multivariate analysis showed that three risk factors were associated with lymph node metastasis: large tumor size, undifferentiated histologic type and submucosal invasion. No statistical relationship was found for age, sex, tumor location, gross type, or DNA ploidy in multivariate analysis. The 5-year survival rate was 94.2% for those without lymph node metastasis and 87.3% for those with lymph node metastasis, and the difference was significant ( $P < 0.05$ ).

**CONCLUSION:** In patients with EGC, the survival rate of patients with positive lymph nodes is significantly worse than that of patients with no lymph node metastasis. Therefore, a standard D2 lymphadenectomy should be performed in patients at high risk of lymph node metastasis: large tumor size, undifferentiated histologic type and submucosal invasion.

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## INTRODUCTION

Early gastric carcinoma (EGC) is defined as a lesion confined to the mucosa or submucosa of the stomach with or without lymph node metastasis<sup>[1]</sup>. The incidence of lymph node metastasis differs in mucosal and submucosal gastric carcinomas. When invasion extends to the submucosal layer, the incidence of lymph node metastasis increases<sup>[2]</sup> and submucosal gastric carcinoma is reported to have a poorer prognosis than mucosal gastric carcinoma<sup>[3]</sup>.

We analyzed data from 673 patients with node-negative EGC, and 75 patients with node-positive EGC who had been surgically treated, to evaluate the clinicopathologic factors related to lymph node metastasis in EGC and to determine the appropriate treatment criteria for patients with EGC.

## MATERIALS AND METHODS

Between 1985 and 1999, 748 Korean patients with EGC underwent surgery at the Division of Gastroenterologic Surgery, Department of Surgery, Chonnam National University Hospital. Of these, 75 patients (10.0%) were found to have lymph node metastasis.

Medical records were reviewed, and data were abstracted for the following factors: clinical findings, tumor size, tumor location, gross appearance, histologic grade, lymph node involvement, operation type, DNA ploidy pattern, and 5-year survival rate.

The clinical features of the 673 patients with node-negative EGC, and the 75 patients with node-positive EGC were compared. Curative resections were defined as histologic or relative curative resections according to the criteria of the Japanese Research Society for Gastric Cancer<sup>[4]</sup>. The data were analyzed statistically using a chi-square test and an unpaired Student's *t*-test. Overall survival rates were calculated using the Kaplan-Meier method. Multivariate analysis was performed using the Cox proportional hazards model with the program SPSS 11.0 to test the variables associated with lymph node metastasis in EGC. A *P* value  $< 0.05$  was considered statistically significant.

## RESULTS

Of the 2 767 patients with gastric carcinoma who underwent surgery in our hospital over the 15-year period, 748 patients (27.0%) were diagnosed as EGC. The incidence of node-positive EGC was 10.0% (75/748) in this study group.

Table 1 describes the clinicopathologic findings in the 673 patients with node-negative EGC, and the 75 patients with node-positive EGC. There was no statistically significant difference between the ages of patients with and without lymph node metastasis. Of the 75 patients with lymph node metastasis, 41 (54.7%) were males and 34 (45.3%) were females. There were 453 males (67.3%) and 220 females (32.7%) in the group of 673 patients with node-negative EGC. There were more males than females in each group and the gender ratio was statistically significant ( $P < 0.05$ ). The mean tumor size of patients with node-positive EGC (3.1 cm) was larger than that of patients with node-negative EGC (2.2 cm), and the difference was statistically significant ( $P < 0.01$ ). Lymph node metastasis was

present in only 10 patients (13.3%) with a tumor <2.0 cm in size. Of these 75 patients with node-positive EGC, 65 patients (86.7%) were found to have a tumor  $\geq$ 2.0 cm in size ( $P<0.01$ ). Most gastric carcinomas were located in the lower portion of the stomach, in both node-negative (445 cases, 66.1%) and node-positive EGC patients (55 cases, 73.3%), but the differences in location were not significant. There was no correlation between lymph node metastasis and macroscopic appearance of the tumor. Based on the degree of anaplasia, 10 (13.3%) patients with node-positive EGC had well-differentiated, 14 (18.7%) had moderately differentiated, 45 (60.0%) had poorly differentiated, and 3 (4.0%) had mucinous adenocarcinomas ( $P<0.01$ ). The submucosal invasion was found more frequently in patients with node-positive EGC (81.3%) than in those with node-negative EGC (46.1%,  $P<0.01$ ). Distant metastasis was found in one patient with node-negative EGC. There was no significant difference between node-negative and node-positive EGC patients in the operative type. The curative resection rate for patients with node-negative EGC was similar to that for patients with node-positive EGC (99.7% vs 97.3%).

**Table 1** Clinicopathologic findings in patients with early gastric carcinoma with and without lymph node metastasis

	Node-negative <i>n</i> =673, (%)	Node-positive <i>n</i> =75, (%)	<i>P</i> value
Age (mean, yr)	55.7±10.7	57.9±10.7	NS
Gender			<0.05
Male	453 (67.3)	41 (54.7)	
Female	220 (32.7)	34 (45.3)	
Age (yr)			NS
≤ 40	71 (10.5)	5 (6.7)	
> 40	602 (89.5)	70 (93.3)	
Tumor size (mean, cm)	2.2±1.45	3.1±1.89	<0.01
< 2	434 (64.5)	10 (13.3)	<0.01
2-3	141 (21.0)	24 (32.0)	
> 3	98 (14.5)	41 (54.7)	
Tumor location			NS
Upper	28 (4.2)	2 (2.7)	
Middle	200 (29.7)	18 (24.0)	
Lower	445 (66.1)	55 (73.3)	
Macroscopic appearance			NS
Protruded	208 (30.9)	21 (28.0)	
Depressed	417 (62.0)	50 (66.7)	
Mixed	48 (7.1)	4 (5.3)	
Stage			<0.01
Ia	672 (99.9)		
Ib		65 (86.7)	
II		6 (8.0)	
IV	1 (0.1)	4 (5.3)	
Histologic type			<0.01
Differentiated	348 (51.7)	24 (32.0)	
Undifferentiated	325 (48.3)	51 (68.0)	
Depth of invasion			<0.01
Mucosa	363 (53.9)	14 (18.7)	
Submucosa	310 (46.1)	61 (81.3)	
Operative type			NS
Total gastrectomy	62 (9.2)	8 (10.7)	
Proximal gastrectomy	4 (0.6)		
Distal gastrectomy	583 (86.8)	65 (86.7)	
Others	24 (3.4)	2 (2.7)	
Lymph node dissection			<0.01
D1	144 (21.4)	8 (10.7)	
D2	484 (71.9)	50 (66.7)	
≥D3	45 (6.7)	17 (22.7)	
Curability			NS
Curative	671 (99.7)	73 (97.3)	
Non-curative	2 (0.3)	2 (2.7)	

NS, not significant.

Univariate analysis showed that male sex, tumor size, depth of invasion, undifferentiated type, and aneuploid pattern were significant factors associated with lymph node metastasis in EGC (Tables 1 and 2).

**Table 2** Lymph node metastasis according to DNA ploidy pattern (*n*=238)

DNA ploidy	Node-negative (%)	Node-positive (%)	<i>P</i> value
Aneuploid	80 (38.5)	17 (56.7)	<0.05
Diploid	128 (61.5)	13 (43.3)	

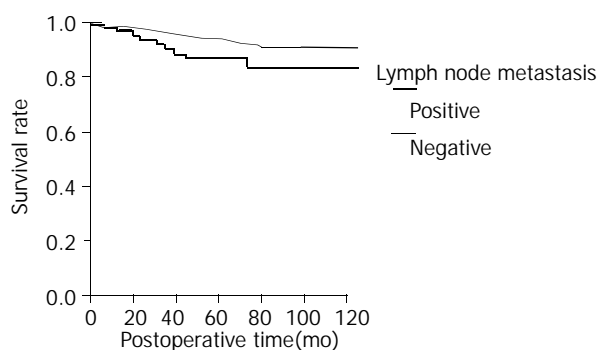
**Table 3** Logistic regression analysis for variables associated with lymph node metastasis in early gastric carcinoma

Variables	Risk ratio	95% CI	<i>P</i> value
Age	1.040	0.996-1.021	0.50
Gender	1.022	0.884-1.121	0.183
Tumor size	1.342	1.134-1.642	0.003
Gross appearance	1.124	0.987-1.342	0.384
Histologic type	0.948	0.737-1.221	0.009
Depth of invasion	1.241	0.949-1.369	<0.001
Tumor location	0.963	0.822-1.522	0.09
DNA ploidy	0.876	0.744-1.675	0.06

CI, confidence interval.

All of the factors listed in Tables 1 and 2 were examined using a logistic regression analysis. The independent risk factors for lymph node metastasis were larger tumor size, undifferentiated type, and submucosal invasion (Table 3).

The postoperative survival rate of the patients without lymph node metastasis was compared with that obtained from those with lymph node metastasis. The 5-year survival rates were 94.2% for those without lymph node metastasis and 87.3% for those with lymph node metastasis, and the difference was significant ( $P<0.05$ , Figure 1).



**Figure 1** Survival curves according to lymph node metastasis. The early gastric carcinoma patients without lymph node metastasis showed a better survival rate than early gastric carcinoma patients with lymph node metastasis (94.2% vs 87.3%,  $P<0.05$ ).

## DISCUSSION

Early gastric carcinoma (EGC) has been defined as gastric carcinoma in which invasion is confined to the mucosa or submucosa, regardless of lymph node metastasis<sup>[1]</sup>. The incidence of EGC has increased due to the advances in technical developments regarding both radiological modalities and endoscopy<sup>[5]</sup>. In our department, 27.0% of the patients had EGC, a rate similar to the 20-40% range previously reported<sup>[6]</sup>. The prognosis of EGC after curative resection was favorable,

with a 5-year survival rate exceeding 90%<sup>[6-8]</sup>. Moreover, the survival and recurrence rates of node-negative EGC were much better than those of node-positive EGC<sup>[7,8]</sup>.

The reported incidence of lymph node metastasis in EGC was 2-4% in mucosal carcinoma<sup>[9-11]</sup>, but increased to 15-25% in submucosal carcinoma<sup>[12]</sup>. Here, we found a 3.7% incidence of lymph node metastasis in mucosal carcinoma and a 16.4% incidence in submucosal carcinoma. The incidence of lymph node metastasis was similar to those in mucosal carcinoma reported by Yamao *et al*<sup>[9]</sup> and Tsujitani *et al*<sup>[10]</sup>, and lower in submucosal carcinoma reported by other investigators<sup>[13,14]</sup>. Some investigators have reported that submucosal invasion is one of the predictive risk factors for lymph node metastasis in EGC patients<sup>[8,15,16]</sup>. Shimada *et al* reported that the number of metastatic lymph nodes occurring in patients with gastric carcinoma was correlated with the survival rate<sup>[6]</sup>. EGC patients with lymph node metastasis had a lower survival rate than patients without lymph node metastasis. Of note, they suggested that the involvement of three or more lymph nodes could predict a poor prognosis in submucosal gastric carcinoma. Seto *et al*<sup>[17]</sup> reported a 5-year survival of 74% in patients with more than 4 positive lymph nodes. Folli *et al*<sup>[11]</sup> also reported a lower 5-year survival, especially for patients who presented more than 3 metastatic lymph nodes.

The presence of lymph node metastasis in EGC worsened the prognosis, as reported by some investigators<sup>[8,13]</sup> and as observed in this study (87.3% vs 94.2%). Nio *et al*<sup>[18]</sup> reported that the 5-year survival of EGC was 93% for N1 patients and 68.4% for N2 patients. Miwa *et al*<sup>[15]</sup> observed similar results. When EGC was subdivided into mucosal and submucosal carcinomas, the survival rate for mucosal carcinoma was significantly better than that for submucosal carcinoma<sup>[19]</sup> because the former had a lower incidence of lymph node metastasis. Nevertheless, submucosal invasion could not always predict a poor prognosis, the survival rates in patients with submucosal carcinoma were the same as those in patients with mucosal carcinoma<sup>[20]</sup>. In our study, the incidence of lymph node metastasis from submucosal carcinoma (16.4%) was significantly higher than that from mucosal carcinoma (3.7%). However, the 5-year survival rate for patients with submucosal carcinoma (88.6%) did not differ from that for patients with mucosal carcinoma (95.2%), because the curative resection rate was high for both submucosal (97.3%) and mucosal (99.7%) carcinomas. We performed gastrectomy with D2 lymphadenectomy for most patients with submucosal gastric carcinoma. Furthermore, some investigators<sup>[12,21]</sup> have recommended that a standard D2 lymphadenectomy is essential, even in cases of mucosal carcinoma.

Lymphadenectomy, a prognostic factor that can be influenced by the surgeon, improves the survival rate in gastric carcinoma, although there has been no extensive prospective randomized trial. Viste *et al*<sup>[22]</sup> reported that the survival of patients who underwent extensive lymph node dissection was higher than that of patients without dissection. Furthermore, lymph node recurrence has been attributed to inadequate lymph node dissection. We found that in patients with submucosal gastric carcinoma, the survival rate with positive lymph nodes was significantly poorer than that with no lymph node metastasis (87.3% vs 94.2%,  $P < 0.05$ ). Therefore, we recommend gastrectomy with D2 lymphadenectomy as the appropriate operative procedure for patients with submucosal carcinoma of the stomach.

There have been several attempts to identify risk factors predicting lymph node metastasis. Maehara *et al*<sup>[6]</sup> found that the risk factors for lymph node metastasis in EGC patients were large tumor, lymphatic involvement, and submucosal invasion. Yamao *et al*<sup>[9]</sup> also reported that lymphatic invasion, histologic type, and large tumor size were independent risk

factors for lymph node metastasis in patients with intramucosal EGC. Abe *et al*<sup>[23]</sup> reported that submucosal invasion, female sex, large tumor size, and lymphatic vessel involvement were significantly and independently related to the presence of lymph node metastasis in depressed EGC. Baba *et al*<sup>[24]</sup> reported that there was no metastasis in lesions less than 1 cm in diameter, but the incidence of positive nodes increased with the size of the primary lesion. Wu *et al*<sup>[25]</sup> reported that poor differentiation, submucosal invasion and large tumor size were independent risk factors for lymph node metastasis in early gastric cancer. Macroscopic classification was not correlated with lymph node metastasis. Sasaki *et al*<sup>[26]</sup> reported that DNA aneuploidy was a useful indicator of lymph node metastasis in EGC patients. We studied the DNA ploidy pattern in 238 patients with EGC and found that there was a correlation between lymph node metastasis and DNA ploidy pattern in univariate analysis. But we found there was no correlation between lymph node metastasis and DNA ploidy pattern in multivariate analysis (Table 3). In our study, the univariate analysis showed that lymph node metastasis in EGC patients was associated with male sex, large tumor size, submucosal invasion, and undifferentiated histologic grade, while the multivariate analysis showed that metastasis was associated with large tumor size, undifferentiated type and submucosal invasion (Table 3).

In conclusion, this study suggests that tumor size, depth of tumor invasion and undifferentiated histologic grade are risk factors for lymph node metastasis in EGC. Therefore, standard D2 lymphadenectomy should be performed in patients with these high-risk factors.

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