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Carcinomatous Lymphatic Invasion in Early Gastric Cancer Invading Into the Submucosa

Sumiya Ishigami, MD, Shoji Natsugoe, MD, Shuuichi Hokita, MD, Masahiro Tokushige, MD, Tetsushi Saihara, MD, Teruhiko Watanabe, MD, Kuniaki Aridome, MD, Hirohumi Iwashige, MD, and Takashi Aikou, MD

Background: Lymphatic invasion is a risk factor for lymph node metastases in patients with gastric cancer. No studies have been reported, however, on the correlation between lymphatic invasion and lymph node metastasis in early gastric cancer invading into the submucosa.

Methods: We performed a retrospective analysis of lymphatic invasion in 170 patients with early gastric cancer invading into the submucosa.

Results: Lymphatic invasion was found in 76 patients. Lymphatic invasion correlated significantly with the presence of lymph node metastasis and vascular invasion ($P < .05$) and with the degree of cancerous submucosal involvement ($P < .05$). The presence of lymph node metastasis also correlated with the grade of submucosal invasion and lymphatic invasion. The 5-year survival of patients with lymphatic invasion was poorer than that of patients without lymphatic invasion ($P < .05$). Node-negative patients had similar survival, regardless of the presence of lymphatic invasion. All patients with severe lymphatic invasion had sm3 invasion and lymph node metastases.

Conclusion: Although lymphatic invasion is the first stage of lymph node metastasis, lymphatic invasion in itself does not have clinical importance except for severe invasion in early gastric cancer. It is possible to predict lymph node metastases from the combined evaluation of degree of lymphatic invasion and submucosal involvement of the tumor in patients with early gastric cancer invading into the submucosa.

Key Words: Lymphatic invasion—Early gastric cancer—Lymph node metastasis.

Improvements in endoscopic techniques and the prevalence of mass screening have increased the rate of detection of patients with early gastric cancer (EGC) in Japan.[1–3] The presence or absence of lymph node metastases is a critical determinant of whether less invasive treatment, such as endoscopic mucosal resection or pylorus-preserving gastrectomy, can be performed.[4–6] Lymphatic invasion by cancer cells often is seen in patients with gastric cancer and may be the first stage of lymph node metastasis.[7] Evaluation of lymphatic invasion in resected specimens is useful for the prediction of lymph node metastases because of the close correlation between lymph node metastases and lymphatic invasion.[8,9] The presence of lymphatic invasion in patients with EGC, therefore, may be an indication for gastrectomy with lymph node dissection. There are many node-negative patients with EGC invading into the submucosa,[10] and the clinical features of ECG that is node-negative but accompanied by positive lymphatic invasion are unclear. The aim of this study was to clarify the clinicopathologic characteristics and surgical outcome in patients with lymphatic invasion–positive EGC invading into the submucosa.

MATERIALS AND METHODS

We retrospectively studied 170 patients (124 men and 36 women) who underwent curative gastrectomy for EGC invading into the submucosa from 1979 to 1996 in the First Department of Surgery at the Kagoshima Uni-

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From the First Department of Surgery, Kagoshima University School of Medicine, Kagoshima, Japan.

Address correspondence to: Sumiya Ishigami, MD, First Department of Surgery, Kagoshima University School of Medicine 8-35-1, Sakuragaoka Kagoshima 890, Japan.

TABLE 1. *Patient characteristics*

	LY(−) group (n = 94)	LY(+) group (n = 76)	*P* value
Age (y)	62 ± 10	65 ± 11	NS
Sex (male/female)	74/20	60/16	NS
Operation method			
Total gastrectomy	14	5	
Proximal partial gastrectomy	6	8	NS
Distal partial gastrectomy	74	63	
Grade of lymph node dissection			
D0	3	2	
D1	41	45	NS
D2∼	50	29	

versity School of Medicine, Kagoshima University Hospital. No adjuvant chemotherapy was administered preoperatively. The presence of lymph node metastasis and lymphatic invasion was determined by routine hematoxylin and eosin (H & E) staining of the resected specimens. Thirty-seven patients (22%) had a lymph node metastasis.

Distal gastrectomy was performed in 74 patients (44%), and total gastrectomy in the remainder, except for 6 patients (3%) who underwent proximal gastrectomy (Table 1). The resected specimens initially were fixed in 10% formalin, and the whole tumor was cut into longitudinal sections approximately 4 mm thick. Pathologic evaluation was performed on the slide with the deepest invasion, and patients were divided histologically into those with well-differentiated adenocarcinomas and those with undifferentiated adenocarcinomas. Lymphatic invasion was defined as being present when cancer cells were detected floating within an endothelium-lined space.[11]

The number of lymphatic vessels affected in the entire tumor determined the degree of lymphatic invasion. According to the *General Rules for Gastric Cancer Study in Surgery and Pathology*, published by the Japanese Research Society for Gastric Cancer,[12] the degree of lymphatic invasion was divided into three grades: *ly1*, minimal lymphatic invasion, 59 patients; *ly2*, moderate lymphatic invasion 12 patients; and *ly3*, marked lymphatic invasion, visible in every microscopic field, 5 patients. Patients were divided into two groups based on the presence or absence of lymphatic invasion. The positive lymphatic invasion (LY[+]) group contained 76 patients; the negative lymphatic invasion (LY[−]) group contained 94 patients. We paid special attention to the degree of cancerous invasion into the submucosa (Fig. 1). Maximal depth of invasion allowed further equal division into three subgroups (sm1, sm2, and sm3), and the horizontal length of carcinoma invasion into the submucosa also was measured as the maximum width in H & E-stained sections.

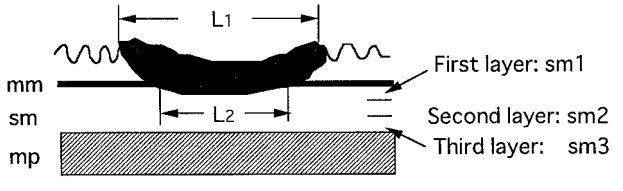

FIG. 1. Schema for evaluation of submucosal invasion. Measurement of maximum dimension of horizontal and vertical invasion. L1, tumor maximum length; L2, diameter of sm invasion. The submucosal layer was divided into three equal portions (sm1, sm2, and sm3).

TABLE 2. *Clinicopathologic characteristics in accordance with lymphatic invasion*

	LY(−) group (n = 94)	LY(+) group (n = 76)	*P* value
Lymph node metastases			
n0	87	46	.01
n(+)	7	30	
Gross type			
Elevated	18	7	
Depressed	47	35	NS
Combined	39	34	
Histology			
Well differentiated	67	56	NS
Undifferentiated	27	20	
Vessel invasion			
Positive	2	16	.05
Negative	92	60	
Tumor diameter (mm)	25 ± 14	28 ± 17	NS
Depth of invasion			
sm1	52	21	
sm2	29	32	.05
sm3	13	23	
Width of invasion (mm)	6 ± 6	13 ± 4	.05

The χ^2 test and Student's *t*-test were used to determine the statistical significance of differences. Survival curves were generated by the Kaplan-Meier method, and analyzed by the generalized Wilcoxon test. A *P* value less than .05 was considered statistical significant.

RESULTS

No significant differences were noted in the clinical characteristics between the LY(−) and LY(+) groups

TABLE 3. *Relationship between submucosal invasion and lymphatic invasion*

	sm1	sm2	sm3	
ly1 (n = 59)	18 (3)*	27 (10)	14 (5)	
ly2 (n = 12)	3 (1)	5 (4)	4 (3)	$p < 0.05$
ly3 (n = 5)	0	0	5 (5)	

* Numbers in parentheses = the number of patients with lymph node metastases.

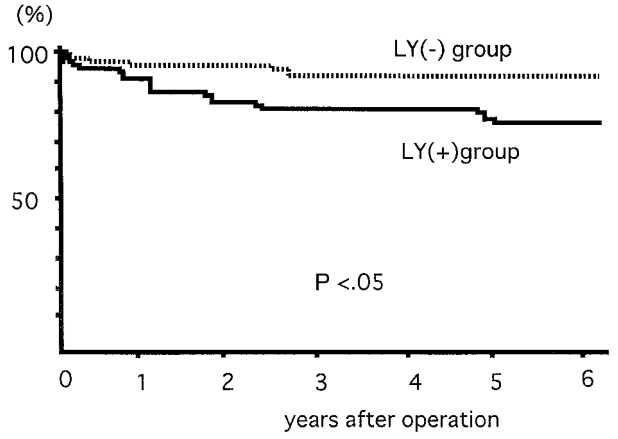

FIG. 2. Survival curves according to lymphatic involvement. The prognosis was significantly better for LY(−) patients than for LY(+) patients.

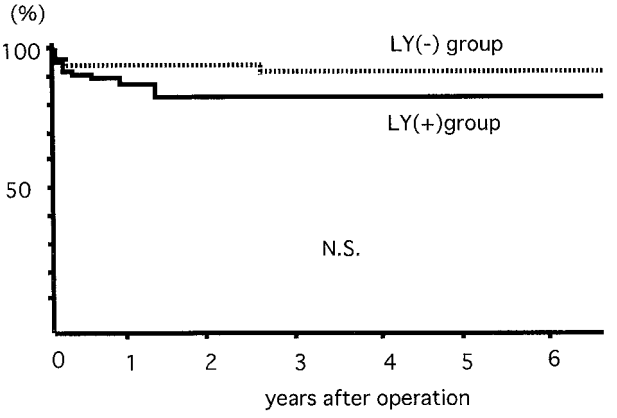

FIG. 3. Survival curves according to lymphatic involvement, confined to node-negative patients. There was no significant difference between the LY(−) group and the LY(+) group.

(see Table 1), and the extent of lymph node dissection was almost the same in the two groups. Thirty of 76 patients (39%) in the LY(+) group had lymph node metastases, a percentage significantly higher than that seen in the LY(−) group [7%, (7/94); $P < .01$]. The rate of vessel invasion in the LY(+) group also was significantly higher than that of the LY(−) group ($P < .05$). Both the width and depth of invasion into the submucosa were greater in the LY(+) group than in the LY(−) group ($P < .05$) (Table 2). The degree of invasion of the tumor into the submucosa correlated significantly with the severity of lymphatic invasion ($P < .05$) (Table 3). Positive lymph node metastasis also correlated with the grade of submucosal invasion and lymphatic invasion.

The overall 5-year survival rates were 81% in the LY(+) group and 91% in the LY(−) group. There was a significant difference in the survival rate between the two groups ($P < .05$) (Fig. 2). However, when only node-negative patients were considered, the difference in survival rates became insignificant (Fig. 3). Five of the 76 LY(+) patients had severe lymphatic invasion (ly3). All of these patients had nodal involvement and sm3 depth of invasion, with more than 10 mm of submucosal invasion. Two of these five patients died of recurrent disease (Table 4).

DISCUSSION

Any gastric carcinoma invading into but confined to the submucosa is defined as an early gastric cancer, whether or not lymph node metastases are present, because of the good prognosis after curative surgery.[13] The incidence of lymph node metastases in EGC invading into the submucosa is higher than that in cancer confined to the mucosa, because the submucosal layer of the gastric wall is rich in lymphatic capillaries. Once a carcinoma has invaded into the submucosal layer, therefore, the incidence of lymph node metastases increases.[14] Several reports detailing carcinomatous lymphatic involvement have been published.[3,7,15,16] In this study, we showed that lymphatic invasion is closely related to the presence of lymph node metastases, as previously reported.[16] Maehara[15] has shown that gastric cancer with lymphatic invasion has a higher proliferation activity and a greater ability to metastasize to distant organs. Kanai[16] has demonstrated in patients with early gastric cancer that lymphatic invasion correlates better with the pres-

TABLE 4. *Presentation of patients with severe lymphatic involvement*

Patient	Age (y)	Sex	Gross type	Histology	N factor	Venous invasion	Tumor size (mm)	Submucosal Depth	Submucosal Width (mm)	Survival
1	57	M	Combined	Mucinous	1	0	33	sm3	12.5	10 y A
2	35	M	Elevated	Well-differentiated	1	1	25	sm3	10	1 y 10 m D
3	51	F	Combined	Well-differentiated	2	0	40	sm3	20	6 y 5 m A
4	67	M	Depressed	Well-differentiated	2	1	50	sm3	10	1 y 3 m A
5	72	M	Combined	Well-differentiated	3	0	30	sm3	20	1 y D

A, alive; D, dead.

ence of lymph node metastases than does p53 oncogenic expression or cell proliferative activity.

We also demonstrated a significant correlation between lymphatic invasion and the degree of submucosal invasion, not only with the depth of invasion but also with the width of tumor infiltration. The wider the tumor invasion into the submucosa, the more likely it was that a patient would have lymphatic invasion. The degree of carcinomatous invasion into the submucosa has been reported previously to affect lymph node metastases.[10] The concurrent evaluation of lymphatic invasion and cancerous submucosal involvement may, therefore, provide details about the presence of lymph node metastases in patients with early gastric cancer invading into the submucosa.

We found a significant difference in survival rates when lymphatic invasion was present, which depended primarily on the presence of lymph node metastases. LY(+) patients without nodal involvement had approximately the same survival rate as did those in the LY(−) group. This result may imply that the minimal volume of the tumor in lymphatic vessels is excluded by the host immunodefense mechanism and lymphatic invasion in itself does not influence lymph node metastasis and survival. However, lymphatic invasion (ly3) and massive infiltration of the tumor (sm3) into the submucosal layer go beyond the self-defense mechanism (the host immunodefense) and leads to a high rate of lymph node metastases and recurrent disease.

In summary, carcinomatous lymphatic invasion correlates with the presence of lymph node metastases and the degree of submucosal invasion. We can predict lymph node metastases from the combined evaluation of the degree of lymphatic invasion and submucosal involvement of the tumor. The overall survival rate of patients without lymph node metastases was not influenced by the presence of lymphatic invasion. On the other hand, patients with severe lymphatic invasion (ly3) have a high risk of relapse and need careful postoperative follow-up, with consideration of adjuvant chemotherapy, just as in advanced gastric cancer.

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