Risk Factors of Submucosal or Lymphovascular Invasion in Early Gastric Cancer <2 cm

Yu Yi Choi, MD, Su Jin Kim, MD, Cheol Woong Choi, MD, PhD, Dae Hwan Kang, MD, PhD, Hyung Wook Kim, MD, PhD, Su Bum Park, MD, PhD, and Hyeong Seok Nam, MD

Abstract: Although prediction of submucosal (SM) or lymphovascular (LV) invasion is important before endoscopic resection of early gastric cancer (EGC), it can only be confirmed following endoscopic resection. After endoscopic resection, patients with SM or LV invasion may require additional surgery due to high risk of lymph node metastasis. We conducted a retrospective study to identify risk factors for SM or LV invasion before endoscopic submucosal dissection (ESD) of EGC. Between January 2009 and May 2014, we reviewed the data of patients with EGC who met the absolute indications for ESD before procedure: well and/or moderately differentiated adenocarcinomas, tumors ≤ 2 cm in length and absence of ulcer or ulcer-scar.

During study period, a total of 308 lesions in 297 patients were included. SM or LV invasion was detected in 34 lesions (34/308, 11.0%). Multivariate analysis revealed that moderately differentiated adenocarcinomas, tumors ≤ 2 cm in length and absence of ulcer or ulcer-scar.

Careful consideration of endoscopic treatment decision might be necessary for the patients with a moderately differentiated adenocarcinoma and EGC located on the upper and middle third of the stomach. (Medicine 95(22):e3822)

Abbreviations: CI = confidence interval, EGC ≈ early gastric cancer, ESD ≈ endoscopic submucosal dissection, EUS ≈ endoscopic ultrasonography, LVl = lymphovascular, OR = odds ratio, SMs = submucosal.

INTRODUCTION

Early gastric cancer (EGC) is a gastric cancer limited to the mucosa or submucosa, irrespective of lymph node metastasis. From the past, surgical gastrectomy with lymph node dissection is a golden standard of treatment for EGC because all gastric cancer may have a possibility of lymph node metastasis. Recently, endoscopic submucosal dissection (ESD) has become widely used as a curative modality for EGC with low risk of lymph node metastasis. Recent reports examining the long-term outcomes of endoscopic resection for EGC (differentiated-type adenocarcinoma; no surface ulceration; and a diameter of <2 cm) showed comparable overall survival with surgery.1–3 For the endoscopic treatment of EGC, Japanese4 and Korean5 gastric cancer treatment guidelines are almost the same. According to the guidelines, ESD is indicated as a standard treatment for lesions meeting the following criteria (absolute indications): well to moderately differentiated adenocarcinoma limited to the mucosa, within 2 cm in length, absence of ulcer or ulcer scar, and without lymphovascular (LV) invasion.4,5

Submucosal (SM) and LV invasions are independent risk factors for lymph node metastases and a critical prognostic factor in patients with EGC.6–10 SM invasion has been reported as an independent risk factor for LV invasion in endoscopically resected EGC, and the incidence of lymph node metastasis is significantly high in SM invasive EGC.6,11,12 This can be explained by the rare distribution of lymph capillaries in the mucosal layer. Although lymph capillaries are found in the deep lamina propria adjacent to and within the muscularis mucosa, most large lymph vessels are located in the submucosa.13,14 However, there is no way to precisely evaluate SM and LV invasion before endoscopic resection. Thus, when SM or LV invasion are found in endoscopically resected specimens, additional surgical treatment is sometimes required.

Therefore, we retrospectively analyzed the clinicopathologic associated factors with SM or LV invasion after endoscopic resection of EGC which met absolute indication before ESD.

PATIENTS AND METHODS

Patients

From January 2009 and May 2014, the medical records of the patients who underwent ESD at Pusan National University Yangsan Hospital in Korea due to EGC were reviewed, retrospectively. During study period, a total of 408 EGC lesions were resected based on an endoscopic forceps biopsy. Before endoscopic resection, lesions with ulceration, a diameter of >2 cm, an undifferentiated or mixed adenocarcinoma histology were excluded from this study. Included lesions were lesions meeting the absolute indication before ESD (well and/or moderately differentiated adenocarcinomas, tumors ≤2 cm in length and absence of ulcer or ulcer-scar tissue before endoscopic resection).2,3 In the present study, the risk factors were analyzed based on individual tumors because some patients had multiple lesions resected. After exclusion, a total 308 EGC lesions (in 297 patients) were included in this study (Figure 1). Written informed consent was obtained from all patients prior to the
A total of 408 EGC lesions were resected during study period

**Inclusion criteria**
- Well and/or moderately differentiated adenocarcinomas
- Tumors \( \leq 2 \) cm in length
- Absence of ulcer or ulcer-scar tissue

**Exclusion criteria**
- Undifferentiated adenocarcinomas \( (n = 8) \)
- Mixed adenocarcinoma \( (n = 11) \)
- Tumors \( > 2 \) cm in length \( (n = 51) \)
- Presence of ulcer or ulcer-scar tissue \( (n = 30) \)

**RESULTS**

During study period, a total of 308 EGC lesions met the inclusion criteria was included in this study. The patients’ mean age was 65.78 ± 9.49 years. The patient population was predominantly male \((246/308, 79.9\%)\). The most common gross type of lesion was the depressed type \((197/308, 64.0\%)\) and the most predominant location was the lower third \((230/308, 74.7\%)\). The mean tumor size of all lesions was 11.05 ± 4.73 mm. Most lesions were solitary \((280/308, 90.9\%)\) and well-differentiated adenocarcinomas \((208/308, 67.5\%)\). Among 308 lesions, 34 showed SM invasion \((11.0\%)\) and 5 showed LV invasion \((1.6\%)\). All of the LV invasive cancer was SM cancers. The baseline characteristics were shown in Table 1.

**TABLE 1. Baseline Characteristics of Patients Included in the Study**

| Characteristic                      | Total \((n = 308)\) |
|-------------------------------------|---------------------|
| Mean age, y \((±SD)\)               | 65.78 ± 9.49        |
| Male, n (%)                         | 246 \((79.9\%)\)    |
| Gross type, n (%)                   |                     |
| Elevated                            | 54 \((17.5\%)\)     |
| Flat                                | 57 \((18.5\%)\)     |
| Depressed                           | 197 \((64.0\%)\)    |
| Surface redness, n (%)              | 210 \((68.2\%)\)    |
| Tumor location, n (%)               |                     |
| Upper                               | 15 \((4.9\%)\)      |
| Middle                              | 63 \((20.4\%)\)     |
| Lower                               | 230 \((74.7\%)\)    |
| Tumor number, n (%)                 |                     |
| Solitary                            | 280 \((90.9\%)\)    |
| Multiple                            | 28 \((9.1\%)\)      |
| Tumor size, n (%) \(≤10\) mm        | 151 \((49.0\%)\)    |
| \(>10\) mm                          | 157 \((51.0\%)\)    |
| Histological type, n (%)            |                     |
| Well differentiated                 | 208 \((67.5\%)\)    |
| Moderately differentiated           | 100 \((32.5\%)\)    |
| SM invasive cancer, n (%)           | 34 \((11.0\%)\)     |
| SM and LV invasive cancer, n (%)    | 5 \((1.6\%)\)       |

LV = lymphovascular, SD = standard deviation, SM = submucosa.
Twelve of 34 patients with SM or LV invasive EGC underwent additional radical surgical treatments within 2 months after ESD. Lymph node metastasis was found in 2 patients (2/12). A local recurrence was found in 1 patient after 6 months after ESD. The patient underwent additional surgical treatment, and there was no lymph node metastasis. Twenty-one patients did not undergo additional surgical treatment, and there was no evidence of recurrence during follow-up period (range, 17–63 months). A flow diagram of the results of 34 patients with SM or LV invasive EGC was shown in Figure 2.

The clinicopathological data of the lesions, with and/or without SM or LV invasion, are summarized in Table 2.

### Table 2. Characteristics and Associated Risk Factors for Submucosa or Lymphovascular Invasive Early Gastric Cancer: Univariate Analysis

|                      | SM/LV Invasion (−) (n = 274) | SM/LV Invasion (+) (n = 34) | P Value |
|----------------------|------------------------------|-----------------------------|---------|
| Mean age, y (±SD)    | 65.83 ± 9.28                 | 65.35 ± 11.21               | 0.782   |
| Male gender, n (%)   | 221 (80.7)                   | 25 (73.5)                   | 0.328   |
| Gross type, n (%)    |                              |                             | 0.532   |
| Elevated             | 46 (16.8)                    | 8 (23.5)                    |         |
| Flat                 | 50 (18.2)                    | 7 (20.6)                    |         |
| Depressed            | 178 (65.0)                   | 19 (55.9)                   |         |
| Surface redness, n (%) | 183 (66.8)              | 27 (79.4)                   | 0.004   |
| Tumor location, n (%) |                             |                             |         |
| Upper                | 10 (3.6)                     | 5 (14.7)                    |         |
| Middle               | 53 (19.3)                    | 10 (29.4)                   |         |
| Lower                | 211 (77.0)                   | 19 (55.9)                   |         |
| Tumor number, n (%)  | 250 (91.2)                   | 30 (88.2)                   | 0.531   |
| Solitary             | 24 (8.8)                     | 4 (11.8)                    |         |
| Multiple             |                              |                             |         |
| Mean tumor size, mm (±SD) | 10.92 ± 4.81              | 12.15 ± 3.96                | 0.153   |
| Tumor size, n (%)    |                              |                             | 0.544   |
| ≤10 mm               | 136 (49.6)                   | 15 (44.1)                   |         |
| >10 mm               | 138 (60.4)                   | 19 (55.9)                   |         |
| Invasion depth, n (%) |                              |                             |         |
| m                    | 274 (100)                    | 1 (2.9)                     |         |
| SM1                  | 0 (0)                        | 16 (47.1)                   |         |
| SM2                  | 0 (0)                        | 8 (23.5)                    |         |
| SM3                  | 0 (0)                        | 9 (26.5)                    |         |
| Mean SM depth, μm (±SD) | 748.97 ± 629.61             |                             | <0.001  |
| Histological type, n (%) |                             |                             |         |
| Well differentiated   | 195 (71.2)                   | 13 (38.2)                   |         |
| Moderately differentiated | 79 (28.2)               | 21 (61.8)                   |         |

LV = lymphovascular, SD = standard deviation, SM = submucosa.
and the most important prognostic factor is lymph node metastasis (compared with well-differentiated adenocarcinoma) was found (OR 4.157; 95% CI 1.920–9.002; P<0.001, odds ratio [OR] 3.100, 95% confidence interval [CI] 1.421–6.766) and moderately differentiated histology (P < 0.001, OR 4.157, 95% CI 0.770–4.908) were significant risk factors (Table 3).

### DISCUSSION

The overall 5-year survival rate for treated EGC is >90%, and the most important prognostic factor is lymph node metastasis.24,25 Ideal indication for ESD is EGC without risk of lymph node metastasis. However, it is impossible to know lymph node metastasis accurately before surgical resection. Therefore, the indications for ESD were determined based on the data of surgical resections to date. Among the absolute indications for endoscopic treatment of EGC, histologic type (well and/or moderately differentiated adenocarcinomas), tumors size (≤2 cm in length), and absence of ulcer can be predicted or diagnosed before endoscopic resection from endoscopic diagnostic approach. However, it is difficult to predict the depth of invasion (lesions limited to the mucosal layer) precisely. In the recent years, accurate prediction of tumor invasion depth in EGC is crucial because we could provide the patients the opportunity of an endoscopic treatment. To date, several studies about the endoscopic prediction of tumor invasion depth in EGC showed 72% to 78% accurate prediction rate by conventional endoscopy.19–22 Although, endoscopic ultrasonography is a widely used for detecting the depth of EGC in many institutions, the reported accurate prediction rate of depth of invasion in EGC was 67.4% to 85%.19,22 In addition, among absolute indication, it is impossible to determine LV involvement before resection.

For the prediction of submucosal invasive cancer, various endoscopic morphologic factors were reported; large tumor size (≥30 mm in diameter), irregular surface (including nodules in the depressed area), SM tumor-like lesions, fold thickness, and fusion of convergent folds in the case of a lesion with fold convergence.20,22 In this study, we included only EGCS met the absolute indication (lesion size <2 cm and no ulceration) before resection. Therefore, the most common reported significant morphologic endoscopic findings were not significant predictable factors for SM or LV invasion.

In the present study, a moderately differentiated adenocarcinoma histology (OR 4.157; 95% CI 1.920–9.002; P<0.001) (compared with well-differentiated adenocarcinoma) was found to be a significant risk factor for SM or LV invasion. Although well to moderately differentiated EGCS are accepted as an absolute indication for ESD, a moderately differentiated adenocarcinoma was a significant risk factor for SM or LV invasion compared with well-differentiated adenocarcinoma.23,24 Furthermore, a moderately differentiated EGC is often associated with a mixed histological type of EGC which is a risk factor for lymph node metastasis.24,25 Mixed histological type EGCS are comprised histologically of nonhomogenous mixtures of intestinal type and diffuse type carcinomas. Although the clinical outcomes and significance of mixed histological type EGCS treated with ESD are poorly understood, complete resection rate was lower and local recurrence was more frequent than other types of EGC.26 In the present study, 11 lesions were mixed histology during data collection, but these lesions were excluded during data analysis because we limited the study EGC lesions with purely well- to moderate-differentiated carcinoma. More precautions are required for moderately differentiated EGCS was found from endoscopic forces biopsy compared with well-differentiated adenocarcinoma before ESD.

Unexpectedly, tumors located in the upper and middle third of the stomach had a significantly higher risk for SM or LV invasion in the present study. Tumors located in the upper and middle third of the stomach were larger (11.63 ± 4.66 mm vs 10.86 ± 4.75 mm, P = 0.214), although the difference was not significant. We could not know why the location of the EGC was the significant risk factor. One study revealed differences in thickness of according to the location of the stomach. The entire wall thickness is thicker in the antrum than the body and cardia. And, the thickness of the SM layer decreased from the antrum to the cardia and the body.14 Thus, EGC located in the upper portion of the stomach might be even deep invasive cancer though same size. The other possible explanation is technical factor associated with endoscopic experience. EGC located lower third of the stomach, especially antrum, might be easily detected by unexperienced hand or unclosed observed endoscopy. However, to detect EGCS in the upper and middle third of the stomach, more experienced handed or closed observed endoscopic procedure might be required. Therefore, EGC lesions located in the upper and middle third of the stomach might be delayed diagnosed. Further studies might be required to elucidate the reasons of this finding.

Gotoda et al8 reported the well or moderately differentiated adenocarcinoma with minute SM invasion (≤500 μm, SM1). However, other studies reported that 6.3% to 15% of superficial SM invasive (SM1, ≤500 μm) associated with lymph node metastasis.23,27 In the present study, 13 of 34 patients with SM or LV invasive EGCS underwent additional radical surgical treatments. Principally, after diagnosis of SM or LV invasive cancer, we explained the risk of lymph node metastasis and

### TABLE 3. Associated Risk Factors for Submucosa or Lymphovascular Invasive Early Gastric Cancer: Multivariate Analysis

| Depressed gross type | 0.631 | 0.289–1.374 | 0.246 |
| Upper and middle location | 3.100 | 1.421–6.766 | 0.004 |
| Tumor size: >10 mm | 1.055 | 0.492–2.265 | 0.890 |
| Tumor number: multiple | 1.848 | 0.548–6.223 | 0.322 |
| Moderately differentiated histology | 4.157 | 1.920–9.002 | <0.001 |
| Surface redness | 1.945 | 0.770–4.908 | 0.159 |

CI = confidence interval.
recommended operation. However, only 12 patients accepted additional operation, just after ESD. Lymph node metastasis was found in 2 patients with SM invasion. One patient presented with a local recurrence during follow-up after ESD. After additional surgery, lymph node metastasis was not found. The remainder of patients did not want additional surgical operation (all lesions were no evidence of LV invasion). During follow-up period, no recurrence of gastric cancer was found during follow-up (range, 17–63 months).

There are several limitations in the present study. First, it was retrospectively conducted in a single center. The number of enrolled cases was lack for supporting for these risk factors definitely. Accumulation of data from multicenter and prospective studies may more accurately predict the SM or LV invasive EGC in small size (<2 cm). However, the identified risk factors, including other studies so far, may be helpful for further studies and evidences to cautious endoscopic treatment of EGC. Second, among endoscopic findings, we used only lesion diameter and macroscopic appearances of lesion for the analyses. If recent diagnostic technologies such as narrow band image, magnifying endoscopy, endoscopic ultrasound, or endomicroscopy might be used, more accurate predictable data might be collected.

In summary, this study identified 11% of EGC lesions showed SM or LV invasions, although those were included in the absolute indications before ESD. Associated risk factors with SM or LV invasions were histologic type (moderately differentiated adenocarcinoma) and location (in the upper and middle third of the stomach) of the lesion. Therefore, precautions are required in the management of patients with these 2 risk factors. Before ESD, for lesions with the 2 risk factors, endoscopists should explain patients for the possibility of SM or LV invasion after ESD.

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