Predictors of lymph node metastasis and residual tumor in early gastric cancer patients after noncurative endoscopic resection: a systematic review and meta-analysis

Bolun Jiang, Li Zhou, Jun Lu, Yizhi Wang and Junchao Guo

Abstract

Background: It is challenging to identify the prevalence of lymph node metastasis (LNM) and residual tumor in patients with early gastric cancer (EGC) who underwent noncurative endoscopic resection (ER). This present meta-analysis was aimed to establish imperative potential predictive factors in order to select the optimal treatment method.

Methods: A systematic literature search of PubMed, Embase, and Cochrane Library databases was performed through 1 February 2019 to identify relevant studies, which investigated risk factors for LNM and residual tumor in patients with EGC who underwent noncurative ER. Eligible data were systematically reviewed through a meta-analysis.

Results: Overall, 12 studies investigating the risk factor of LNM were included, totaling 3015 patients, 7 of which also involved cancer residues. After the present meta-analysis, six predictors, including tumor size >30 mm, tumor invasion depth (≥500 μm from the muscularis mucosae), macroscopic appearance, undifferentiated histopathological type, positive vertical margin, and presence of lymphovascular invasion (including lymphatic invasion and vascular invasion) were significantly associated with LNM, whereas tumor size >30 mm, positive horizontal margin, and positive vertical margin were identified as significant predictors for the risk of residual tumor. No evidence of publication bias was observed.

Conclusions: Six and three variables were established as significant risk factors for LNM and residual tumor in patients with EGC who underwent noncurative ER, respectively. Patients with EGC who present these risk factors after noncurative ER are strongly suggested to receive additional surgery, while others might be suitable for strict follow-up. This might shed some new light on the selection of follow-up treatment for noncurative ER.

Keywords: early gastric cancer, lymph node metastasis, noncurative endoscopic resection, residual tumor, risk factor

Received: 16 September 2019; revised manuscript accepted: 25 May 2020.

Introduction

Gastric cancer has become the third most common cause of cancer death worldwide. The National Central Cancer Registry of China identified gastric cancer, following lung cancer, as the second most incident cancer and leading cause of cancer mortality. Early gastric cancer (EGC) is commonly defined when the depth of tumor invasion is confined to the mucosa or submucosa, regardless of lymph node metastasis (LNM). EGC has been increasingly detected in Asia, especially in Japan, mainly attributed to a nationwide
screening program and novel endoscopic technologies and equipment. In addition to conventional radical gastrectomy, endoscopic resection (ER), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), has become an effective treatment for EGC that intends to perform an en bloc resection and precise histopathological assessment of the lesion with the advantages of being less invasive and more economical.

Based on the common recognition of the prevalence of LNM and residual tumor being the significant prognostic factor for patients with EGC, curability of ER for EGC has been classified into three groups: curative resection, expanded-indication curative resection, and non-curative resection, with additional surgical treatment being indicated for noncurative resection. However, as LNM is present in only 5–13% of patients who underwent noncurative ER, standard radical surgery might be overaggressive. Data on establishing risk factors for prevalence of LNM and residual tumor in patients with EGC who underwent noncurative endoscopic treatments is currently insufficient. This present article conducted a meta-analysis of risk factors for LNM and residual tumor in patients with noncurative ER in order to determine the certain patient population requiring additional gastrectomy, which might shed new light on the current definition of noncurative ER.

Methods
This systematic review was performed in accordance with the methodology proposed by the Meta-analysis Of Observational Studies in Epidemiology group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search strategy
An online systematic literature search of PubMed, Embase, and Cochrane Library databases was conducted, using the following keywords: “early gastric cancer” AND (“endoscopic resection” OR “ER” OR “endoscopic submucosal dissection” OR “ESD” OR “endoscopic mucosal resection” OR “EMR”) AND (“gastrectomy” OR “surgery” OR “gastric resection”) AND (“lymph node metastasis” OR “lymph node involvement” OR “lymphatic metastasis” OR “lymphatic involvement”), from inception through 1 February 2019. Free-text and MeSH searches were performed as appropriate. In addition, manual search of the reference lists from available studies was conducted for potential articles. Two researchers implemented the selection process independently, and the divergences were resolved through discussion.

Eligibility criteria for study selection
Studies were deemed eligible according to the PICO approach.

- **P**: Patients diagnosed with EGC and who underwent noncurative ER.
- **I**: Additional surgery after noncurative ER with available data on LNM and residual tumor.
- **C**: Comparison of patient subgroups with various potential risk factors related to LNM and residual tumor.
- **O**: LNM and residual tumor.

The inclusion criteria for eligible studies were as follows: (1) study design (randomized controlled trial, cohort, or case–control); (2) articles published in English; (3) patients underwent noncurative ER for EGC, with noncurative resection defined by the Japanese gastric cancer treatment guidelines 2010 (version 3); (4) patients underwent additional gastrectomy after noncurative ER; (5) adequate information about risk factors for LNM and residual tumor, with available data for extraction to calculate the pooled odds ratio (OR) or mean difference (MD). When dual (or multiple) studies were reported by the same authors and/or institution, study of higher quality or the most recent publication was included in the analysis. In addition, abstracts, case reports, reviews, letters to editor, editorials, expert opinions, conference abstracts, or meeting proceedings were excluded.

Data abstraction and quality assessment
Two researchers reviewed the title and abstract of each article searched independently. Full-text versions of the original articles were acquired and required information was prudently extracted in a standardized manner. A third researcher was asked to audit the study in case of any discrepancies. The following information was collected: first author, publication year, country of publication, data collection period, study design, number
of patients, baseline and clinicopathological characteristics of patients, risk factors of LNM and residual tumor, relevant OR, MD, and 95% confidence interval (CI) (or provide sufficient data for calculation).

Two researchers independently evaluated the quality of the eligible studies using the modified Newcastle–Ottawa Quality Assessment Scales (NOS). Quality categories were defined as high quality (score 7–9), medium quality (score 4–6) and low quality (score 0–3).

Statistics
Sensitivity analyses were performed using Review Manager version 5.3 to calculate the pooled OR with a 95% CI for dichotomous variables, and the MD with a 95% CI for continuous variables, which were reexamined by Stata version 15.0. Heterogeneity among included studies was measured using a Q test and I² statistic. When the p value of Q test >0.1 and I² <50% indicated no evident heterogeneity, a fixed-effects model was used; otherwise, a random-effects model was carried out. A p value <0.05 was considered a statistically significant difference. Publication bias was evaluated with a funnel plot via Review Manager version 5.3, and Begg’s and Egger’s tests via Stata version 15.0.

Results

Eligible studies and study characteristics
The searching strategy initially identified 593 potentially relevant articles via PubMed (n=211), Embase (n=367), and Cochrane Library databases (n=15), of which 173 studies were excluded for duplication. After scanning the titles and abstracts of the remaining articles, a total of 388 studies were excluded, owing to irrelevance and inaccurate article types, which leaves 32 studies for full-text evaluation. Among the remaining studies, 2 papers were excluded for study population overlap; 10 were removed due to inadequate data; 8 were removed for enrolled patients’ inconformity of noncurative ER criteria; eventually, 12 papers met the inclusion criteria and were subjected to further meta-analysis (Figure 1).11–13,17–25

The baseline characteristics of the 12 studies included in the meta-analysis are presented (Table 1). All studies were performed in East Asian countries, including eight in Japan and four in South Korea, which enrolled a total number of 3015 patients. All the included studies were retrospective observational studies, which enrolled patients with EGC who underwent additional surgery after noncurative ESD or EMR, with the indications of noncurative resection following the Japanese gastric cancer treatment guidelines 2010 (version 3).9 All the 12 observational studies reported the risk factors for postoperative pathological diagnosed LNM, and 7 of them also investigated risk factors for residual tumor as the outcome. Among the enrolled 12 studies, LNM was reported in 247 patients (8.2%), whereas residual tumor was presented in 141 patients (13.5%) from the 7 included studies. In terms of the NOS quality assessment, all the included studies were graded as high quality (score 7–9).

Risk factors for LNM

Tumor size. The relationship between tumor size and prevalence of LNM was evaluated in eight studies, of which six studies using the cutoff value of 30 mm. For the cutoff value of 30 mm subgroup, a fixed-effects model was used to assess the data (p=0.96, I²=0%). The pooled analysis elucidated that the risk of LNM was significantly higher in patients with tumor size >30 mm than that of ≤30 mm (pooled OR = 1.63, 95% CI = 1.20–2.22, p = 0.002) (Figure 2). In contrast, no statistical significance of a cutoff value of 20 mm was revealed (pooled OR = 1.15, 95% CI = 0.36–3.69, p = 0.82) through a fixed-effects model (p = 0.33, I² = 0%).

Tumor invasion depth. The influence of tumor invasion depth on the risk of LNM was reported in 11 studies. Based on no statistically significant heterogeneity (p = 0.98, I² = 0%), a fixed-effects model was applied to analyze the data. This pooled analysis suggested that patients with tumor invasion depth ≥SM2 (≥500 μm from the muscularis mucosae) had significantly higher prevalence of LNM than patients with tumor invasion depth <SM2 (pooled OR = 2.88, 95% CI = 2.07–3.99, p < 0.00001) (Figure 2).

Macroscopic appearance. Six studies investigated the relationship between the prevalence of LNM and tumor macroscopic appearance. A fixed-effects model was adopted to analyze data for no statistically significant heterogeneity among
studies ($p=0.43$, $I^2=0\%$). This pooled analysis suggested that patients with flat or elevated tumor macroscopic appearance had significantly higher risk of LNM than patients with depressed tumor macroscopic appearance (pooled OR = 2.17, 95% CI = 1.32–3.58, $p=0.002$) (Figure 2).

**Histopathological type.** Ten studies investigated the relationship between risk of LNM and tumor histopathological type. No statistically significant heterogeneity was detected ($p=0.23$, $I^2=23\%$), and a fixed-effects model was applied to assess the data. The pooled analysis revealed that the prevalence of LNM was significantly higher in patients with histologically undifferentiated type than that of differentiated type (pooled OR = 1.41, 95% CI = 1.03–1.92, $p=0.03$) (Figure 2).

**Vertical margin.** There were 10 studies that assessed the relationship between the risk of LNM and resection vertical margin. A fixed-effects model was applied to analyze data due to no statistically significant heterogeneity ($p=0.40$, $I^2=4\%$). Findings from this pooled analysis revealed that the prevalence of LNM was significantly higher in patients with positive vertical
margin than in patients with negative vertical margin (pooled OR = 2.02, 95% CI = 1.50–2.73, p < 0.00001) (Figure 2).

**Lymphovascular invasion.** There were four, seven, and six studies that reported the influence of tumor lymphovascular invasion (LVI), lymphatic invasion (LI), and vascular invasion (VI) on the risk of LNM, respectively. For the four studies providing data of lymphovascular invasion, a random-effects model was applied to analyze data for significant heterogeneity (p = 0.06, I² = 59%). This pooled analysis revealed that patients with tumor lymphovascular invasion had significantly higher risk of LNM than patients without tumor lymphovascular invasion (pooled OR = 3.46, 95% CI = 1.35–8.87, p = 0.01) (Figure 3).

For the LI subgroup, a fixed-effects model was used due to nonsignificant heterogeneity (p = 0.59, I² = 0%). Results showed that patients with tumor LI had a statistically significant higher risk of LNM than patients without tumor LI (pooled OR = 5.60, 95% CI = 3.85–8.14, p < 0.00001) (Figure 3). Similarly for the vascular invasion subgroup, a statistically significant association was revealed between the prevalence of LNM and tumor vascular invasion (pooled OR = 2.42, 95% CI = 1.64–3.57, p < 0.00001) (Figure 4).

| Study                  | Publication year | Country   | Study interval       | Study design   | Study population | Number of cases | Number of cases with LNM | Number of cases with residual tumor |
|------------------------|------------------|-----------|----------------------|----------------|------------------|------------------|------------------------|-------------------------------------|
| Hatta et al.           | 2017             | Japan     | 2000.01–2011.08      | Retrospective study | ESD              | 1101             | 94 (8.5%)              | NA                                  |
| Ishida et al.          | 2018             | Japan     | 2008.01–2016.08      | Retrospective cohort | ESD              | 83               | 10 (12%)               | 12 (14%)                           |
| Ishii et al.           | 2016             | Japan     | 1997.03–2013.03      | Retrospective cohort | ER               | 112              | 12 (10.7%)             | NA                                  |
| Ito et al.             | 2013             | Japan     | 2001.04–2012.12      | Retrospective study | ER               | 41               | 4 (9.8%)               | 6 (14.6%)                          |
| Jung et al.            | 2017             | South Korea | 2007.01–2015.01     | Retrospective cohort | ER               | 321              | 23 (7.2%)              | NA                                  |
| Kikuchi et al.         | 2017             | Japan     | 2004.01–2013.08      | Retrospective study | ER               | 73               | 8 (11%)                | 8 (11%)                            |
| Kim et al.             | 2015             | South Korea | 2000–2011           | Retrospective cohort | ER               | 194              | 11 (5.7%)              | 10 (5.2%)                          |
| Kim et al.             | 2017             | South Korea | 2004.07–2014.07     | Retrospective cohort | ER               | 350              | 30 (8.5%)              | 73 (20.8%)                         |
| Park et al.            | 2013             | South Korea | 2003.01–2012.12     | Retrospective study | ESD              | 102              | 13 (12.7%)             | NA                                  |
| Sunagawa et al.        | 2017             | Japan     | 2005.01–2015.10      | Retrospective study | ESD              | 200              | 15 (7.5%)              | 23 (11.5%)                         |
| Suzuki et al.          | 2017             | Japan     | 1999–2010            | Retrospective study | ESD              | 338              | 18 (5.3%)              | NA                                  |
| Toyokawa et al.        | 2016             | Japan     | 2004.04–2013.12      | Retrospective cohort | ESD              | 100              | 9 (9%)                 | 9 (9%)                             |

LNM, lymph node metastasis; EGC, early gastric cancer; ER, endoscopic resection; ESD, endoscopic submucosal dissection; NA, not available.
### Tumor size

| Study or Subgroup | >30mm | ≤30mm | Odds Ratio | Odds Ratio |
|-------------------|-------|-------|------------|------------|
|                   | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Hatta 2017        | 53     | 479   | 1.76 (1.15, 2.70)   |
| Ishida 2018       | 5      | 35    | 1.47 (0.39, 5.51)   |
| Ishii 2016        | 3      | 31    | 0.86 (0.22, 3.40)   |
| Kim 2017          | 15     | 142   | 1.67 (0.79, 3.55)   |
| Sunagawa 2017     | 8      | 80    | 1.73 (0.60, 4.98)   |
| Suzuki 2017       | 8      | 120   | 1.49 (0.57, 3.87)   |

Total (95% CI) 869 1312 100.0% 1.63 (1.20, 2.22)

### Tumor invasion depth

| Study or Subgroup | ≤SM2 | M/SM1 | Odds Ratio | Odds Ratio |
|-------------------|------|-------|------------|------------|
|                   | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Hatta 2017        | 30    | 197   | 2.36 (1.48, 3.75)   |
| Ishida 2018       | 8     | 54    | 2.25 (0.46, 11.87)  |
| Ishii 2016        | 12    | 65    | 2.20 (1.28, 3.85)   |
| Ito 2013          | 1     | 4     | 2.59 (0.13, 53.12)  |
| Jung 2017         | 100   | 207   | 2.78 (0.92, 8.38)   |
| Kitahara 2015     | 1     | 7     | 2.38 (0.26, 20.02)  |
| Jung 2017         | 14    | 144   | 3.36 (0.46, 29.31)  |
| Sunagawa 2017     | 15    | 207   | 3.16 (1.32, 7.58)   |
| Suzuki 2016       | 8     | 71    | 3.56 (0.42, 29.80)  |

Total (95% CI) 1348 1565 100.0% 2.88 (2.07, 3.99)

### Macroscopic appearance

| Study or Subgroup | Flat | Elevate | Odds Ratio | Odds Ratio |
|-------------------|------|---------|------------|------------|
|                   | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Ishida 2018       | 7     | 35     | 1.75 (0.99, 15.73) |
| Ishii 2016        | 5     | 39     | 1.18 (0.41, 3.70)  |
| Ito 2013          | 1     | 16     | 5.54 (0.52, 58.76) |
| Jung 2017         | 5     | 15     | 1.23 (0.51, 2.99)  |
| Sunagawa 2017     | 9     | 56     | 4.40 (1.49, 13.03) |
| Toyokawa 2016     | 6     | 49     | 2.23 (0.53, 9.48)  |

Total (95% CI) 390 467 100.0% 2.17 (1.32, 3.58)

### Histopathological type

| Study or Subgroup | undifferentiated | differentiated | Odds Ratio | Odds Ratio |
|-------------------|-----------------|----------------|------------|------------|
|                   | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Hatta 2017        | 79    | 701   | 2.10 (1.27, 3.47) |
| Ishida 2018       | 5     | 31    | 1.81 (0.48, 6.43)  |
| Ishii 2016        | 5     | 38    | 1.45 (0.43, 4.92)  |
| Ito 2013          | 0     | 7     | 0.54 (0.03, 11.27) |
| Jung 2017         | 10    | 96    | 1.27 (0.52, 3.11)  |
| Kitahara 2015     | 1     | 8     | 0.21 (0.03, 1.38)  |
| Kim 2017          | 6     | 106   | 0.52 (0.22, 1.99)  |
| Sunagawa 2017     | 1     | 30    | 0.38 (0.05, 3.00)  |
| Suzuki 2017       | 3     | 67    | 0.80 (0.22, 2.85)  |
| Toyokawa 2016     | 4     | 18    | 2.40 (0.05, 16.44) |

Total (95% CI) 1101 1616 100.0% 1.41 (1.03, 1.92)

### Vertical margin

| Study or Subgroup | >30mm | ≤30mm | Odds Ratio | Odds Ratio |
|-------------------|-------|-------|------------|------------|
|                   | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Hatta 2017        | 53    | 479   | 1.76 (1.15, 2.70) |
| Ishida 2018       | 5     | 35    | 1.47 (0.39, 5.51) |
| Ishii 2016        | 3     | 31    | 0.86 (0.22, 3.40) |
| Kim 2017          | 15    | 142   | 1.67 (0.79, 3.55) |
| Sunagawa 2017     | 8     | 80    | 1.73 (0.60, 4.98) |
| Suzuki 2017       | 8     | 120   | 1.49 (0.57, 3.87) |

Total (95% CI) 869 1312 100.0% 1.63 (1.20, 2.22)

---

Figure 2. Forest plot for the relationship between LNM and tumor size, tumor invasion depth, macroscopic appearance, histopathological type and vertical margin, respectively. LNM, lymph node metastasis.
Lymphovascular invasion

| Study or Subgroup | Positive Events | Total | Negative Events | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|------------------|----------------|-------|----------------|-------|--------|-----------------------------|-----------------------------|
| Kim 2015         | 6              | 113   | 5              | 81    | 25.3%  | 0.85 [0.25, 2.89]           |                             |
| Kim 2017         | 22             | 128   | 8              | 222   | 32.6%  | 5.55 [2.39, 12.89]          |                             |
| Suzuki 2017      | 13             | 136   | 5              | 202   | 28.4%  | 4.16 [1.45, 11.97]          |                             |
| Toyokawa 2016    | 8              | 48    | 1              | 52    | 13.6%  | 10.20 [1.22, 84.95]         |                             |
| Total (95% CI)   | 425            | 557   | 100.0%         |       |        | 3.46 [1.35, 8.87]           |                             |

Total events: 49
Heterogeneity: Tau^2 = 0.52, I^2 = 7.36, df = 19 (P = 0.06); I^2 = 59%
Test for overall effect: Z = 2.58 (P = 0.010)

Nonsignificant risk factors. In the present meta-analysis of the risk factors for the prevalence of LNM after noncurative ER, patient’s age over 70 years (pooled OR = 0.92, 95% CI = 0.48–1.78, p = 0.81), age (MD = −0.52, 95% CI = −5.71–4.67, p = 0.84), sex (pooled OR = 0.70, 95% CI = 0.44–1.12, p = 0.14), ulcerative findings (pooled OR = 0.85, 95% CI = 0.58–1.23, p = 0.39), tumor location (pooled OR = 1.03, 95% CI = 0.66–1.62, p = 0.88), tumor positive horizontal margin (pooled OR = 0.69, 95% CI = 0.39–1.23, p = 0.21), treatment options between EMR and ESD (pooled OR = 0.91, 95% CI = 0.26–3.15, p = 0.88) were revealed as nonsignificant risk factors (Table 2; Supplemental Figures 1 to 8).

Vascular invasion

| Study or Subgroup | Positive Events | Total | Negative Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|------------------|----------------|-------|----------------|-------|--------|-----------------------------|-----------------------------|
| Hatta 2017       | 69             | 443   | 25             | 658   | 65.0%  | 4.67 [2.90, 7.51]           |                             |
| Ishida 2018      | 6              | 33    | 4              | 50    | 10.0%  | 2.56 [0.66, 9.87]           |                             |
| Ishii 2016       | 10             | 48    | 2              | 64    | 5.2%   | 8.16 [1.70, 39.25]          |                             |
| Ito 2013         | 3              | 20    | 1              | 21    | 3.2%   | 3.53 [0.34, 37.15]          |                             |
| Jung 2017        | 19             | 130   | 4              | 191   | 10.6%  | 8.00 [2.65, 24.12]          |                             |
| Kikuchi 2017     | 8              | 39    | 0              | 34    | 1.6%   | 18.62 [1.03, 335.95]        |                             |
| Sunagawa 2017    | 13             | 72    | 2              | 128   | 4.5%   | 13.88 [3.03, 63.50]         |                             |
| Total (95% CI)   | 785            | 1146  | 100.0%         |       |        | 5.60 [3.85, 8.14]           |                             |

Total events: 128
Heterogeneity: Chi^2 = 4.66, df = 6 (P = 0.59); I^2 = 0%
Test for overall effect: Z = 9.03 (P < 0.00001)

Figure 3. Forest plot for the relationship between LNM and lymphovascular invasion, lymphatic invasion, and vascular invasion, respectively.

LNM, lymph node metastasis.

CI = 1.69–3.46, p < 0.00001) through a fixed-effects model (p = 0.59, F = 0%) (Figure 3).

Nonsignificant risk factors. In the present meta-analysis of the risk factors for the prevalence of LNM after noncurative ER, patient’s age over 70 years (pooled OR = 0.92, 95% CI = 0.48–1.78, p = 0.81), age (MD = −0.52, 95% CI = −5.71–4.67, p = 0.84), sex (pooled OR = 0.70, 95% CI = 0.44–1.12, p = 0.14), ulcerative findings (pooled OR = 0.85, 95% CI = 0.58–1.23, p = 0.39), tumor location (pooled OR = 1.03, 95% CI = 0.66–1.62, p = 0.88), tumor positive horizontal margin (pooled OR = 0.69, 95% CI = 0.39–1.23, p = 0.21), treatment options between EMR and ESD (pooled OR = 0.91, 95% CI = 0.26–3.15, p = 0.88) were revealed as nonsignificant risk factors (Table 2; Supplemental Figures 1 to 8).

Risk factors for residual tumor

Tumor size. The relationship between tumor size and prevalence of residual tumor was evaluated in three studies, which applied the tumor size with 30 mm as a cutoff value. A fixed-effects model was used to assess the data (p = 0.55, F = 0%). The pooled analysis exhibited that the risk of residual tumor was significantly higher in patients...
with tumor size $\geq 30\,\text{mm}$ than in patients with tumor size $<30\,\text{mm}$ (pooled OR = 2.89, 95% CI = 1.89–4.43, $p < 0.00001$) (Figure 4).

**Horizontal margin.** The influence of ER horizontal margin on the risk of residual tumor was investigated in six studies. Based on nonsignificant heterogeneity ($p = 0.60, I^2 = 0\%$), a fixed-effects model was applied to analyze data. Findings from this meta-analysis suggested a significant difference for the prevalence of residual tumor between patients with positive horizontal margin and patients with negative horizontal margin (pooled OR = 12.70, 95% CI = 8.20–19.66, $p < 0.00001$) (Figure 4).

**Vertical margin.** Six studies assessed the relationship of the risk of residual tumor and the resection vertical margin. A random-effects model was applied to analyze data due to statistically significant heterogeneity ($p = 0.05, I^2 = 54\%$). Results from this meta-analysis revealed that the prevalence of residual tumor was significantly higher in patients with positive vertical margin than in patients with negative vertical margin (pooled OR = 2.37, 95% CI = 1.14–4.92, $p = 0.02$) (Figure 4).

### Table 2. Meta-analysis identified risk factors for LNM in patients with EGC who underwent noncurative ER.

| Predictors                      | Number of studies | Heterogeneity | Pooled OR/MD (95% CI) | $p$ value | Begg's test ($Pr > |z|)$ | Egger's test ($P > |t|$) |
|---------------------------------|-------------------|---------------|-----------------------|-----------|-------------------------|-------------------------|
| Age ($\geq 70\,\text{years}$)  | 4                 | 0% (0.78)     | 0.92 (0.48–1.78)      | 0.81      | 0.734                   | 0.140                   |
| Age (mean $\pm$ SD)            | 3                 | 87% (0.0004)  | $-0.52$ (-5.71–-4.67) | $0.84$    | 0.296                   | 0.218                   |
| Sex                            | 8                 | 0% (0.62)     | 0.70 (0.44–1.12)      | 0.14      | 0.711                   | 0.136                   |
| Tumor size ($>30\,\text{mm}$)  | 6                 | 0% (0.96)     | 1.63 (1.20–2.22)      | 0.002     | 0.133                   | 0.104                   |
| Tumor size ($>20\,\text{mm}$)  | 2                 | 0% (0.33)     | 1.15 (0.36–3.69)      | 0.82      | 1.000                   | –                       |
| Histopathological type         | 10                | 23% (0.23)    | 1.41 (1.03–1.92)      | 0.03      | 0.721                   | 0.259                   |
| Tumor invasion depth ($\geq$SM2)| 11                | 0% (0.98)     | 2.88 (2.07–3.99)      | $<0.00001$| 0.640                   | 0.079                   |
| Ulceration                     | 8                 | 5% (0.39)     | 0.85 (0.58–1.23)      | 0.39      | 0.536                   | 0.782                   |
| Tumor location                 | 6                 | 39% (0.14)    | 1.03 (0.66–1.62)      | 0.88      | 0.707                   | 0.998                   |
| Macroscopic appearance         | 6                 | 0% (0.43)     | 2.17 (1.32–3.58)      | 0.002     | 0.452                   | 0.256                   |
| Treatment                      | 2                 | 0% (0.43)     | 0.91 (0.26–3.15)      | 0.88      | 1.000                   | –                       |
| Lymphovascular invasion        | 4                 | 59% (0.06)    | 3.46 (1.35–8.87)      | 0.01      | 0.734                   | 0.944                   |
| Lymphatic invasion             | 7                 | 0% (0.59)     | 5.60 (3.85–8.14)      | $<0.00001$| 0.548                   | 0.326                   |
| Vascular invasion              | 6                 | 0% (0.59)     | 2.42 (1.69–3.46)      | $<0.00001$| 0.260                   | 0.310                   |
| Horizontal margin              | 8                 | 2% (0.41)     | 0.69 (0.39–1.23)      | 0.21      | 0.711                   | 0.438                   |
| Vertical margin                | 10                | 4% (0.40)     | 2.02 (1.50–2.73)      | $<0.00001$| 0.152                   | 0.201                   |

*aMean difference (95% CI).
CI, confidence interval; EGC, early gastric cancer; LNM, lymph node metastasis; ER, endoscopic resection; MD, mean difference; OR, odds ratio; SM2, invasion depth of 500 μm from the muscularis mucosae.
Tumor size

| Study or Subgroup | > 30mm Events | Total | ≤30mm Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|-------|---------------|-------|--------|-----------------------------|-----------------------------|
| Ishida 2018       | 7             | 35    | 5             | 49    | 13.9%  | 2.20 (0.64, 7.61)           |                             |
| Kim 2017          | 43            | 124   | 30            | 226   | 57.7%  | 3.47 (2.03, 5.91)           |                             |
| Sunagawa 2017     | 13            | 80    | 10            | 116   | 28.4%  | 2.06 (0.83, 4.96)           |                             |
| Total (95% CI)    | 239           |       | 391           |       | 100.0% | 2.89 (1.89, 4.43)           |                             |
| Total events      | 63            |       | 45            |       |        |                             |                             |
| Heterogeneity: Chi² = 1.21, df = 2 (P = 0.55); I² = 0% | | | | | | | |
| Test for overall effect: Z = 4.87 (P < 0.00001) | | | | | | | |

Horizontal margin

| Study or Subgroup | Positive Events | Total | Negative Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-----------------|-------|-----------------|-------|--------|-----------------------------|-----------------------------|
| Ishida 2018       | 6               | 9     | 6               | 74    | 4.8%   | 22.67 (4.50, 114.29)        |                             |
| Ito 2013          | 3               | 4     | 3               | 37    | 1.6%   | 34.00 (2.65, 436.55)        |                             |
| Kikuchi 2017      | 3               | 6     | 5               | 67    | 4.5%   | 12.40 (1.97, 78.20)         |                             |
| Kim 2017          | 52              | 92    | 21              | 258   | 52.7%  | 14.67 (7.99, 26.93)         |                             |
| Sunagawa 2017     | 11              | 34    | 12              | 166   | 30.3%  | 6.14 (2.43, 15.53)          |                             |
| Toyokawa 2016     | 5               | 12    | 4               | 88    | 6.1%   | 15.00 (1.27, 68.87)         |                             |
| Total (95% CI)    | 157             |       | 690            |       | 100.0% | 12.70 (8.20, 19.66)         |                             |
| Total events      | 60              |       | 51             |       |        |                             |                             |
| Heterogeneity: Chi² = 3.69, df = 5 (P = 0.66); I² = 0% | | | | | | | |
| Test for overall effect: Z = 11.39 (P < 0.00001) | | | | | | | |

Vertical margin

| Study or Subgroup | Positive Events | Total | Negative Events | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------------|-------|-----------------|-------|--------|-----------------------------|-----------------------------|
| Ishida 2018       | 6               | 17    | 6               | 66    | 16.3%  | 5.45 (1.48, 20.04)          |                             |
| Ito 2013          | 4               | 14    | 2               | 27    | 10.7%  | 5.00 (0.79, 31.77)          |                             |
| Kikuchi 2017      | 2               | 12    | 6               | 61    | 11.6%  | 1.83 (0.32, 10.41)          |                             |
| Kim 2017          | 17              | 75    | 56              | 275   | 27.2%  | 1.15 (0.62, 2.12)           |                             |
| Sunagawa 2017     | 10              | 35    | 13              | 165   | 21.8%  | 4.68 (1.85, 11.81)          |                             |
| Toyokawa 2016     | 2               | 26    | 7               | 74    | 12.5%  | 0.80 (0.15, 4.11)           |                             |
| Total (95% CI)    | 179             |       | 668            |       | 100.0% | 2.37 [1.14, 4.92]           |                             |
| Total events      | 41              |       | 90             |       |        |                             |                             |
| Heterogeneity: Tau² = 0.41; Chi² = 10.88, df = 5 (P = 0.05); I² = 54% | | | | | | | |
| Test for overall effect: Z = 2.32 (P = 0.02) | | | | | | | |

Figure 4. Forrest plot for the relationship between residual tumor and tumor size, horizontal margin, and vertical margin, respectively.

(pooled OR = 1.12, 95% CI = 0.62–2.01, p = 0.72), macroscopic appearance (pooled OR = 1.20, 95% CI = 0.63–2.28, p = 0.57), tumor LVI (pooled OR = 0.55, 95% CI = 0.11–2.68, p = 0.46), LI (pooled OR = 1.31, 95% CI = 0.71–2.40, p = 0.39), and VI (pooled OR = 1.51, 95% CI = 0.79–2.89, p = 0.21) were revealed as nonsignificant risk factors (Table 3; Supplemental Figures 9 to 17).

Discussion

The diagnosis of EGC is generally made when the depth of tumor invasion is confined to the mucosa or submucosa, irrespective of lymph node status, which was adopted by the Japanese Gastric Cancer Association in the 1998 edition and remains the accepted definition to this day. However, the prevalence of LNM and residual tumor has been generally consented as the significant prognostic factor for patients with EGC. The attempt to update the definition of EGC has been carried out in order to improve the ability to determine the risk factors for the prevalence of LNM and residual tumor.

Publication bias

Funnel plot, Begg’s test, and Egger’s test were applied to evaluate the possibility of publication bias for each risk factors via Review Manager version 5.3 and Stata version 15.0 (Tables 2 and 3). No substantial publication bias was identified in all pooled analyses (p > 0.05).
intended to advance preoperative lymph node staging of early cancer, the accuracy of detection from several studies’ data appeared to be unpromising, which leaves them out of the staging algorithm of presumed EGC. In addition, the identification efficacy of 18F-fluorodeoxyglucose positron emission tomography and 18F-deoxyfluorothymidine positron emission tomography has also turned out to be unsatisfied due to relative high false negative rate related to tumor differentiation. Since ER, including EMR and ESD, became one of the main methods for treating EGC, capable of performing a precise histopathological staging after an en bloc resection of the lesion, the Japanese Gastric Cancer Association (JGCA) and the Japan Gastroenterological Endoscopy Society has classified the curability of ER into three potential groups. The lesion meeting none of the absolute or expanded indications is considered as noncurative resection. Surgical treatment is recommended in the patients with EGC who underwent noncurative resection, due to potential risk of LNM and cancer residue. Nevertheless, approximately 8.2% and 13.5% of patients with EGC who underwent noncurative ER presented with LNM and residual tumor, respectively. Thus, the potential risk of developing recurrence needs to be weighed against surgical trauma. Latent risk factors for the prevalence of LNM and residual tumor in patients with EGC who underwent noncurative endoscopic treatments are imperative to be assessed and established. Therefore, a meta-analysis of 12 relative studies has been carried out. In the present meta-analysis, tumor size with a cutoff value of 30 mm was identified as a significant predictor for both LNM and residual tumor, respectively. One of the reasons might be attributed to the lymphatic

| Predictors                          | Number of studies | Heterogeneity I² (p value) | Pooled OR (95% CI) | p value | Begg’s test (Pr > |z|) | Egger’s test (P > |t|) |
|------------------------------------|-------------------|---------------------------|--------------------|---------|------------------|--------|------------------|
| Age (≥70 years)                    | 3                 | 0% (0.61)                 | 1.52 [0.67–3.43]   | 0.32    | 0.296            | 0.227  |
| Sex                                | 3                 | 0% (0.53)                 | 0.75 [0.28–2.03]   | 0.57    | 1.000            | 0.968  |
| Tumor size (>30 mm)                | 3                 | 0% (0.55)                 | 2.89 [1.89–4.43]   | <0.00001| 1.000            | 0.323  |
| Histopathological type             | 6                 | 34% (0.18)                | 1.30 [0.85–1.97]   | 0.22    | 1.000            | 0.672  |
| Tumor invasion depth (≥SM2)        | 6                 | 78% (0.0004)              | 0.67 [0.23–1.92]   | 0.46    | 0.707            | 0.262  |
| Ulceration                         | 5                 | 40% (0.15)                | 1.12 [0.62–2.01]   | 0.72    | 1.000            | 0.472  |
| Macroscopic appearance             | 4                 | 0% (0.61)                 | 1.20 [0.63–2.28]   | 0.57    | 0.734            | 0.520  |
| Lymphovascular invasion            | 2                 | 77% (0.04)                | 0.55 [0.11–2.68]   | 0.46    | 1.000            | –      |
| Lymphatic invasion                 | 4                 | 0% (0.73)                 | 1.31 [0.71–2.40]   | 0.39    | 0.734            | 0.796  |
| Vascular invasion                  | 4                 | 35% (0.20)                | 1.51 [0.79–2.89]   | 0.21    | 0.308            | 0.066  |
| Horizontal margin                  | 6                 | 0% (0.60)                 | 12.70 [8.20–19.66] | <0.00001| 0.452            | 0.589  |
| Vertical margin                    | 6                 | 54% (0.05)                | 2.37 [1.14–4.92]   | 0.02    | 1.000            | 0.437  |

CI, confidence interval; EGC, early gastric cancer; ER, endoscopic resection; OR, odds ratio; SM2, invasion depth of 500 μm from the muscularis mucosae.
higher risk of positive LNM. In fact, in the suggestive of lymphatic invasion and showed a adenocarcinoma component were more likely reported that patients with EGC with a papillary lymph node involvement. Further investigations susceptible to perigastric and extra-perigastric depressed portion such as IIc and III were more susceptible to perigastric and extra-perigastric lymph node involvement. Further investigations have to be implemented to determine the genuine relationship between macroscopic appearance of EGC and LNM.

In terms of tumor histopathological type, our pooled analysis revealed that the prevalence of LNM was significantly higher in patients with histologically undifferentiated type (p=0.03), despite 8 of the 10 eligible studies involved yielding no statistical significance between the two subgroups. The discrepancies might be ascribed to the relatively small sample size of each study, which undermined the statistical power and disqualified the final results. In fact, Miyahara et al. reported that an undifferentiated component in submucosal invasion was the independent predictor for LNM, and the incidence of LNM increased significantly for a predominant undifferentiated type (p=0.005) and undifferentiated component (p<0.001) in submucosal invasion as the deeper the tumor invading into submucosa.

For the assessment of the impact of macroscopic appearance on LNM, Sunagawa et al. elucidated that the difference for the prevalence of LNM between patients with flat or elevated tumor macroscopic type and patients with depressed tumor macroscopic type was found statistically significant not only in univariate analysis (p=0.004), but in multivariate analysis as well (p=0.011), which is consistent with the result of our present pooled analysis (p=0.002). It is currently unclear why the flat or elevated type was associated with LNM, although several studies have reported similar results. Jung et al. presumed that there might be difficulties to estimate the invasion depth during diagnostic endoscopy in EGC cases with the elevated type tumor. Sekiguchi et al. reported that patients with EGC with a papillary adenocarcinoma component were more likely suggestive of lymphatic invasion and showed a higher risk of positive LNM. In fact, in the Sunagawa et al. study, a papillary adenocarcinoma component was found more frequently in patients with a flat or elevated type (19.6%) than in patients with a depressed type (6.9%) (p=0.012). Nevertheless, Baba et al. illustrated a low prevalence of LNM associated with lesions of elevated types of I and IIa, and the flat type of IIb, whereas macroscopic types consisting of depressed portion such as IIc and III were more susceptible to perigastric and extra-perigastric lymph node involvement. Further investigations have to be implemented to determine the genuine relationship between macroscopic appearance of EGC and LNM.
and total length of lateral resection margin involvement, which showed 100% sensitivity and 49% specificity for residual or recurrent tumors. Interestingly, Noh et al. suggested that close surveillance might be a feasible strategy for patients with EGC who present positive vertical margin without LVI or deep submucosa invasion, especially for whom surgery might be risky.

A scoring system, named as eCura, was established to categorize patients into three risk groups in order to address the risk of LNM in Japan. In its validation stage, noncurative ESD followed by additional surgery was recommended for patients in the high LNM risk group, whose 5-year cancer-specific survival appeared to be 90.1%. Furthermore, after bringing the Hatta et al. study above into the eligible studies for our meta-analysis, two novel additional predictors emerged, which were histopathological type and macroscopic appearance. That is, patients with EGC whose pathology results after noncurative ER present histologically undifferentiated type or flat or elevated tumor macroscopic appearance should also be recommended with additional surgery in case of LNM. In fact, the eCura scoring system did not take the residual tumor after ESD into consideration. Although ESD has a burning effect that sometimes leads to no remnant cancer after ESD even if there is a positive lateral margin, the risk of cancer residue should still be under vigilance when R0 resection is not achieved. For this reason, our pooled analysis also investigated the potential predictors for residual tumor, which identified positive horizontal margin as a significant risk factor apart from the indicators mentioned above. Therefore, patients meeting the noncurative resection criteria solely for the presence of ulcerative findings might avoid excessive additional surgery.

In the cases that patients with EGC who have undergone noncurative ER and appear to harbor the risk factors indicated in this present meta-analysis, additional surgical treatment should be strongly recommended. Yamanouchi et al. reported that the incidence of hypertension was significantly higher in the follow-up group compared with the additional surgery group (51.0% versus 25.9%; p = 0.03). The Li et al. meta-analysis, which enrolled 4225 patients, revealed that additional surgery significantly provided better 5-year overall survival (pooled OR = 3.50, 95% CI = 2.89–4.24, p < 0.001) and disease-specific survival (pooled OR = 3.99, 95% CI = 2.50–6.36, p < 0.001) than observation. In terms of surgical method, Katsube et al. reported that 15 patients underwent additional surgery with lymphadenectomy (D1+) (laparoscopy-assisted distal gastrectomy, n = 7; distal gastrectomy, n = 2; total gastrectomy; and proximal gastrectomy, n = 2) and 2 patients underwent local resection. The 5-year survival rate was 93% and no gastric cancer-specific death was documented, which might substantially shed light on the possibility of a less radical procedure. As regards the specific surgical methods and the scope of lymph node dissection of additional gastrectomy after noncurative ER, no particular prospective study has been designed to investigate the difference of therapeutic effect, complication and prognosis among various surgical procedures after noncurative resection. In addition, overall survival in patients who underwent additional surgery after noncurative ESD was significantly higher in the nonelderly (<70 years) and elderly groups (70–79 years) (p < 0.001), whereas the difference was not significant in patients ≥80 years (p = 0.23). Therefore, elderly patients with high risk of LNM and high performance status should undergo additional surgery, and establishment of criteria for selecting treatment methods after noncurative ESD in elderly patients is required. In fact, regarding patients with impaired physical conditions or no personal consent for additional surgery, sentinel lymph node biopsy with subserosal or submucosal injection of blue dye or radioactive tracer might serve as a further promising strategy for detection of lymph node involvement, with an accuracy rate range from 75% to 100% due to various lymphatic drainage of the gastric region. In addition, repeated ESD, endoscopic coagulation, and close observation are also recommended by JGCA as alternatives for this patient population. Together, the combination of the risk factor for LNM and cancer residue and sentinel lymph node biopsy might advance the detection of lymph node status and prediction of cancer recurrence. These findings might alter the definition of noncurative ER to some extent, especially when patients harbouring these nonsignificant predictors might avoid radical additional surgery.

**Conclusion**

The available results from the present meta-analysis exhibited that tumor size >30 mm, tumor invasion depth ≥SM2, macroscopic appearance,
undifferentiated histopathological type, positive vertical margin, and LVI (including LI and VI) were statistically significant risk factor for the prevalence of LNM. Meanwhile tumor size >30 mm, positive horizontal margin, and positive vertical margin were identified as significant predictors for residual tumor. All of the 12 included studies were conducted in Japan or South Korea, which might neglect the impact of ethnicity. Prospective cohort study is essential to be conducted in order to construct an optimal combined predictive model for the prevalence of LNM and residual tumor in patients with EGC who underwent noncurative ER, which might allow surgeons to identify the population that would benefit the most from strict follow-up or additional surgery.

Acknowledgements
Our deepest gratitude goes to the Managing Editor, Alessandro Baliani, the Associate Editor, Robert Benamouzig, the Peer Review Supervisor, Kanika Kamboj, and the reviewers for their careful work and thoughtful suggestions that have helped improve this paper substantially.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article. The present study was supported by the National Natural Science Foundation of China (grant number 81972324), the China Academy of Medical Sciences Innovation Fund for Medical Sciences (grant number 2016-I2M-3-019).

Conflict of interest statement
The authors declare that there is no conflict of interest.

Ethics approval statement
Ethics approval was not required for this study.

Informed consent statement
Informed consent was not required for this study.

ORCID iD
Junchao Guo https://orcid.org/0000-0002-6759-5147

Supplemental material
Supplemental material for this article is available online.

References
1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359–E386.
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115–132.
3. Murakami T. Early cancer of the stomach. World J Surg 1979; 3: 685–691.
4. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225–229.
5. Gotoda T. Endoscopic resection of early gastric cancer. Gastric Cancer 2007; 10: 1–11.
6. Gotoda T, Yamamoto H and Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929–942.
7. Gotoda T, Yanagisawa A, Sasaki M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219–225.
8. Hirasawa T, Gotoda T, Miyata S, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer 2009; 12: 148–152.
9. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011; 14: 113–123.
10. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Dig Endosc 2016; 28: 3–15.
11. Suzuki H, Oda I, Abe S, et al. Clinical outcomes of early gastric cancer patients after noncurative endoscopic submucosal dissection in a large consecutive patient series. Gastric Cancer 2017; 20: 679–689.
12. Park WY, Shin N, Kim JY, et al. Pathologic definition and number of lymphovascular emboli: impact on lymph node metastasis in endoscopically resected early gastric cancer. Hum Pathol 2013; 44: 2132–2138.
13. Ishida R, Kanaji S, Maehara R, et al. Significance of additional gastrectomy including endoscopic submucosal dissection scar for gastric cancer. Anticancer Res 2018; 38: 5289–5294.
14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology:
26. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 2nd English edition. Gastric Cancer 1998; 1: 10–24.

27. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101–112.

28. Barreto SG and Windsor JA. Redefining early gastric cancer. Surg Endosc 2015; 30: 24–37.

29. Pech O, Gunter E and Ell C. Endosonography of high-grade intra-epithelial neoplasia/early cancer. Best Pract Res Clin Gastroenterol 2009; 23: 639–647.

30. Cardoso R, Coburn N, Seevaratnam R, et al. A systematic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. Gastric Cancer 2012; 15(Suppl. 1): S19–S26.

31. Papanikolaou IS, Triantafyllou M, Triantafyllou K, et al. EUS in the management of gastric cancer. Ann Gastroenterol Oncol 2011; 24: 9–15.

32. Shimada H, Okazumi S, Koyama M, et al. Japanese gastric cancer association task force for research promotion: clinical utility of (1) (8)F-fluoro-2-deoxyglucose positron emission tomography in gastric cancer. A systematic review of the literature. Gastric Cancer 2011; 14: 13–21.

33. Herrmann K, Ott K, Buck AK, et al. Imaging gastric cancer with PET and the radiotracers 18F-FLT and 18F-FDG: a comparative analysis. J Nucl Med 2007; 48: 1945–1950.

34. Seevaratnam R, Cardoso R, McGregor C, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer 2012; 15(Suppl. 1): S3–S18.

35. Ahmad NA, Kochman ML, Long WB, et al. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. Gastrointest Endosc 2002; 55: 390–396.

36. Katsube T, Konnno S, Hamaguchi K, et al. The efficacy of endoscopic mucosal resection for early gastric cancer: a meta-analysis. Gastrointest Endosc 2011; 63: 1369–1401.

37. Kim HS, Ahn JY, Kim SO, et al. Can further gastrectomy be avoided in patients with incomplete endoscopic resection? Surg Endosc 2017; 31: 4735–4748.

38. Sunagawa H, Kinoshita T, Kaito A, et al. Additional surgery for non-curative resection after endoscopic submucosal dissection for gastric cancer: a retrospective analysis of 200 cases. Surg Today 2017; 47: 202–209.

39. Toyokawa T, Ohira M, Tanaka H, et al. Optimal management for patients not meeting the inclusion criteria after endoscopic submucosal dissection for gastric cancer. Surg Endosc 2016; 30: 2404–2414.
39. Maehara Y, Orita H, Okuyama T, et al. Predictors of lymph node metastasis in early gastric cancer. Br J Surg 1992; 79: 245–247.

40. Saito H, Osaki T, Murakami D, et al. Macroscopic tumor size as a simple prognostic indicator in patients with gastric cancer. Am J Surg 2006; 192: 296–300.

41. Listrom MB and Fenoglio-Preiser CM. Lymphatic distribution of the stomach in normal, inflammatory, hyperplastic, and neoplastic tissue. Gastroenterology 1987; 93: 506–514.

42. Park YD, Chung YJ, Chung HY, et al. Factors related to lymph node metastasis and the feasibility of endoscopic mucosal resection for treating poorly differentiated adenocarcinoma of the stomach. Endoscopy 2008; 40: 7–10.

43. Holscher AH, Drehber U, Monig SP, et al. Early gastric cancer: lymph node metastasis starts with deep mucosal infiltration. Ann Surg 2009; 250: 791–797.

44. Miyahara K, Hatta W, Nakagawa M, et al. The role of an undifferentiated component in submucosal invasion and submucosal invasion depth after endoscopic submucosal dissection for early gastric cancer. Digestion 2018; 98: 161–168.

45. Ishigami S, Hokita S, Natsugoe S, et al. Carcinomatous infiltration into the submucosa as a predictor of lymph node involvement in early gastric cancer. World J Surg 1998; 22: 1056–1059.

46. Jung H, Bae JM, Choi MG, et al. Surgical outcome after incomplete endoscopic submucosal dissection of gastric cancer. Br J Surg 2011; 98: 73–78.

47. Sekiguchi M, Kushima R, Oda I, et al. Clinical significance of a papillary adenocarcinoma component in early gastric cancer: a single-center retrospective analysis of 628 surgically resected early gastric cancers. J Gastroenterol 2015; 50: 424–434.

48. Baba H, Maehara Y, Okuyama T, et al. Lymph node metastasis and macroscopic features in early gastric cancer. Hepatogastroenterology 1994; 41: 380–383.

49. Kim H, Kim JH, Park JC, et al. Lymphovascular invasion is an important predictor of lymph node metastasis in endoscopically resected early gastric cancers. Oncol Rep 2011; 25: 1589–1595.

50. Kang HJ, Kim DH, Jeon TY, et al. Lymph node metastasis from intestinal-type early gastric cancer: experience in a single institution and reassessment of the extended criteria for endoscopic submucosal dissection. Gastrointest Endosc 2010; 72: 508–515.

51. Nasu J, Nishina T, Hirasaki S, et al. Predictive factors of lymph node metastasis in patients with undifferentiated early gastric cancers. J Clin Gastroenterol 2006; 40: 412–415.

52. Dicken BJ, Graham K, Hamilton SM, et al. Lymphovascular invasion is associated with poor survival in gastric cancer: an application of gene-expression and tissue array techniques. Ann Surg 2006; 243: 64–73.

53. Hwang JJ, Park KJ, Park YS, et al. A scoring system for patients with a tumor-positive lateral resection margin after endoscopic resection of early gastric cancer. Surg Endosc 2016; 30: 2751–2758.

54. Noh GY, Ku HR, Kim YJ, et al. Clinical outcomes of early gastric cancer with lymphovascular invasion or positive vertical resection margin after endoscopic submucosal dissection. Surg Endosc 2015; 29: 2583–2589.

55. Yamanouchi K, Ogata S, Sakata Y, et al. Effect of additional surgery after noncurative endoscopic submucosal dissection for early gastric cancer. Endosc Int Open 2015; 4: E24–E29.

56. Li D, Luan H, Wang S, et al. Survival benefits of additional surgery after non-curate endoscopic resection in patients with early gastric cancer: a meta-analysis. Surg Endosc 2019; 33: 711–716.

57. Katsube T, Murayama M, Yamaguchi K, et al. Additional surgery after non-curative resection of ESD for early gastric cancer. Anticancer Res 2015; 35: 2969–2974.

58. Kawata N, Kakushima N, Tokunaga M, et al. Influence of endoscopic submucosal dissection on additional gastric resections. Gastric Cancer 2015; 18: 339–345.

59. Esaki M, Hatta W, Shimosegawa T, et al. Age affects clinical management after noncurative endoscopic submucosal dissection for early gastric cancer. Dig Dis 2019; 37: 423–433.

60. Miwa K, Kinami S, Taniguchi K, et al. Mapping sentinel nodes in patients with early-stage gastric carcinoma. Br J Surg 2003; 90: 178–182.

61. Dong LF, Wang LB, Shen JG, et al. Sentinel lymph node biopsy predicts lymph node metastasis in early gastric cancer: a retrospective analysis. Dig Surg 2012; 29: 124–129.

62. Hayashi H, Ochiai T, Mori M, et al. Sentinel lymph node mapping for gastric cancer using a dual procedure with dye- and gamma probe-guided techniques. J Am Coll Surg 2003; 196: 68–74.

63. Cozzaglio L, Bottura R, Di Rocco M, et al. Sentinel lymph node biopsy in gastric cancer: possible applications and limits. Eur J Surg Oncol 2011; 37: 55–59.