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RESEARCH

# The Risk Factors of Lymph Node Metastasis in Early Gastric Cancer

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**Abstract** Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is an effective alternative treatment for early gastric cancer. However, a major concern is the likelihood of lymph node metastasis. From December 1987 to December 2006, 391 patients who underwent curative surgery for gastric cancer with mucosal (T1a, $n$=265) or submucosal (T1b, $n$=126) invasion and a retrieved lymph node number≧15 were enrolled. The frequency and risk factors of lymph node metastasis were analyzed. The frequency of lymph node metastasis was 4.9 % in T1a lesions and 21.4 % in T1b lesions. Although the depth of submucosal tumor invasion was<2 mm, there was a 28.6 % chance of lymph node metastasis. A T1b lesion, i.e., the width of the submucosal tumor invasion was<5 mm, resulted in fewer lymph node metastases than lesions>5 mm in width. Multivariate analysis demonstrated that Lauren's diffuse type and lymphatic invasion were independent risk factors for lymph node metastasis in T1a lesions, while lymphatic invasion was the strongest risk factor for lymph node metastasis in T1b lesions. EMR/ESD is a good alternative for T1a intestinal type adenocarcinoma without lymphatic invasion. Surgical resection is necessary for patients with T1b gastric cancer with lymphatic invasion.

**Keywords** Early gastric cancer · Lymph node metastasis · Lymphatic invasion

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## Introduction

Early gastric cancer (EGC) is defined as cancer invasion that is confined to the mucosa or submucosa (T1), irrespective of the presence of lymph node metastasis [1]. Using endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) to treat EGC has increased in popularity, particularly in Asian countries. The current indications for EMR are well-differentiated, elevated lesions measuring<2 cm and small (≦1 cm) depressed lesions without ulceration [1]. The introduction of ESD has allowed en bloc resection of EGC lesions>2 cm and ulcerated EGC [2]. ESD also allows for precise histological assessment of the resected specimens [2, 3]. Furthermore, ESD might also benefit patients who are unsuitable for surgery, such as elderly and high surgical risk

patients. However, the probability of lymph node metastasis, which cannot be treated using EMR/ESD and may lead to disease recurrence and metastasis, does exist.

A previous report showed that patients with gastric cancer with upper-third (m1) or middle-third (m2) mucosal invasion display no lymphatic metastasis and that the rate of lymph node metastasis is 13 % in patients with lower-third (m3) mucosal invasion. In patients with submucosal invasion, the rate of lymph node metastasis is 21 % for sm1 (upper third), 16 % for sm2 (middle third), and 40 % for sm3 (lower third) [4]. However, this analysis was based on specimens obtained through curative surgery. For patients who received EMR/ESD, the depth of the submucosal tumor invasion could not be classified as above and could only be measured the actual depth of invasion by the pathologists.

In the present study, we identify the risk factors for lymph node metastasis in both intramucosal (T1a) and submucosal invasion (T1b) gastric adenocarcinomas. This study provides useful treatment information for EGC patients and their physician.

## Materials and Methods

According to a prospective gastric cancer database in the Department of Surgery of the Taipei Veterans General Hospital, 1380 gastric cancer patients who received curative resection with a retrieved lymph nodes number ≧15 were enrolled in this study. Patients with fewer than 15 lymph nodes were excluded to avoid inaccurate N-staging. The exclusion criteria also included synchronous gastric double cancer, a previous history of surgery for gastric cancer, or gastric stump cancer. The pathological staging was performed according to the AJCC 7th edition [5]. The present study was approved by the Institutional Review Board of the Taipei Veterans General Hospital.

Total or distal subtotal gastrectomy was performed, depending on the distance between the cardia and the tumor. A 3 cm margin is needed for superficial, well-defined tumors, and a 5 cm margin is needed for advanced or poorly defined tumors. Subtotal gastrectomy is the standard procedure for distal gastric cancer, and total gastrectomy is more frequently performed for proximal gastric cancer.

### Pathological Review

The 391 lesions, including 265 T1a (intramucosal) and 126 T1b (submucosal) lesions were reviewed by one pathologist (F.-Y. Li), who was blinded to the lymph node metastasis statuses. The depth and width of submucosal tumor invasion were measured and recorded in detail. The depth of submucosal invasion was measured at the deepest point of cancer cell penetration in the submucosal layer on all tumor sections. The width of submucosal invasion was measured as the length of the widest point of cancer cell penetration in the submucosal layer on all tumor sections. For intestinal type gastric cancer, lymphatic invasion was defined using Hematoxylin and eosin (H&E) staining. For diffuse type gastric cancer, both H&E staining and immunohistochemical CK (cytokeratin) staining were used to define lymphatic invasion.

The following histological criteria were previously available from the pathological report: Lauren's classification, Ming's classification, stoma reaction type, cell differentiation, and lymphatic invasion.

### Statistical Analysis

The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) (version 16.0, SPSS Inc., Chicago, IL, USA). Categorical data were compared using a Chi squared test (with a Yates correction) or Fisher's exact test. Multivariate analysis of the factors affecting lymph node metastasis was performed, with the Cox proportional hazards model and a forward logistic regression stepwise procedure; $P<0.05$ was considered to be statistically significant.

## Results

### Patients and Characteristics

A total of 391 patients with EGC were enrolled in this study; 265 of these patients were diagnosed with T1a lesions, and 126 patients were diagnosed with T1b lesions.

### Gastric Cancer with T1a Lesions

As shown in Table 1, among the 265 T1a patients, 13 patients (4.9 %) had lymph node metastasis. Univariate analysis indicated that tumor size, Lauren's type, cell differentiation and lymphatic invasion were risk factors for lymph node metastasis in T1a lesions. The multivariate analysis showed that the Lauren's classification of diffuse type and positive for lymphatic invasion were independent risk factors for lymph node metastasis.

### Gastric Cancer with T1b Lesions

As shown in Table 2, tumor depth and width in the submucosa were correlated with pathological N category. Univariate analysis indicated that tumor size, tumor width in submucosa, Ming's classification of infiltrative type, and lymphatic invasion were risk factors for lymph node metastasis in T1b gastric lesions. The multivariate analysis indicated that lymphatic

**Table 1** Risk factors of lymph node metastasis in gastric cancer patients with intramucosal adenocarcinoma (T1a)

| | No lymph node metastasis $n$=252 | Lymph node metastasis $n$=13 | Univariate analysis | Multivariate analysis | |
|---|---|---|---|---|---|
| | | | $P$ value | Odds ratio | $P$ value |
| Age (y/o) | | | 0.384 | | |
| <65 | 98 (93.3) | 7 (6.7) | | | |
| ≧65 | 154 (96.3) | 6 (3.7) | | | |
| Gender | | | 0.198 | | |
| M/F | 185/67 | 7/6 | | | |
| Tumor size | | | 0.025 | | |
| <2 cm | 77 (96.3) | 3 (3.7) | | | |
| 2–4 cm | 116 (95.9) | 5 (4.1) | | | |
| ≧4 cm | 59 (92.2) | 5 (7.8) | | | |
| Lauren's type | | | 0.032 | | 0.026 |
| Intestinal type | 173 (97.2) | 5 (2.8) | | 1.00 | |
| Diffuse type | 78 (90.7) | 8 (9.3) | | 4.87 | |
| Stromal reaction type | | | 0.966 | | |
| Medullary | 229 (95) | 12 (5) | | | |
| Intermediate | 22 (95.7) | 1 (4.3) | | | |
| Scirrhous | 1 (100) | 0 | | | |
| Ming's classification | | | 0.252 | | |
| Expanding | 158 (96.0.3) | 6 (3.7) | | | |
| Infiltrative | 94 (93.1) | 7 (6.9) | | | |
| Cell differentiation | | | 0.030 | | |
| Poor | 85 (90.4) | 9 (9.6) | | | |
| Moderate | 149 (97.4) | 4 (2.6) | | | |
| Well | 18 (100) | 0 | | | |
| Lymphatic invasion | | | <0.001 | | <0.001 |
| Absent | 249 (96.9) | 8 (3.1) | | 1.00 | |
| Present | 3 (37.5) | 5 (62.5) | | 68.9 | |

invasion was the strongest independent risk factor for lymph node metastasis (Table 3).

Of the 126 patients with T1b lesions, 56 patients had a submucosal tumor invasion depth of<2 mm. Among these 56 patients, 16 patients (28.6 %) had lymph node metastasis. In addition, patients with lymphatic invasion were more likely to have lymph node metastasis than those without invasion (50 % vs. 10 %, respectively, $P$=0.002). Tumor size, Lauren's type, cell differentiation, Ming's classification, and stromal reaction type were not risk factors for lymph node metastasis in T1b EGC in our study.

## Discussion

The present study indicates that the frequency of lymph node metastasis is 4.9 % in T1a gastric cancer and increases to 21.4 % with tumor invasion into the submucosa. Unfavorable factors, including diffuse type and lymphatic invasion, increase the risk of lymph node metastasis in T1a lesions, and lymphatic invasion is the strongest risk factor for lymph node metastasis in T1b lesions.

EMR/ESD provides reliable oncological outcomes in most selected T1a lesions, but close follow up is indicated. In patients with intramucosal cancer, the incidence of lymph node metastasis can reach 3 %. In comparison, the frequency of lymph node metastasis increases up to 20 % when the cancer involves the deep submucosa [6]. Our results align with these findings. For intramucosal gastric cancer cells (T1a), EMR/ESD provides reliable oncological outcomes with tumor sizes measuring<2 cm [4, 7–9]. The following are the current indications for EMR: (1) papillary or tubular (differentiated) adenocarcinoma, (2)<2 cm in diameter, (3) no ulceration within the tumor, and (4) no lymphatic–vascular involvement [10]. Expanded criteria for endoscopic resection have been proposed, particularly because large en bloc resection can be performed with ESD [11]. Recently, one study reported finding no lymph node metastasis in 310 patients with poorly

**Table 2** The correlation between lymph node metastasis and tumor depth/width in submucosa in gastric cancer patients with submucosal invasion (T1b)

| | Lymph node metastasis | | pN1 | pN2 | pN3 | *P* value |
|---|---|---|---|---|---|---|
| | n (%) | *P* value | n (%) | n (%) | n (%) | |
| Tumor depth in submucosa | | 0.146 | | | | 0.136 |
| <2 mm (*n*=56) | 16 (59.3) | | 14 (73.7) | 2 (28.6) | 0 | |
| 2–5 mm (*n*=65) | 11 (40.7) | | 5 (26.3) | 5 (71.4) | 1 (100) | |
| >5 mm (*n*=5) | 0 | | 0 | 0 | 0 | |
| Tumor width in submucosa | | 0.073 | | | | 0.048 |
| <5 mm (*n*=55) | 17 (63) | | 15 (78.9) | 2 (28.6) | 0 | |
| 5–10 mm (*n*=55) | 8 (29.6) | | 3 (15.8) | 4 (57.1) | 1 (100) | |
| >10 mm (*n*=16) | 2 (7.4) | | 1 (5.3) | 1 (14.3) | 0 | |

differentiated adenocarcinoma and/or signet-ring cell EGC (<2 cm in diameter, without ulceration or lymphatic or vascular involvement) [12]. However, in our series, 20 patients with T1a lesions fulfilled the above criteria, and one patient (5 %) with a 1.5 cm tumor presented with lymph node metastasis. Among the eight patients with T1b lesions fulfilling the above criteria, one patient (12.5 %) with a 0.8 cm tumor size also presented with lymph node metastasis. Consequently, our results demonstrate that EMR/ESD for poorly differentiated adenocarcinoma is unreliable, even without unfavorable factors.

For T1a gastric cancer, the frequency of lymph node metastasis is relatively low. Nam et al. reported a large series of 2524 patients with T1a gastric cancer that showed only 57 (2.2 %) patients with lymph node metastasis. Univariate analysis showed that tumor size, the presence of middle and lower stomach cancer, poorly differentiated adenocarcinoma, signet-ring cell carcinoma, diffuse type cancer, and lymphatic invasion correlated with lymph node metastasis. Multivariate analysis showed that lymphatic invasion and tumor size were significant predictors of lymph node metastasis [13]. Similar findings were also observed in the present study. Among the patients with T1a gastric cancer, 4.9 % demonstrated lymph node metastasis. Diffuse type and lymphatic invasion were the independent risk factors for lymph node metastasis in patients with T1a gastric lesions. In the present study, among the patients with T1a lesions, 9.3 % of the patients with diffuse type gastric cancer and 62.5 % of the patients with lymphatic invasion also had lymph node metastasis. For patients with unfavorable factors, including both diffuse type and lymphatic invasion, the frequency of lymph node metastasis was 100 % (3/3). Consequently, ESD/EMR is a promising treatment for T1a gastric cancer, with a low rate of lymph node metastasis. For patients with diffuse type gastric cancer and the presence of lymphatic invasion, subsequent surgical resection is necessary.

It is unknown whether tumor depth in the submucosa is correlated with the frequency of lymph node metastasis and whether there is a critical safe cut-off value for ESD treated T1b lesions; these questions require further study. The rate of lymph node metastasis is 13 % in patients with lower-third (m3) mucosal invasion [4]. Hölscher et al. [4] divided submucosal invasion into upper-third (sm1), middle-third (sm2), and lower-third (sm3) subgroups. In that study, the rate of lymph node metastasis increased when the invasion of cancer was deeper. However, the above findings could only be applied to surgically resected specimens and cannot provide useful information for patients receiving EMR/ESD. Thus, in the present study, the depth of submucosal invasion was defined by the actual length measured by the pathologist. As shown in Table 2, even with 2 mm of submucosal invasion, the frequency of lymph node metastasis reached 28.6 %. The ESD treated T1b patients must be followed up carefully. Lymphatic invasion is the only factor associated with lymph node metastasis. Our results showed that the width of submucosal tumor invasion is associated with the pathological N category. One possible reason for this finding is that wider tumor invasion may significantly increase the number of affected lymphatic ducts, which will lead to increased lymph node metastasis. Tumor width in the submucosa might play an important role in lymphatic spread in gastric cancer. We suggest that the width of submucosal tumor invasion in ESD specimens should be measured to estimate the likelihood of lymph node metastases. Ishigami et al. [14] distinguished between different depths of invasion and considered the horizontal length of cancer invasion into the submucosa, measured as the maximum width in hematoxylin and eosin-stained sections. The authors found that all patients with sm1 invasion and less than 5 mm of submucosal invasion were free of nodal involvement. However, our results showed that even for T1b patients with less than 5 mm width of submucosal invasion, the frequency of lymph node metastasis is 63 %. As a result, there is still risk of

**Table 3** Risk factors of lymph node metastasis in gastric cancer patients with submucosal invasion (T1b)

| | No lymph node metastasis $n$=99 | Lymph node metastasis $n$=27 | Univariate analysis | Multivariate analysis | |
|---|---|---|---|---|---|
| | | | $P$ value | Odds ratio | $P$ value |
| Age (y/o) | | | 0.819 | | |
| <65/≧65 | 33/66 | 10/17 | | | |
| Gender | | | | | |
| M/F | 72/27 | 16/11 | 0.236 | | |
| Tumor size | | | 0.025 | | |
| <2 cm | 21 (87.5) | 3 (12.5) | | | |
| 2–4 cm | 60 (82.2) | 13 (17.8) | | | |
| ≧4 cm | 18 (62.1) | 11 (37.9) | | | |
| Tumor depth in submucosa | | | 0.146 | | |
| <2 mm | 40 (71.4) | 16 (28.6) | | | |
| 2–5 mm | 54 (83.1) | 11 (16.9) | | | |
| >5 mm | 5 (100) | 0 | | | |
| Tumor width in submucosa | | | 0.073 | | |
| <5 mm | 38 (69.1) | 17 (30.9) | | | |
| 5–10 mm | 47 (85.5) | 8 (14.5) | | | |
| >10 mm | 14 (87.5) | 2 (12.5) | | | |
| Lauren's type | | | 0.812 | | |
| Intestinal type | 72 (79.1) | 19 (20.9) | | | |
| Diffuse type | 27 (77.1) | 8 (22.9) | | | |
| Stromal reaction type | | | 0.255 | | |
| Medullary | 34 (87.2) | 5 (12.8) | | | |
| Intermediate | 61 (75.3) | 20 (24.7) | | | |
| Scirrhous | 4 (66.7) | 2 (33.3) | | | |
| Ming's classification | | | 0.042 | | |
| Expanding | 67 (84.8) | 12 (15.2) | | | |
| Infiltrative | 32 (68.1) | 15 (31.9) | | | |
| Cell differentiation | | | 0.411 | | |
| Poor | 32 (72.7) | 12 (27.3) | | | |
| Moderate | 65 (81.3) | 15 (18.7) | | | |
| Well | 2 (100) | 0 | | | |
| Lymphatic invasion | | | 0.001 | | 0.001 |
| Absent | 80 (86) | 13 (14) | | 1.00 | |
| Present | 18 (56.3) | 14 (43.7) | | 4.79 | |

lymph node metastases even the width of submucosal invasion less than 5 mm in T1b lesions.

Tumor size, submucosal invasion, and lymphatic invasion are independent risk factors for lymph node metastasis in EGC [15]. Among these factors, lymphatic invasion is the most important factor for lymph node metastasis [16]. In the present study, lymphatic invasion was associated with lymph node metastasis in both T1a and T1b lesions. Therefore, EGC with lymphatic invasion is associated with a high frequency of lymph node metastasis, and surgical resection is necessary.

## Conclusion

Our results showed that the frequency of lymph node metastasis is 4.9 % in T1a lesions and 21.4 % in T1b lesions. With 2 mm of submucosal invasion, the frequency of lymph node metastasis was 28.6 %. The tumor width in the submucosa is associated with the extent of lymph node metastasis. Lymphatic invasion is the strongest predictor of lymph node metastasis for both T1a and T1b lesions. We hope that our results provide useful treatment information for EGC patients and their physicians, particularly for patients who are concerned with the EMR/ESD treatment. The present NCCN guidlines do not give precise invasion depth of submucosal tumors in the indication of ESD ("does not penetrate beyond superficial submucosa"), hence measurement of width of the infiltration could be a useful plus parameter in the indication of gastrectomy after ESD.

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