

Lymph node metastasis in early gastric cancer with submucosal invasion: Feasibility of minimally invasive surgery

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Abstract

AIM: To explore the feasibility of performing minimally invasive surgery (MIS) on subsets of submucosal gastric cancers that are unlikely to have regional lymph node metastasis.

METHODS: A total of 105 patients underwent radical gastrectomy with lymph node dissection for submucosal gastric cancer at our hospital from January 1995 to December 1995. Besides investigating many clinicopathological features such as tumor size, gross appearance, and differentiation, we measured the depth of invasion into submucosa minutely and analyzed the clinicopathologic features of these patients regarding lymph node metastasis.

RESULTS: The rate of lymph node metastasis in cases where the depth of invasion was $<500\ \mu\text{m}$, $500\text{--}2\ 000\ \mu\text{m}$, or $>2\ 000\ \mu\text{m}$ was 9% (2/23), 19% (7/36), and 33% (15/46), respectively ($P < 0.05$). In univariate analysis, no significant correlation was found between lymph node metastasis and clinicopathological characteristics such as age, sex, tumor location, gross appearance, tumor differentiation, Lauren's classification, and lymphatic invasion. In multivariate analysis, tumor size ($>4\ \text{cm}$ vs $\leq 2\ \text{cm}$, odds ratio = 4.80, $P = 0.04$) and depth of invasion ($>2\ 000\ \mu\text{m}$ vs $\leq 500\ \mu\text{m}$, odds ratio = 6.81, $P = 0.02$) were significantly correlated with lymph node metastasis. Combining the depth and size in cases where the depth of invasion was less than $500\ \mu\text{m}$, we found that lymph node metastasis occurred where the tumor size was greater than $4\ \text{cm}$. In cases where the tumor size was less than $2\ \text{cm}$, lymph node metastasis was found only where the depth of tumor invasion was more than $2\ 000\ \mu\text{m}$.

CONCLUSION: MIS can be applied to submucosal gastric cancer that is less than $2\ \text{cm}$ in size and $500\ \mu\text{m}$ in depth.

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INTRODUCTION

Minimally invasive surgeries (MIS) such as endoscopic mucosal resection or laparoscopic surgery are performed as a treatment of early gastric cancer. This limited surgery should be conducted on strict indication in early gastric cancer which has a limited invasion in mucosa. Such a surgery can be attained without lymph node dissection. However, if the case is diagnosed as submucosal gastric cancer after MIS, the patient needs additional gastrectomy and lymph node dissection owing to the limitations of current diagnostic methods in assessing the depth of invasion and lymph node status.

Since the incidence of lymph node metastasis in submucosal gastric cancer is reported as less as about 20%, it can be expected that the chance of further operations will be reduced if we choose patients who have low risk of lymph node metastasis. Thus, we analyzed in our study the clinicopathological factors related to lymph node metastasis in submucosal gastric cancers retrospectively, in order to find out the subsets of submucosal gastric cancers to which MIS can be applied, and to establish the suitable treatment policy of submucosal gastric cancers.

MATERIALS AND METHODS

This study enrolled 105 submucosal gastric cancer cases that were pathologically proven after gastrectomy by lymph node dissection at Seoul National University Hospital from January 1995 to December 1995. The relationship between clinicopathological factors (sex, age, tumor location, gross appearance, tumor size, depth of invasion, tumor differentiation, Lauren's classification, and lymphatic invasion) and lymph node metastasis was investigated. Submucosal layer was divided into 3 layers (upper third = SM1, middle third = SM2, and lower third = SM3) and submucosal depth of invasion was directly measured from muscularis mucosae by a micrometer (Figure 1). χ^2 test and logistic regression analysis were used to evaluate risk factors for lymph node metastasis and $P < 0.05$ was considered statistically significant.

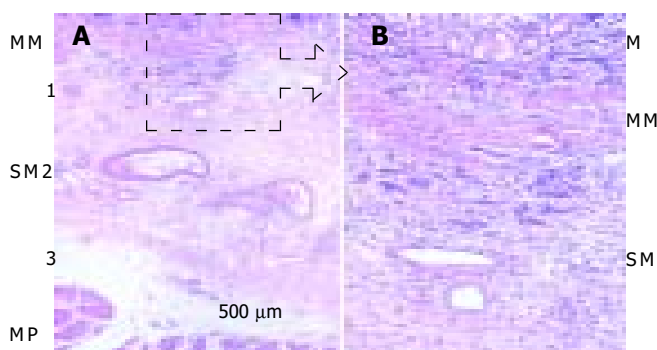


Figure 1 Depth of submucosal invasion of gastric cancer (arrow) in hematoxylin and eosin staining in A ($\times 10$) and B ($\times 100$). M: mucosa, MM: muscularis mucosae, SM: submucosa, MP: muscularis propria. This case was classified as SM1 or less than $500\ \mu\text{m}$ from muscularis mucosae.

RESULTS

Patient characteristics

A total of 105 patients with submucosal gastric cancer were included in the study. Of them, 74 were males and 31 were females. Their mean age was 54.9 years (18-80 years). The rate of lymph node metastasis was 22.9% (24/105 cases).

Depth of invasion (Table 1)

According to the SM category, SM1, SM2, and SM3 lesions were 28 (27%), 47 (45%), and 30 (28%) respectively. The depth of invasion measured directly from muscularis mucosae was less than 500 μm in 68% of SM1 gastric cancers, more than 1 000 μm (1 mm) in 75% of SM2 gastric cancers, and more than 2 000 μm in 84% of SM3 gastric cancers.

Table 1 Depth of submucosal invasion as compared with three SM category measurements

Depth (μm)	SM1 (%)	SM2 (%)	SM3 (%)
≤ 500 ($n = 23$)	19 (68)	4 (8)	0 (0)
500-1 000 ($n = 17$)	8 (28)	8 (17)	1 (3)
1 000-2 000 ($n = 19$)	1 (4)	14 (30)	4 (13)
$> 2 000$ ($n = 46$)	0 (0)	21 (45)	25 (84)
Total	28	47	30

Relationship between clinicopathological factors and lymph node metastasis (Table 2)

In univariate analysis, there was no significant factor related to lymph node metastasis among sex, age, tumor location, gross appearance, tumor differentiation, Lauren's classification, and lymphatic invasion.

Table 2 Relationship between clinicopathological factors and lymph node metastasis

	Total	Node-negative	Node-positive (n, %)	P
Sex				
M	74	57	17 (23.0)	0.965
F	31	24	7 (22.6)	
Age (yr)	105	54.8 \pm 12.5	55.4 \pm 12.2	0.822
Tumor location				
Upper	1	1	0 (0)	0.614
Middle	53	42	11 (20.8)	
Lower	48	35	13 (27.1)	
Entire	3	3	0 (0)	
Gross appearance				
Elevated	23	15	8 (34.8)	0.055
Flat	6	3	3 (50.0)	
Depressed	76	63	13 (17.1)	
Tumor differentiation				
Differentiated	47	35	12 (25.5)	0.557
Undifferentiated	58	46	12 (20.7)	
Lauren's classification				
Intestinal	44	35	9 (20.5)	0.572
Diffuse	53	41	12 (22.6)	
Mixed	8	5	3 (37.5)	
Depth of invasion				
SM1	28	24	4 (14.3)	0.448
SM2	47	35	12 (25.5)	
SM3	30	22	8 (26.7)	
Lymphatic invasion				
Absence	86	69	17 (19.8)	0.109
Presence	19	12	7 (36.8)	

Lymph node status in term of depth of invasion (Table 3)

The depth of invasion was significantly associated with lymph node metastasis. Especially, when the depth of invasion was more than 1 000 μm , three cases out of 65 (4.6%) were revealed to have more than 7 lymph node metastases (N2 stage).

Table 3 Lymph node status according to depth of invasion

Depth (μm)	Lymph node status (%)			
	pN0	pN+	pN1	pN2
≤ 500 ($n = 23$)	21 (91)	2 (9) ^a	2	0
500-1 000 ($n = 17$)	14 (82)	3 (18)	3	0
1 000-2 000 ($n = 19$)	15 (79)	4 (21)	3	1
$> 2 000$ ($n = 46$)	31 (67)	15 (33) ^a	13	2

^a $P < 0.05$.

Lymph node status in term of tumor size (Table 4)

Though there was no statistical significance in univariate analysis, the rate of lymph node metastasis was increased as the tumor size increased (≤ 2 cm, 11%; 2-4 cm, 26%; > 4 cm, 29%).

Table 4 Lymph node status according to tumor size

Size (cm)	Lymph node status (%)			
	pN0	pN+	pN1	pN2
≤ 2 ($n = 27$)	24 (89)	3 (11)	3	0
2-3 ($n = 30$)	22 (73)	8 (27)	7	1
3-4 ($n = 20$)	15 (75)	5 (25)	5	0
> 4 ($n = 28$)	20 (71)	8 (29)	6	2

$P = 0.403$.

Logistic regression analysis of factors associated with lymph node metastasis in submucosal gastric cancer (Table 5)

In multivariate analysis, the tumor size (> 4 cm in diameter vs ≤ 2 cm, odds ratio = 4.80, $P = 0.04$) and depth of invasion ($> 2 000$ μm of depth vs ≤ 500 μm , odds ratio = 6.81, $P = 0.02$) were significantly associated with lymph node metastasis.

Table 5 Logistic regression analysis for factors associated with lymph node metastasis in submucosal gastric cancer

Variables	Odds ratio	95% CI	P-value
Depth of invasion (μm)			
≤ 500	1		
500-1 000	2.02	0.30-13.86	0.473
1 000-2 000	3.14	0.49-20.24	0.228
$> 2 000$	6.81	1.36-34.17	0.020
Tumor size (cm)			
≤ 2	1		
2-3	4.35	0.95-19.96	0.059
3-4	4.05	0.78-20.97	0.096
> 4	4.80	1.05-22.06	0.044

CI: confidence interval.

Lymph node status in term of size and depth in submucosal gastric cancer (Table 6)

Lymph node status was analyzed in terms of tumor size and depth of invasion in submucosal gastric cancer. In cases where

the depth of invasion was less than 500 μm , lymph node metastasis was found only when the tumor size was greater than 4 cm. In cases where the tumor size was less than 2 cm, lymph node metastasis was found only when the depth of invasion was more than 2 000 μm .

Table 6 Lymph node status assessed by co-factor of size and depth in submucosal gastric cancer

Depth (μm)	Size (cm)			
	≤ 2	2-3	3-4	> 4
≤ 500 ($n = 23$)	0 ^a /4 ^b	0/6	0/6	2/7
500-1 000 ($n = 17$)	0/1	1/6	1/4	1/6
1 000-2 000 ($n = 19$)	0/5	2/8	1/2	1/4
$> 2 000$ ($n = 46$)	3/17	5/10	3/8	4/11

^aNumber of cases with lymph node metastasis; ^bNumber of total cases.

DISCUSSION

Gastric cancer is the most prevalent cancer in Korea, which accounted for 20.3% of the whole cancer cases^[1]. According to the report of Korea Gastric Cancer Association, the ratio of early gastric cancer was increased from 28.6% in 1995 to 32.8% in 1999^[2], while this tendency was more obvious in Japan, where the ratio of early gastric cancer in the last 20 years was increased from 18% to 57%^[3].

Lymph node metastasis was the most important prognostic factor in gastric cancer^[4,5]. Radical gastrectomy with D2 lymph node dissection, therefore, has been recognized as the standard surgical operation for early gastric cancer. But, as the five year survival rate of early gastric cancer patients has reached 93-98% recently, there arises more interest in preservation of body function and maintenance of quality of life rather than in radical treatment in order to reduce complications or sequelae, such as Dumping syndrome, reflux gastroesophagitis, nutritional deficit, and weight loss. Therefore, interest in MIS such as endoscopic mucosal resection and laparoscopic surgery or function-preserving surgery has been increased.

MIS with no or limited lymph node dissection should be applied to tumors that are unlikely to metastasize into lymph nodes. Endoscopic ultrasonography (EUS) has been introduced recently to diagnose the depth of invasion and lymph node status. An overall accuracy of EUS was reported over 80%^[6,7]. Yet, as the accuracy of EUS is not high enough to predict accurate lymph node status, it is important to know the prognostic factors related to lymph node metastasis. There have been already many reports on the prognostic factors associated with lymph node metastasis in early gastric cancer^[8-16], such as sex^[8], tumor size^[3,9,10,12], depth of invasion^[11], gross appearance of tumor^[8], tumor differentiation^[13] and lymphatic invasion^[14,15]. If we combine these prognostic factors successfully in the diagnosis of certain subtypes that have no lymph node metastasis, then they may become an indication of MIS. For example, the current indications of endoscopic mucosal resection of early gastric cancer are as follows, namely differentiated adenocarcinoma, mucosal cancer < 10 mm in diameter in IIb and IIc lesions without ulcer or ulcer scar, and mucosal cancer < 20 mm in diameter in IIa lesion^[17,18]. The reason why endoscopic mucosal resection can be applied to them is that these lesions are considered to have no lymph node metastasis.

When the depth of invasion reached mucosa in early gastric cancer, the rate of lymph node metastasis was reported as 1-3%, and submucosa as 11-20%^[19]. At present if endoscopic mucosal resection for early gastric cancer can detect the invasion of submucosal layer, additional gastrectomy and lymph node dissection are regarded necessary. However, as the incidence

of lymph node metastasis was about 20% in submucosal gastric cancer, lymph node dissection could be omitted if we chose cases with good selection of indications. In our study on submucosal gastric cancer, we found that sex, age, tumor location, tumor differentiation, Lauren's classification, gross appearance of tumor, were not associated with lymph node metastasis, but tumor size and depth of invasion were associated with lymph node metastasis. A recent study reported that there was a significant difference in the rate of lymph node metastasis according to submucosal depth of invasion, and the possibility of limited surgery for superficial submucosal gastric cancer was therefore suggested^[20]. We divided submucosal layer minutely into SM1, SM2, and SM3 on microscopic field and measured the depth of invasion by a micrometer directly from muscularis mucosae. Actually, because there was some difference between SM 1, 2, 3 categories and the directly measured depth associated with lymph node metastasis, it was considered more objective to use directly measured depth rather than SM category to describe submucosal tumor invasion. Ishigami *et al.*^[21] reported that patients with both slight invasion into submucosa and horizontal expansion that was < 5 mm were often negative in lymph node involvement. Kurihara *et al.*^[22] reported that when the pathological report revealed SM1 invasion after laparoscopic or endoscopic surgery, reoperation should be regarded unnecessary because SM1-carcinoma with its diameter less than 2 cm did not usually metastasize to lymph nodes. Moreover, Yasuda *et al.*^[23] showed that local resection could be applied when the depth of submucosal invasion was < 300 μm and tumor size was < 1 cm. Yamada *et al.*^[24] also showed that local resection might be possible when the depth of submucosal invasion was < 500 μm and tumor size was < 1.5 cm. Gotoda *et al.*^[25] proposed to expand the criteria for local treatment of submucosal gastric cancer by showing that none of the 145 differentiated adenocarcinomas, < 30 mm in diameter and without lymphatic or venous permeation, was associated with lymph node metastasis, provided the lesion invaded less than 500 μm into submucosa. In our study, the tumor size and depth of invasion as independent prognostic factors associated with lymph node metastasis were joined together. In cases where the depth of invasion was < 500 μm , lymph node metastasis was not found when the tumor size was < 4 cm. In cases where the tumor size was less than 2 cm, lymph node metastasis was not found when the depth of invasion was less than 2 000 μm . Therefore, the results suggest that additional operation is unnecessary when the depth of submucosal invasion is less than 500 μm and the tumor size is smaller than 2 cm after local excision. Moreover, in case that patients cannot endure general anesthesia because of old age or cardiopulmonary disability, in case that gastrectomy itself (with or without lymph node dissection) is considered to be dangerous to patients, or when patients refuse the operation, local excisions such as endoscopic mucosal resection, can be applied to submucosal gastric cancer.

In conclusion, the depth of invasion measured directly by a micrometer is more objective to describe cancer permeation into submucosal layer because it is associated more with lymph node metastasis than with SM category.

Our results suggest that additional operation is not necessary after MIS for submucosal gastric cancer when the depth of invasion is less than 500 μm and the tumor size is smaller than 2 cm.

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