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ORIGINAL ARTICLE

Risk Factors Associated with Lymph Node Metastasis for Early Gastric Cancer Patients Who Underwent Non-curative Endoscopic Resection: a Systematic Review and Meta-analysis

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Abstract

Background Recently, increased evidence indicated that additional surgery should be performed in highly selected patients with non-curative endoscopic resection. In this study, we performed a systematic review and meta-analysis to evaluate the risk factors associated with lymph node metastasis for the patients with non-curative endoscopic resection of early gastric cancer.

Methods The related studies were identified by searching PubMed and Embase databases. According to the status of lymph node metastasis, all patients were classified into node-negative group and node-positive group. The relevant clinicopathologic factors were extracted, and the pooled odds ratio (OR) and 95% confidence interval (CIs) were assessed using a fixed effects model or random effects model.

Results A total of nine relevant studies involving 1720 early gastric cancer patients who underwent additional surgery following the non-curative endoscopic resection were included in this meta-analysis. The results indicated that deeper submucosal invasion (SM2) (OR 3.44, 95% CI 1.94–6.10, $P < 0.001$; $I^2 = 0\%$), positive vertical margin (OR 2.35, 95% CI 1.57–3.53, $P < 0.001$; $I^2 = 0\%$), lymphatic invasion (OR 11.06, 95% CI 5.47–22.36, $P < 0.001$; $I^2 = 0\%$), and vascular invasion (OR 2.79, 95% CI 1.68–4.64, $P < 0.001$; $I^2 = 0\%$) were significantly associated with lymph node metastasis for these patients. However, horizontal margin, tumor size, differentiation type, and ulceration were not identified as risk factors associated with lymph node metastasis.

Conclusion Lymphatic invasion, vascular invasion, deeper submucosal invasion (SM2), and positive vertical margin should be strongly considered in selecting the candidates for additional surgery treatment.

Keywords Early gastric cancer · Endoscopic submucosal dissection (ESD) · Non-curative endoscopic resection · Lymph node metastasis · Additional surgery

Introduction

Gastric cancer (GC) is one of the most common malignancy diseases in the world and the third leading cause of cancer-related deaths.[1] With the improvement of diagnostic technique and the prevalence of endoscopic screening program, an increasing number of GC patients could be diagnosed at the early stage of disease despite the vague clinical manifestation and sign.[2] Due to the relatively low risk of lymph node metastasis, minimally invasive resection was recommended in early GC patients. In the recent decade, endoscopic submucosal dissection (ESD) has been routinely performed in many research institutions, especially for the patients with negligible risk of lymph node metastasis.[3–5] However, it is difficult to determine the depth of tumor invasion and lymphovascular invasion before endoscopic resection. Therefore, the non-curative resection was not uncommon among early GC patients who underwent ESD treatment.[6–8] For those patients who underwent non-curative endoscopic resection, additional gastrectomy with adequate lymphadenectomy was usually recommended due to the potential risk of lymph node metastasis.[9–11] However, the rate of lymph node metastasis accounted for only 5–11% of the patients who underwent additional surgery according the previous reports.[12–21] Some studies reported that non-curative endoscopic resection did not always result in the tumor recurrence and cancer-related death, and close follow-up with endoscopy may be an

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alternative modality for the selected patients such as older patients.[8,22–24] To avoid the unnecessary additional surgery, identifying the risk factors associated with lymph node metastasis should be indispensable. According to the current studies and reports, patient age, tumor size, lymphovascular invasion, deeper submucosal invasion, positive vertical margin, undifferentiated type, tumor location, and macroscopic findings (elevated type) were proved to be the significant factors associated with lymph node metastasis for the patients who underwent non-curative endoscopic resection.[6,12–21,25] However, there was no consensus opinion on these potential risk factors. In view of the limited sample size and inconsistent results, we reviewed the related studies and performed a systematic review and meta-analysis to clarify the association between lymph node metastasis and these clinicopathologic factors.

Methods

Literature Search Strategy

To identify related studies and published literature, the systematic search strategy was performed using PubMed, Embase, and Cochrane Library databases. In addition, the references from relevant articles were electronically searched to further find potentially relevant studies. The following Medical Subject Headings (MeSH) were used in the search strategy: "endoscopic submucosal dissection," "non-curative endoscopic resection," "additional surgery," "lymph node metastasis," and "early gastric cancer." The search strategy was changed according to different requirements. By screening the title and abstract, the related literatures were further selected. Due to language limitation, only studies published in the English and Chinese language were included.

Inclusion and Exclusion Criteria

According to the Japanese gastric cancer treatment guidelines (JGCA 2010, 3rd version),[9] absolute indications for ESD treatment include the following several clinicopathologic features: tumor size ≤ 2 cm, T1a stage (mucosal invasion, M), differentiated type, and no ulceration. The expanded indications for ESD treatment were as follows: (1) T1a, differentiated type, no ulceration but tumor size > 2 cm. (2) T1a, differentiated type, tumor size ≤ 3 cm but ulceration finding. (3) T1a, tumor size ≤ 2 cm, no ulceration but undifferentiated type. (4) tumor size < 3 cm, no ulceration, differentiated type but T1b (submucosal invasion < 500 mm, SM1). In addition, lymphatic invasion, vascular invasion, and tumor involvement at the vertical margin and horizontal margin were pathologically evaluated. The patients were diagnosed as the non-curative resection when the resected lesion met at least one of the following criteria: (1) beyond the expanded indications for ESD treatment, (2) lymphatic invasion (+), (3) vascular invasion (+), (4) positive vertical margin, (5) positive horizontal margin, and (6) without en bloc resection.

The inclusion and exclusion criteria of this meta-analysis were as follows: (1) All patients underwent endoscopic submucosal dissection of early GC and were identified as the non-curative endoscopic resection according to the Japanese gastric cancer treatment guidelines, (2) All patients underwent additional gastrectomy with lymphadenectomy, and the resected specimens and retrieved lymph nodes were pathologically evaluated, (3) All patients were classified into node-negative group and node-positive group. The studies evaluated the risk factors associated with lymph node metastasis for the patients who underwent additional surgery following the non-curative endoscopic resection, and (4) The related data and clinicopathologic factors could be extracted directly or calculated from the original studies indirectly. If there were duplicated studies derived from the same research institution or author, only the most informative or highest quality was included in this meta-analysis. Conference abstracts and reports were excluded due to the incomplete information.

Data Extraction and Quality Assessment

Two investigators reviewed the abstracts and full text according to the eligibility criteria mentioned above, and data extraction was completed independently. Disagreements were resolved by discussion with a third investigator. The following information of each included studies was collected: first author, year of publication, country of study population, study period, sample size, median or mean age, follow-up period (median, range), the rate of lymph node metastasis, and survival data (5-year overall survival rate). For the purpose of this meta-analysis, the following clinicopathologic factors were extracted from the original studies: gender (male vs female), age (≥ 70 vs < 70 years), tumor location (upper and middle 1/3 vs low 1/3), tumor size (≥ 2 vs < 2 cm or ≥ 3 vs < 3 cm), differentiation type (undifferentiated type vs differentiated type), depth of tumor invasion (SM2 vs SM1 and M), lymphatic invasion (yes vs no), vascular invasion (yes vs no), lymphovascular invasion (yes vs no), vertical margin (positive vs negative), horizontal margin (positive vs negative), and ulceration finding (yes vs no). All predefined outcomes were summarized in a 2 × 2 contingency table for further analysis.

The methodological quality of all included studies was assessed by two investigators independently according to the Newcastle-Ottawa quality assessment scale (NOS).[26] Each included study was assigned a score, and ≥ 7 points were identified as high-quality studies. Discrepancies were resolved by discussion.

Statistical Analysis

The categorical variables were evaluated using the odds ratio (OR) and 95% confidence intervals (CIs). The study heterogeneity was quantified and assessed using Cochran's Q test and I^2 statistic. $I^2 > 50\%$ and/or $P < 0.01$ indicated that there was a significant statistical heterogeneity, and the random effects model should be used; otherwise, a fixed effects model should be used. The forest plots were constructed to assess the pooled OR and 95% CIs. To assess the potential publication bias, the funnel plot was constructed and Harbord's modified test was performed. All statistical analyses were performed using the Stata 13.0 software (Stata Corporation, College Station, TX, USA). The P value < 0.05 was considered to be statistically significant.

Results

Search Results and Included Study

The flow diagram of literature search is shown in Fig. 1. According to the predefined search strategy, a total of 210 potentially relevant studies were initially identified through database and manual search. After scanning the title and abstract, 164 irrelevant studies were excluded and the remaining 46 studies were further assessed via the full text view. Of these 46 studies, 37 articles were removed due to inconsistent inclusion criteria, incomplete information, and unavailable data. Ultimately, nine relevant studies that met the inclusion and exclusion criteria were included in this meta-analysis.[13–21]

All of the included studies were retrospective in nature and were published between 2013 and 2017. There were 1720 early GC patients who underwent additional surgery following the non-curative endoscopic resection, with a range of sample size from 41 to 356. Among these studies, seven studies were from Japan and two studies were from Korea. The research period ranged from 1997 to 2015. The characteristics of all included studies are summarized in Table 1.

Risk Factors Associated with Lymph Node Metastasis

A total of eight studies involving 1397 patients were included in the meta-analysis for the association between the depth of tumor invasion and lymph node metastasis. As shown in Fig. 2, the risk of lymph node metastasis was significantly higher in the patients with submucosal invasion ≥ 500 mm (SM2) than in those with SM1 or M invasion (OR 3.44, 95% CI 1.94–6.10, $P < 0.001$; $I^2 = 0\%$).

A total of eight studies involving 1526 patients evaluated the impact of vertical margin and horizontal margin and differentiation type on lymph node metastasis for the patients with non-curative endoscopic resection, respectively. The pooled result revealed that positive vertical margin was a risk factor related to lymph node metastasis for the patients with non-curative endoscopic resection (OR 2.35, 95% CI 1.57–3.53, $P < 0.001$; $I^2 = 0\%$) (Fig. 3). However, the similar result was not validated in the analysis of horizontal margin (OR 0.62, 95% CI 0.33–1.17, $P > 0.05$; $I^2 = 1.6\%$) (Fig. 4) and differentiation type (OR 1.12, 95% CI 0.71–1.77, $P > 0.05$; $I^2 = 0\%$) (Fig. 5).

Based on the description of lymphatic invasion and vascular invasion, five studies involving 749 patients who underwent additional surgery following the non-curative endoscopic resection were included in this study. The analytic result indicated that both lymphatic invasion (OR 11.06, 95% CI 5.47–22.36, $P < 0.001$; $I^2 = 0\%$) and vascular invasion (OR 2.79, 95% CI 1.68–4.64, $P < 0.001$; $I^2 = 0\%$) were

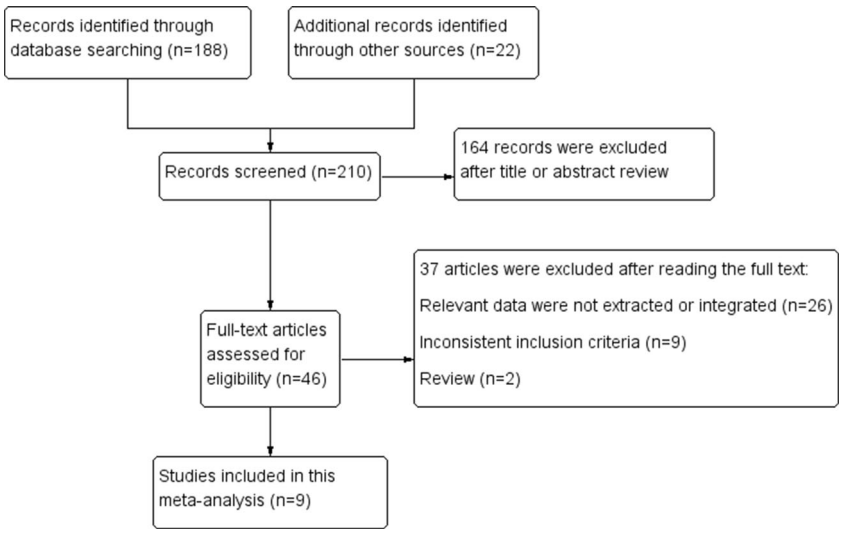

Fig. 1 The flow diagram of study selection

Table 1 Baseline characteristics of included studies

Study	Country	Inclusion period	Sample size (S/F)	Age median (range)/mean ± SD	Follow-up median (range)	LNM (%)	Survival data (S vs F)	Quality
Kawata et al.[13]	Japan	2002–2012	506 (323/183)	S, 69 (37–89); F, 77 (41–93)	S, 65 mo (3–169); F, 61 mo (1–149)	9.3%	5-OS, 90.0 vs 72.0%	7
Sunagawa et al.[14]	Japan	2005–2015	S, 200	S, 68 (43–81)	S, 25.3 mo (1–126)	7.5%	N/A	7
Ito et al.[15]	Japan	2001–2012	S, 41	S, 67.7 (46–83)	S, 23.0 mo	9.8%	N/A	7
Kim et al.[16]	Korea	2000–2011	274 (194/80)	S, 69.4 (42–86); F, 63 (44–84)	60.5 mo (6–141)	5.7%	5-OS, 94.3 vs 84.7%	7
Toyokawa et al.[17]	Japan	2004–2013	167 (100/67)	S, 69 (63–73); F, 76 (72–80)	S, 43.5 mo; F, 36 mo	9.0%	N/A	7
Suzuki et al.[18]	Japan	1999–2010	568 (356/212)	N/A	S, 76 mo (3–154); F, 70 mo (1–181)	5.3%	5-OS, 94.7 vs 83.8%	7
Kikuchi et al.[19]	Japan	2004–2013	150 (73/77)	S, 68.8; F, 74.3	S, 58 mo (6–143); F, 56 mo (2–142)	11.0%	5-OS, 85.0 vs 79.4%	7
Jung et al.[20]	Korea	2007–2015	S, 321	S, 62.1 ± 9.5	N/A	7.2%	N/A	7
Ishii et al.[21]	Japan	1997–2013	S, 112	S, 67 (40–87)	N/A	10.7%	5-OS, 94.7% (S group)	7

OS, overall survival; *mo*, months; *S*, surgery group; *F*, follow-up group; *LNM*, lymph node metastasis

significantly associated with high risk of lymph node metastasis (Figs. 6 and 7). In addition, five studies involving 1294 patients especially compared the association between lymphovascular invasion and lymph node metastasis, and the similar result can still be observed (Fig. 8).

The data on the ulceration finding were reported in six studies. The meta-analysis result demonstrated that the presence of ulceration had no higher risk of lymph node metastasis compared with the no ulceration finding. In addition, we investigated the association between other clinicopathologic factors and lymph node metastasis. However, we found that age, gender, tumor location, and tumor size had no significant impact on lymph node metastasis for the patients with non-curative endoscopic resection (Table 2).

Publication Bias

The asymmetry was not significantly observed in the funnel plots (Fig. 9). The Harbord's modified test also showed that there was no publication bias in the analysis of vertical margin, indicating that the pooled results were unlikely to be explained by publication bias ($P = 0.390$). The publication bias for other pooled results was not observed.

Discussion

To date, endoscopic submucosal dissection (ESD) has become a routine treatment method in many institutions, and the therapeutic outcome for early GC patients was satisfactory.[3,4,27] However, the depth of tumor invasion and other clinicopathologic features may not be always accurately assessed by endoscopy, endoscopic ultrasonography, and even diagnostic biopsy before endoscopic resection.[28] A portion of early GC patients were identified as the non-curative resection after ESD treatment, even though they met the absolute or expanded indications. Due to the potential risk of lymph node metastasis, additional gastrectomy with adequate lymphadenectomy was usually recommended.[9] However, whether the patients with non-curative endoscopic resection could gain benefit from additional surgery remains controversial. Some studies reported that the patients who underwent additional surgery following the non-curative endoscopic resection had a better long-term survival than those who received a single follow-up.[11,29–31] On the contrary, several studies indicated that close surveillance with endoscopy may instead of additional surgery as an acceptable option for those patients who refuse surgery or with comorbidity.[8,22–24] Hatta et al. reviewed and collected survival data of 1969 early GC patients who underwent non-curative endoscopic resection, and their results indicated that the overall survival of additional surgery group was significantly better than that of the follow-up group, but the prognostic difference in cancer-specific survival (CSS) between

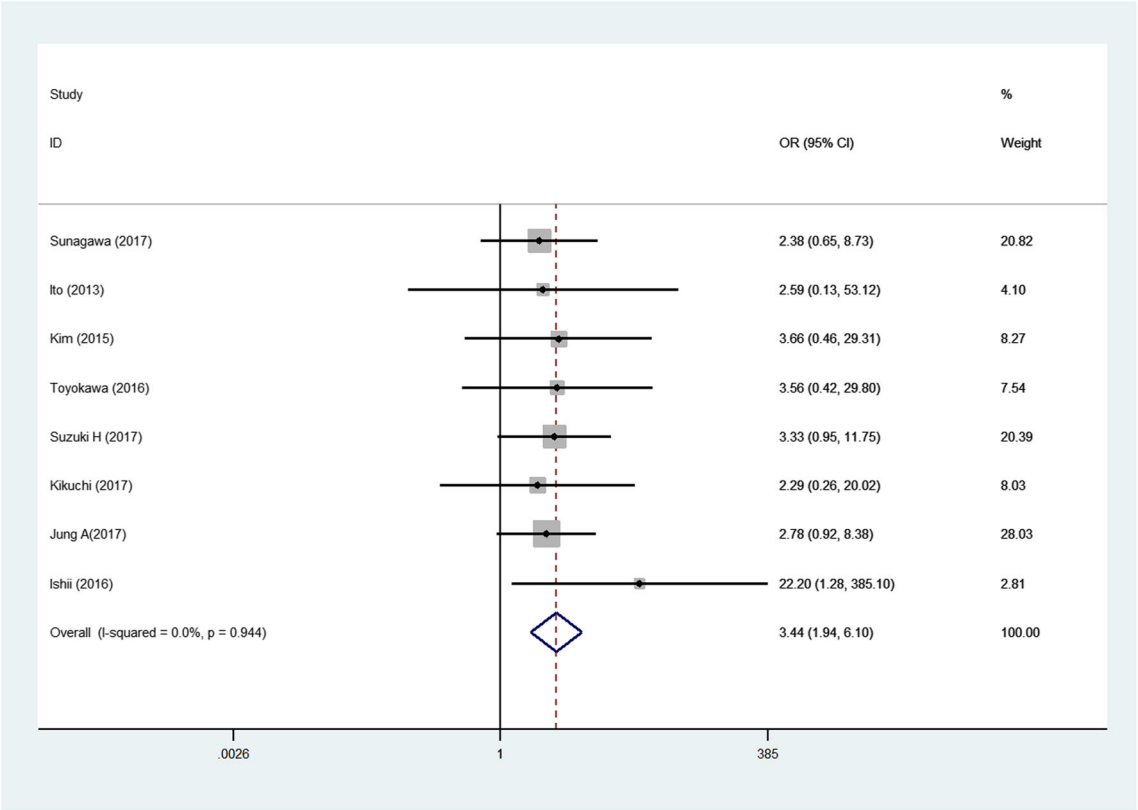

Fig. 2 Forest plots evaluating the association between the depth of tumor invasion and lymph node metastasis

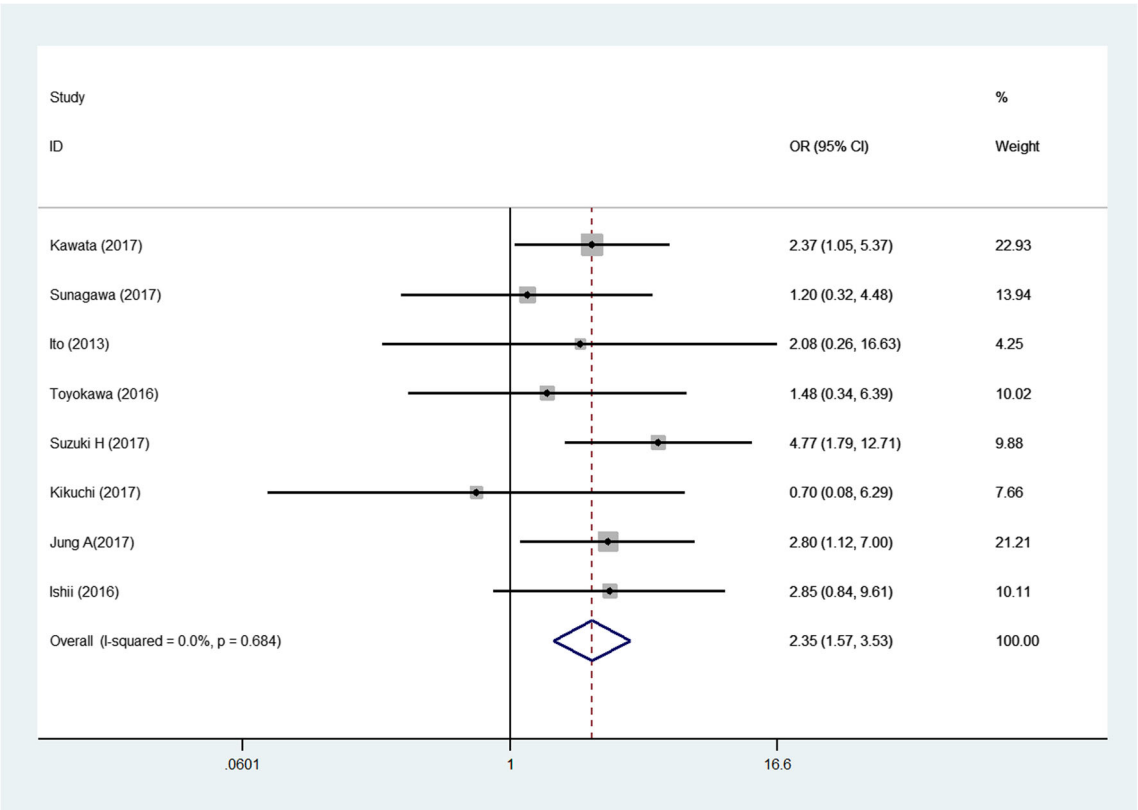

Fig. 3 Forest plots evaluating the association between vertical margin and lymph node metastasis

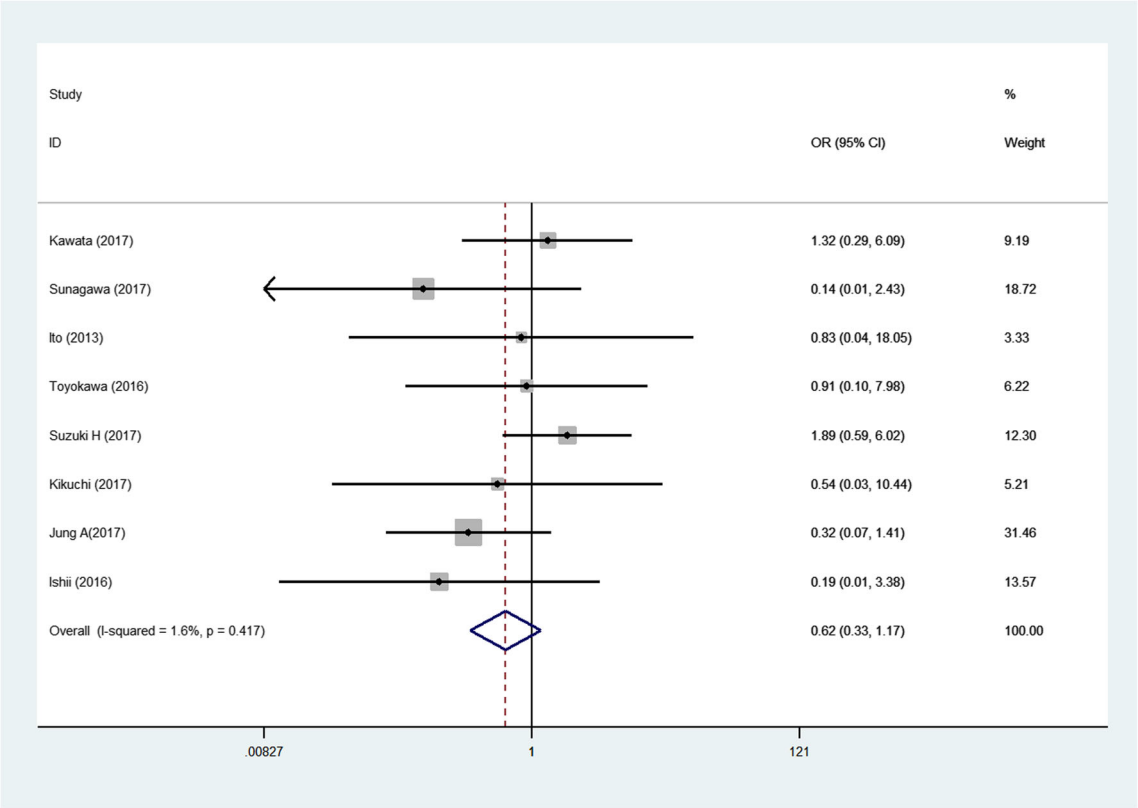

Fig. 4 Forest plots evaluating the association between horizontal margin and lymph node metastasis

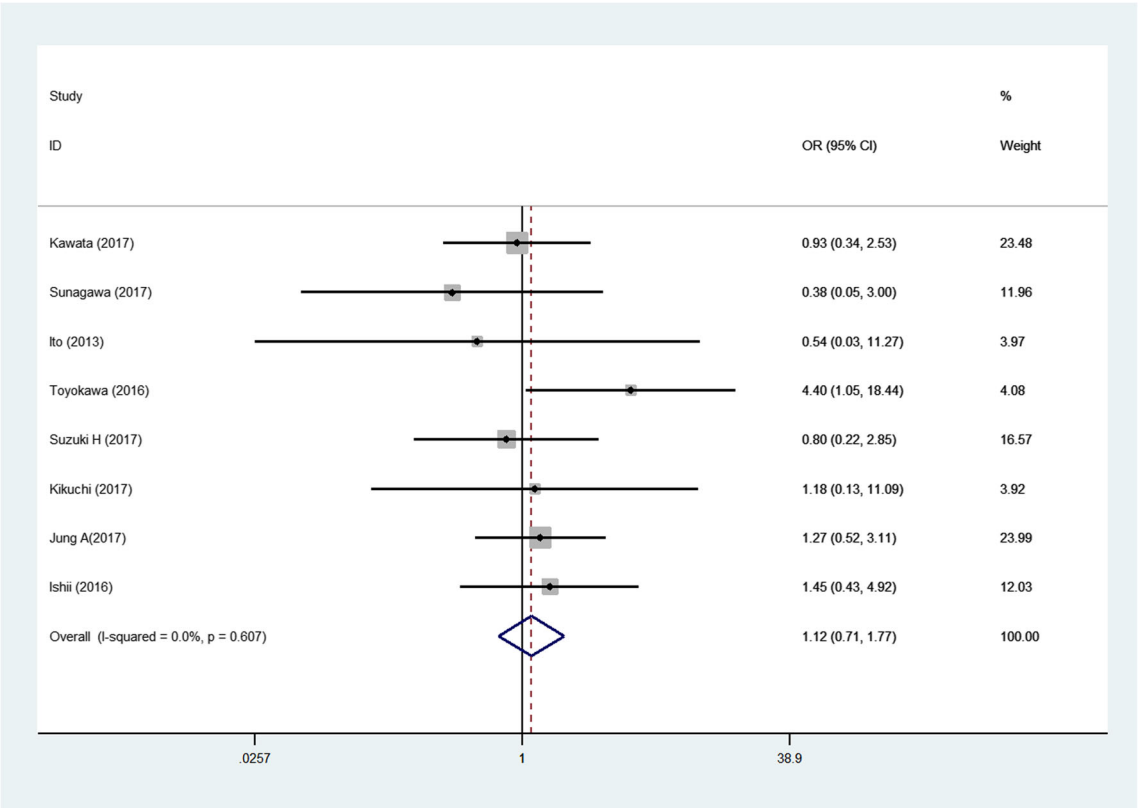

Fig. 5 Forest plots evaluating the association between differentiation type and lymph node metastasis

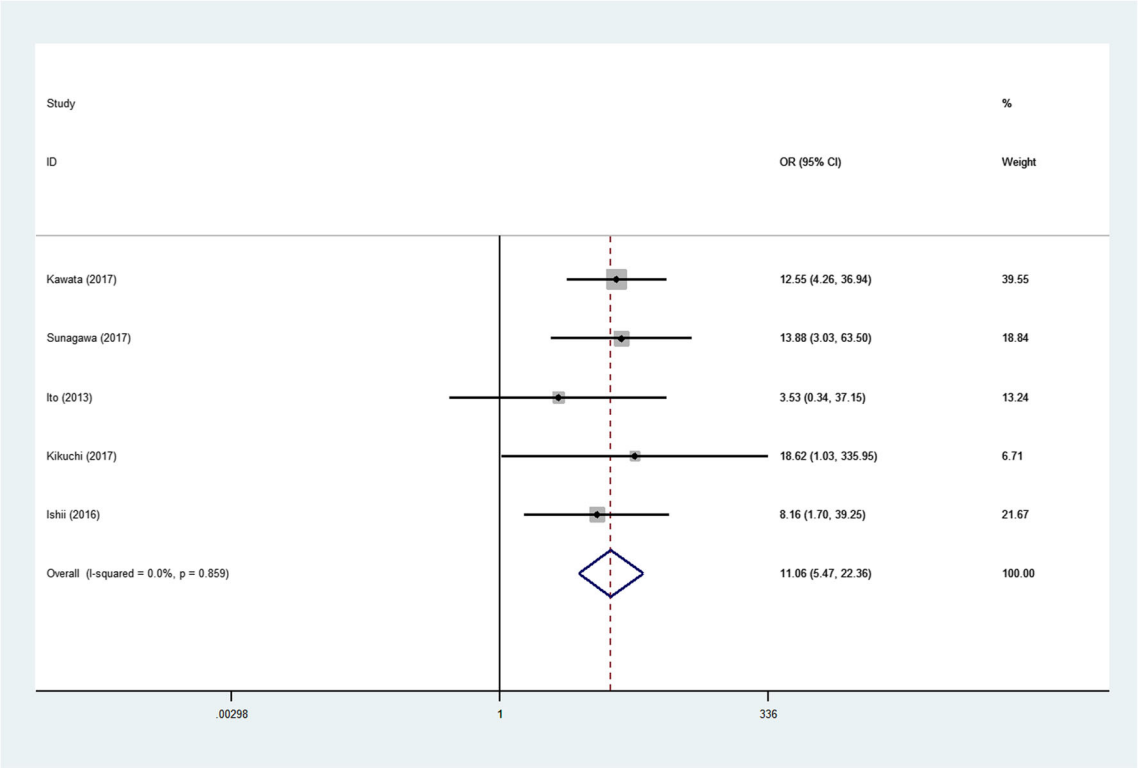

Fig. 6 Forest plots evaluating the association between lymphatic invasion and lymph node metastasis

two groups was rather small.[6] Similarly, Kawata et al. showed that the 5-year CSS rate of additional surgery group was not significantly different from that of follow-up group.[13] The overall survival difference between additional surgery

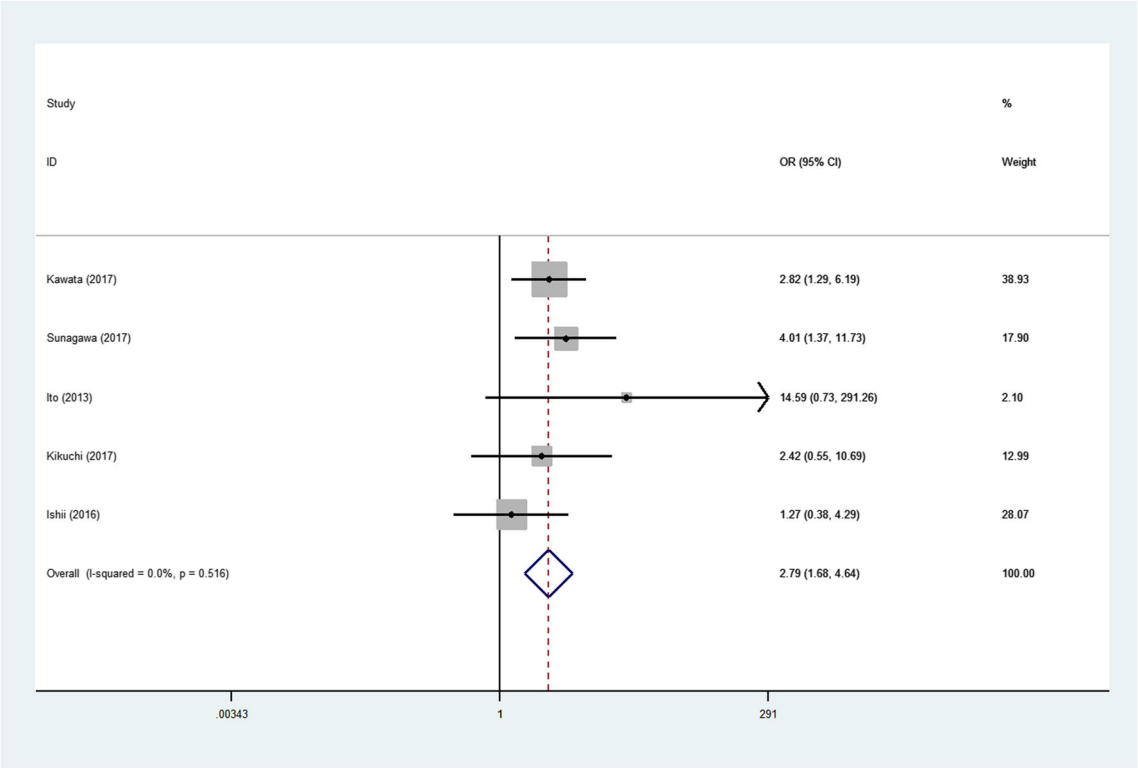

Fig. 7 Forest plots evaluating the association between vascular invasion and lymph node metastasis

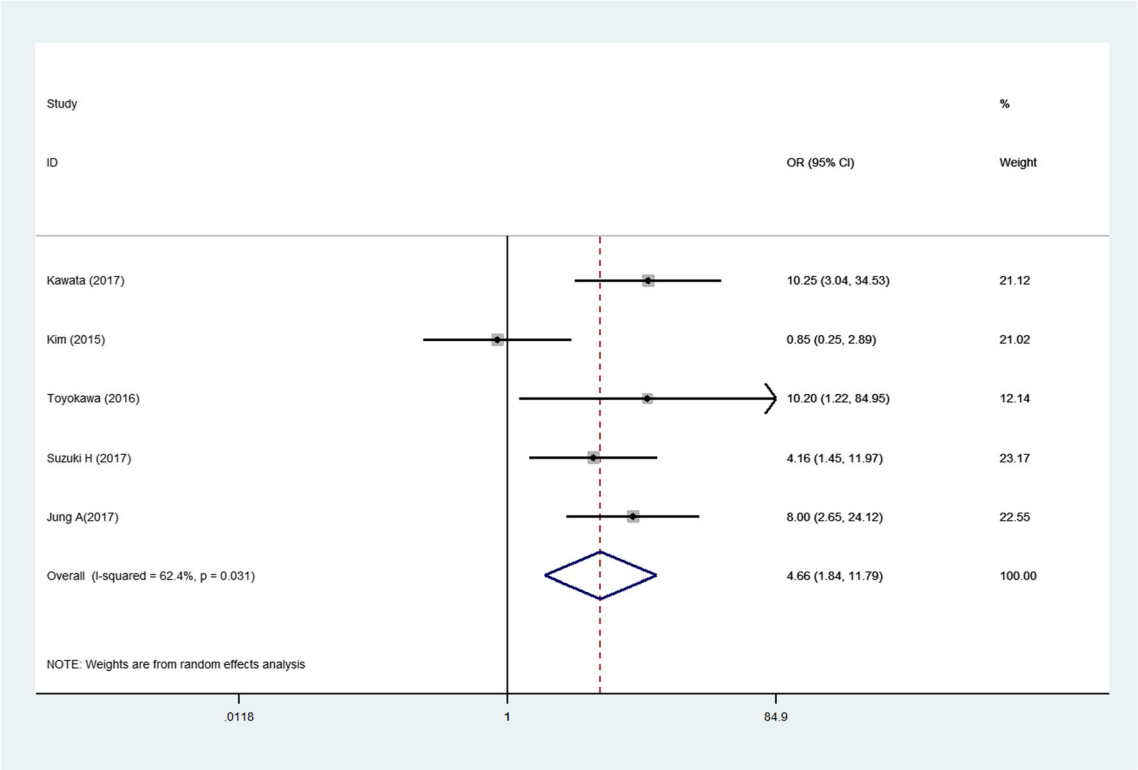

Fig. 8 Forest plots evaluating the association between lymphovascular invasion and lymph node metastasis

group and the follow-up group may partly attribute to other causes rather than cancer-related causes. The patients with older age and concomitant diseases were more likely to accept the conservative follow-up rather than additional surgery after non-curative endoscopic resection. According to the previous reports, actually, lymph node metastasis was detected in only 5–11% of the patients who underwent additional surgery.[12–21] A large proportion of the patients with non-curative endoscopic resection may undergo unnecessary surgery treatment. Therefore, it is necessary for the patients with non-curative resection to predict the potential risk of lymph node metastasis before additional surgery. Although some studies evaluated the impact of various clinicopathologic factors on lymph node metastasis for these patients, there has been no consensus answer due to the limited sample size. In the present study, we performed a systematic review and meta-

Table 2 Meta-analysis results for the relationship between lymph node metastasis and clinicopathological factors in the early GC patients who underwent non-curative endoscopic resection

Factors	Studies	Patients	Pooled OR (95% CI)	*P* value	Heterogeneity I^2 (*P* value)
Age (≥ 70 years)	4	609	1.27 (0.67–2.39)	0.460	0% ($P = 0.619$)
Gender (male)	7	1447	0.67 (0.43–1.05)	0.083	0% ($P = 0.714$)
Tumor location (upper and middle 1/3)	5	727	0.83 (0.51–1.35)	0.443	22.2% ($P = 0.273$)
Differentiation (undifferentiated)	8	1526	1.12 (0.71–1.77)	0.617	0% ($P = 0.607$)
Lymphatic invasion (yes)	5	749	11.06 (5.47–22.36)	< 0.001	0% ($P = 0.859$)
Vessel invasion (yes)	5	749	2.79 (1.68–4.64)	< 0.001	0% ($P = 0.516$)
Lymphovascular invasion (yes)	5	1294	4.66 (1.84–11.79)	< 0.001	62.4% ($P = 0.031$)
Tumor size (≥ 2 cm)	3	464	0.98 (0.50–1.93)	0.957	0% ($P = 0.589$)
Tumor size (≥ 3 cm)	3	668	1.39 (0.74–2.49)	0.720	0% ($P = 0.625$)
Invasion depth (≥ SM2)	8	1397	3.44 (1.44–6.10)	< 0.001	0% ($P = 0.944$)
Ulcer finding (yes)	6	1132	0.65 (0.36–1.16)	0.144	0% ($P = 0.672$)
Vertical margin (positive)	8	1526	2.35 (1.57–3.53)	< 0.001	0% ($P = 0.684$)
Horizontal margin (positive)	8	1526	0.62 (0.33–1.17)	0.140	1.6% ($P = 0.417$)

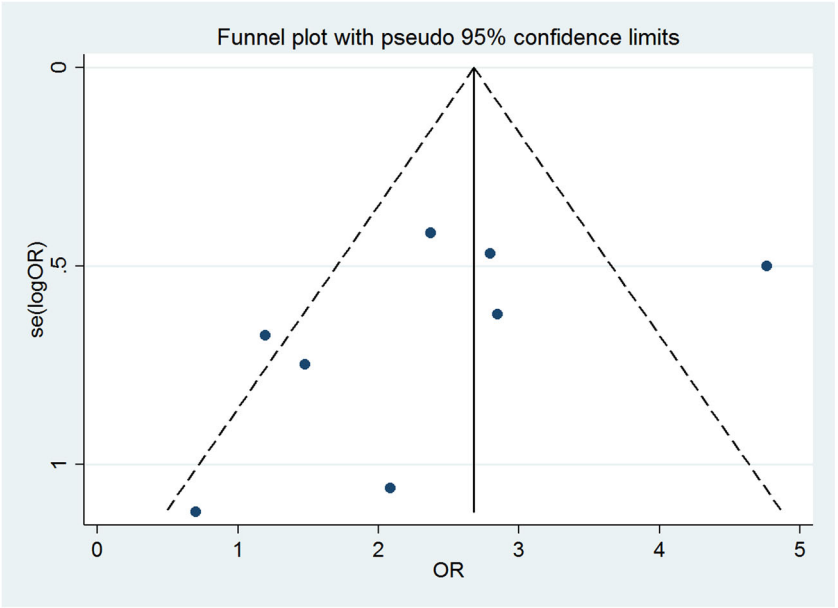

Fig. 9 Funnel plot for the analysis of the association between vertical margin and lymph node metastasis

analysis to assess the risk factors associated with lymph node metastasis for the patients with non-curative endoscopic resection.

The results revealed that deeper submucosal invasion (SM2), positive vertical margin, and lymphovascular invasion (lymphatic invasion or vascular invasion) were significantly associated with lymph node metastasis for the patients who underwent additional surgery following the non-curative endoscopic resection. Lymphovascular invasion was regarded as the initial step of lymph node metastasis and distant metastasis. Some studies found that lymph node metastasis and distant metastasis were not observed among the patients without lymphovascular invasion.[13,17,32] Lymphovascular invasion has been proved to be an independent risk factor for lymph node metastasis in those patients who underwent non-curative endoscopic resection.[6,13,14,17,18,25] A recent retrospective study showed that the prognosis of the patients with lymphovascular invasion in the additional surgery group was significantly better than that of those in the follow-up group.[13] Therefore, a careful pathological evaluation for lymphovascular invasion should be indispensable for the patients who underwent endoscopic resection. Immunohistological examination may provide a more reliable method for the detection of lymphovascular invasion.[33]

In this study, positive horizontal margin was not a risk factor influencing lymph node metastasis. However, positive horizontal margin was significantly associated with local residual tumor according to the current evidence.[14,17,34] Sunagawa et al. reported that local residual tumor could be found in 32.4% of the patients with positive horizontal margin after ESD treatment.[14] However, some scholars found that the incidence of lymph node metastasis was very low when positive horizontal margin was the only non-curative factor.[35,36] Therefore, additional ESD treatment may be feasible for these patients.[37,38] Unlike horizontal margin, positive vertical margin may represent the deeper tumor invasion. Therefore, the detailed detection for vertical margin was also necessary during the pathological evaluation of endoscopic-resected specimens. With the increased depth of tumor invasion, higher risk of lymph node metastasis could be observed among early GC patients who underwent non-curative endoscopic resection.[12,13,17] Toyokawa et al. showed that the rate of lymph node metastasis in mucosal and submucosal invasion cancer was 3.5% and 11.3%, respectively.[17] In addition, some studies reported that there was a significant association between the occurrence of lymph node metastasis and the increased number of risk factors.[12,14,25] Yang et al. reported that the prognosis of the patients with at least two risk factors in the surgery group was better than that of those in the non-surgery group.[25] Therefore, the additional surgery with lymphadenectomy should be strongly recommended when a patient who underwent non-curative endoscopic resection had two or more risk factors associated with lymph node metastasis.

Due to the decreased surgical trauma, fewer postoperative complications, and faster recovery, laparoscopic gastrectomy or laparoscopic lymph node dissection without gastrectomy has been generally used for early GC patients with potential risk of lymph node metastasis.[10,39] Son et al. reported the status of lymph node metastasis among 147 patients who underwent lymph node dissection following the non-curative endoscopic resection, and the result indicated that the extent of lymph node involvement was limited to $D1^+$ dissection level despite the presence of skip metastasis and extra-perigastric metastasis.[12] $D1^+$ lymph node dissection may be an acceptable surgical method for the patients receiving additional surgery, but D2 lymph node dissection still be considered when

these patients concurrently had multiple risk factors associated with lymph node metastasis.

In this meta-analysis, larger tumor size, undifferentiated type, and presence of ulceration were not proven to be risk factors associated with lymph node metastasis for those patients who underwent additional surgery. Although these clinicopathologic factors were important considerations for ESD indications, similar results were not observed in surgically resected specimens. The discrepancy may partly attribute to the limited sample size in some studies and the detective difference between endoscopic specimens and surgical specimens.[17]

Some limitations should be emphasized in the present study. Firstly, all included studies were retrospective in nature, and the results could have been influenced by some confounding or unknown factors. Although the JGCA guidelines (2010, 3rd version) was used in all the included studies, it has been revised several times during the study period (1997–2015). The definition of non-curative resection and the indications for additional surgery may be different among some patients, which could result in the heterogeneity of study population. Secondly, due to older age and concomitant diseases, some patients who underwent non-curative endoscopic resection may accept conservative follow-up rather than additional surgery. In the present study, we evaluated the risk factors associated with lymph node metastasis for those patients who underwent additional surgery following the non-curative endoscopic resection. Therefore, the selection bias should not be ignored. In addition, all included studies in this meta-analysis were from Japan and Korea. Further studies involving larger patient cohort and multicenter need to be performed to determine who could benefit from additional surgery.

In summary, the results of this meta-analysis indicated that deeper submucosal invasion (SM2), positive vertical margin, and lymphovascular invasion (lymphatic invasion or vascular invasion) were important risk factors associated with lymph node metastasis for the patients who underwent non-curative endoscopic resection. These clinicopathologic factors should be considered in selecting the candidates for additional surgery treatment. We expected that these results could provide some evidence to identify the predictors of lymph node metastasis, and further guide individualized treatment for those patients with non-curative endoscopic resection.

Author Contributions Study conception and design: Bochao Zhao and Baojun Huang; collection and acquisition of data: Bochao Zhao, Jiale Zhang, and Rui Luo; analysis and interpretation of data: Bochao Zhao, Jingting Zhang, and Jiale Zhang; drafting of manuscript: Bochao Zhao and Jingting Zhang; critical revision: Zhenning Wang, Huimian Xu, and Baojun Huang.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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