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Review Article

Lymph Node Metastasis and Its Risk Factors for Early Gastritis Individuals Who Underwent Noncurative Endoscopic Resection: A Systematic Review and Meta-Analysis

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Abstract

Background: In the present review, we carried out a systematic review and meta-analysis to analyze possible lymph node metastasis (LNM) hazards in individuals with endoscopic resection of gastric cancer.

Methods: Relevant literature was selected by evaluating the PubMed, Cochrane Library, and Google Scholar electronic databases since from inception to March 2022. Corresponding clinicopathological outcomes were summarized, and pooled log odds ratios and 95% confidence intervals were assessed. The random effect model was preferred if variations among studies is high otherwise fixed effect model was preferred.

Results: Overall, 12 associated papers, including 4808 early gastric cancer individuals who endured more surgery after noncurative endoscopic resection, were entered into this analysis. The outcomes showed that submucosal invasion (log odd ratio 1.75, 95% (CI): 0.77–3.95, I^2 = 80.0%); vertical margin (log odd ratio 6.53, 95% (CI): 2.81-15.17, I^2 = 65%); horizontal margin (log Odd ratio 0.69 95% (CI): 0.22-2.14, I^2 = 52%), lymphatic invasion (Odd ratio 6.33 95% (CI): 1.98-20.24, I^2 = 91%), and vascular invasion (Odd ratio 3.55, 95% (CI): 1.31-9.58, I^2 = 92%) was significantly related to metastasis of lymph node for these patients.

Conclusion: There was a significant association of LNM hazards in individuals with endoscopic resection of gastric cancer. Therefore, invasion to lymph, vascular, submucosa and positive vertical margin should be strongly noticed when selecting surgical treatment factors.

Keywords: Noncurative endoscopic resection; Early gastric cancer; Endoscopic dissection

Introduction

Gastric cancer is known as a common malignant disease in the world (1). The diagnosis of this disease in the early stages is due to the progress in diagnostic methods, including screening endoscopies, which leads to the identification of an increasing number of patients in the first stages of the illness besides the presence of clinical manifestations (2). In early gastric cancer (EGC) patients, minimally invasive resection is usually recommended because of the proportionally low risk for lymph node metastasis (LNM). In recent years, endoscopic submucosal dissection (ESD) has been used for patients with the possibility of metastasis to lymph nodes (3-5).

However, it is hard to characterize the extent of deep invasion of tumors and lymph vessels in this method (6-8). For noncurative endoscopic resection (nCER) individuals, extra gastrectomy with sufficient lymphadenectomy is generally counseled due to the possibility of metastasis to the lymph node (9, 10). Although, according to previous reports, the extent of LNM was observed in only 5% to 19% of patients with additional surgery (11-22).

Some studies reported that nCER does not always cause tumour recurrence and cancer-related death, but short-term surveillance through endoscopy can be an alternative to surgery in older patients (8, 23–25). To prevent unnecessary additional surgery, it is necessary to identify the risk factors associated with LNM. According to the available reports, age, size of the tumour, invasion of vascular/lymphatic and submucosa, positive vertical margin, location of the tumour, and findings macroscopy in nCER patients are important factors related to lymph node metastasis (10, 12-16, 19, 21, 26-29).

ESD, or endoscopic submucosal dissection, in EGC patients has had satisfactory results (30–32). However, there is a possibility of not accurately assessing some clinical pathological features, such as the depth of tumour invasion, with methods such as endoscopy, endoscopic ultrasound, and biopsy before endoscopic resection. ESD treatment in some EGC patients is identified as noncurative resection, or nCER, and it is recommended to perform additional gastrectomy along with lymphadenectomy due to the hazard of metastasis to lymph nodes (33). Although the main question is whether additional surgery can benefit nCER patients; further surgery after nCER increases survival more than patients without surgery (10, 34, 35). On the other hand, endoscopy and close monitoring of the patient could be a practical option and alternative to additional surgery for patients who are not eligible for surgery (8, 23–25).

A large number of patients with nCER may endure inessential surgical therapy. However, the results of studies are conflicting among each other as well as most of studies have low sample size which ultimately restrict us to draw any valid conclusion. Further, to best of our knowledge, no meta-analysis has been conducted so far to analyze the possible lymph node metastasis (LNM) hazards in individuals with endoscopic resection of gastric cancer. The predicting the possibility of LNM before additional surgery in nCER patients is essential.

Therefore, we have conducted a systematic literature review (SLR) and meta-analysis of lymph node metastasis and its risk factors for early gastritis individuals who underwent nCER.

Methods

Study design

A thematic search strategy was used in PubMed, Cochrane Library, and Google Scholar databases to identify potentially relevant articles in the published literature. In addition, sources of related articles were also screened to identify associated studies. MeSH was applied in the search plan with proper use of Boolean operators: "endoscopic dissection" AND "noncurative resection", "surgery" AND "metastasis of lymph node", AND "early gastric cancer".

However, due to the limitations of language, only papers published in English were entered. The studies were searched since from inception to Mar 2022.

Inclusion and Exclusion Criteria

The studies were screened and selected based on inclusion and exclusion criteria. Studies were included if patients diagnosed with gastric cancer, patients undergone endoscopic submucosal dissection are considered as nCER patients; patients undergoing additional surgery with lymphadenectomy, who's removed samples were pathologically evaluated in terms of lymph nodes; both gender and all age groups, studies evaluated the risk factors associated with LNM for patients who underwent additional surgery after nCER were included

The case reports, case series, narrative reviews, systematic literature reviews, meta-analysis were excluded from the study.

Extraction of Data

Two researchers evaluated the text of the selected paper based on the inclusion/exclusion criteria and extracted data separately. All the disagreements were discussed with third researcher. Data extracted from each study includes author, publication year, sample, age, rate of LNM, and 5-year overall survival rate.

The following clinicopathological outcomes were summarized from the papers: depth of tumor invasion, invasion to lymph and vascular, vertical and horizontal margin.

Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to check the quality of included studies. Two researchers separately evaluated the quality of included studies (29). Points were assigned to each included study, and a score of more than seven was defined as high-quality studies.

Assessment of Publication bias

Funnel plot was used to assess the publication bias qualitatively.

Statistical analysis

Categorical outcomes were analyzed using log OR (odds ratio) and 95% CI (confidence intervals). Cochran's Q test and I^2 statistic examined and evaluated the heterogeneity. Forest plots were pooled to determine log OR, and a 95% CI was designed. In addition, a funnel plot was made to survey potential publication bias. All statistical analyses were done by RevMan 5.4 software, and a *P*-value <0.05 was considered statistically significant in statistical.

Results

The literature search flow chart is shown in Fig. 1.

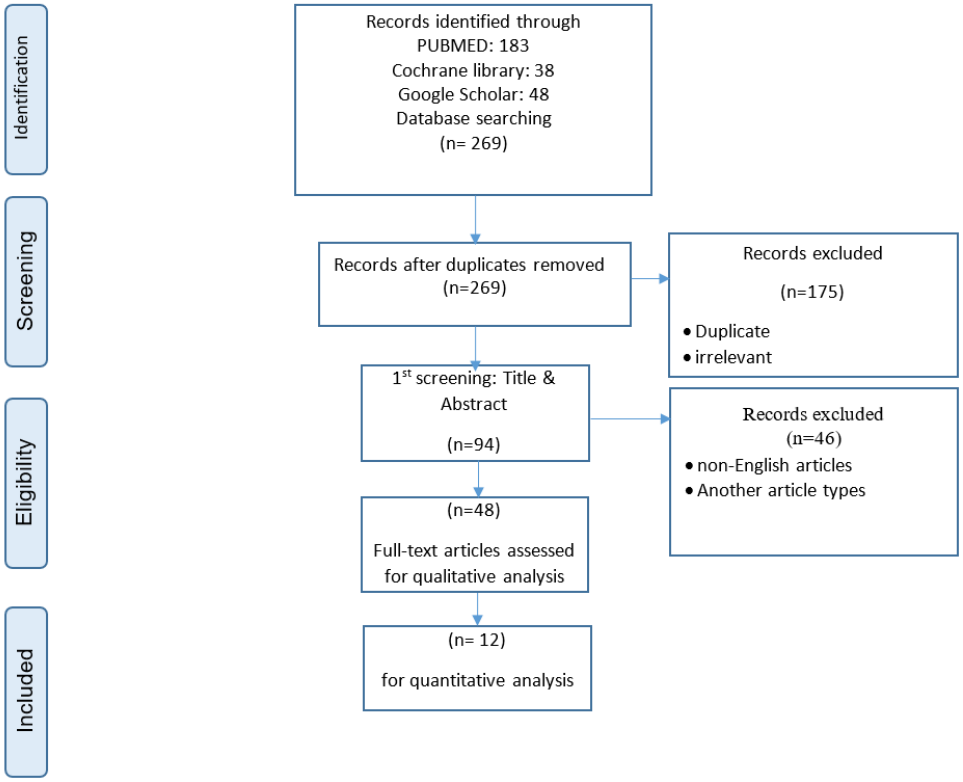

Fig. 1: Flow charts for the selected studies in the present review

Based on the defined search strategy, 269 potentially relevant studies were found through electronic databases and manual searches. After screening the titles and abstracts, 175 papers were excluded, and the 94 remaining articles were analyzed through complete article evaluation. Of these, 46 studies were excluded based on the inclusion and exclusion criteria as well as due to the insufficient information. Finally, 12 studies had adequate criteria for entrance into this review (10-19, 21, 22). All selected papers were retrospective. In addition, 4,808 individuals with EGC endured additional surgery after endoscopic resection. The principal characteristics of the selected documents are shown in Table 1. The quality assessment results have indicated the fair and good quality of included studies as compiled in Table 2.

Table 1: Summarized characteristics of selected studies

Variable			***Participants***		***Age (mean± SD)***	***Lymphatic metastasis%***	***5-year survival rate***
Author (Reference number)			Surgery group	Follow-up group	Surgery group		
Ito et al (13)	2013	41	41	-	67.7 (46–83)	9.8	-
Kim et al (16)	2015	274	194	80	69.4 (42–86)	5.7	94.3
Ishii et al (12)	2016	112	112	-	67 (40–87)	10.7	94.7
Toyokawa et al (21)	2016	167	100	67	69 (63–73)	9.0	-
Sunagawa et al (19)	2017	200	200	-	68 (43–81)	7.5	-
Kawata et al (14)	2017	506	323	183	69 (37–89)	9.3	90
Suzuki et al (20)	2017	568	356	212	NR	5.3	94.7
Kikuchi et al (15)	2017	150	73	77	68.8	11	85.0
Chu et al (11)	2019	1262	182	1080	60 (43-81)	14.4	96
Liang et al (17)	2020	203	203	-	54 (22-84)	19.7	94.7
Ren et al (18)	2021	691	691	-	61 (38-80)	16.5	95
Yang et al (22)	2021	634	270	364	60.1±10.4	9.6	95

NR: not reported

Table 2: Quality assessment using new castle Ottawa scale

Study & Year	*Selection*	*Comparability*	*Exposure*	*Total Score*	*Quality of the Study*
Ito et al (2013) (13)	**	*	***	6	Fair
Kim et al (2015) (16)	***	*	***	7	Good
Ishii et al (2016) (12)	***	*	***	7	Good
Toyokawa et al (2016) (21)	****	**	***	9	Good
Sunagawa et al (2017) (19)	***	*	***	7	Good
Kawata et al (2017) (14)	****	*	***	8	Good
Suzuki et al (2017) (20)	***	*	***	7	Good
Kikuchi et al (2017) (15)	**	**	***	7	Fair
Chu et al (2019) (11)	**	**	***	7	Fair
Liang et al (2020) (17)	***	*	**	6	Good
Ren et al (2021) (18)	**	*	**	5	Fair
Yang et al (2021) (22)	**	*	***	6	Fair

Risk factors correlated to LNM.

Twelve studies (10-19, 21, 22), including 4696 individuals, were entered into the study for the relationship between the depth of tumor invasion and metastasis to lymph nodes.

Eight studies, including 2378 individuals, evaluated the effect of vertical margin, and six studies, including 1594 patients of horizontal margin, on metastasis to lymph nodes for individuals with noncurative endoscopic resection.

Assessing the relationship between the depth of tumor invasion and LNM

The overall estimate was 1.75 [0.77, 3.95] which indicate non-significant association between the depth of tumor invasion and LNM. Further, the heterogeneity among studies was found to be 80% (Fig. 2).

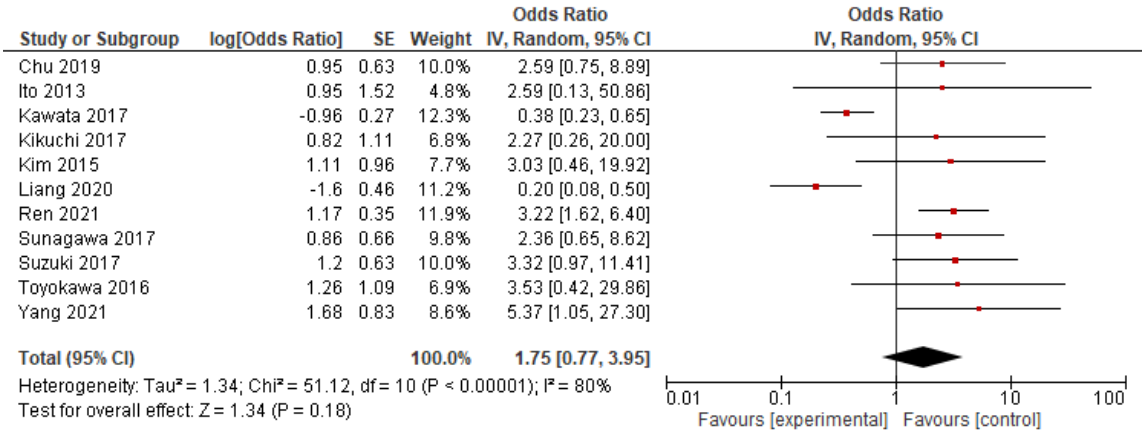

Fig. 2: Assessing the relationship between the depth of tumor invasion and LNM

Publication bias

The funnel plot has indicated less involvement of publication bias (Fig. S1) (Not published. Note the end of the paper).

Sensitivity analysis

The sensitivity analysis results have shown no impact of individual studies (after removal of five studies) on the outcome (Fig. S2 a-e). However,

after removal of six and more studies, association between the depth of tumor invasion and LNM was found significant (Fig. 4f-i).

Assessing the relationship between the vertical margin and LNM

The overall estimate was found to be 6.53 [2.81, 15.17] which indicate the significant association between the vertical margin and LNM. The heterogeneity among studies was found to be 65% (Fig. 3).

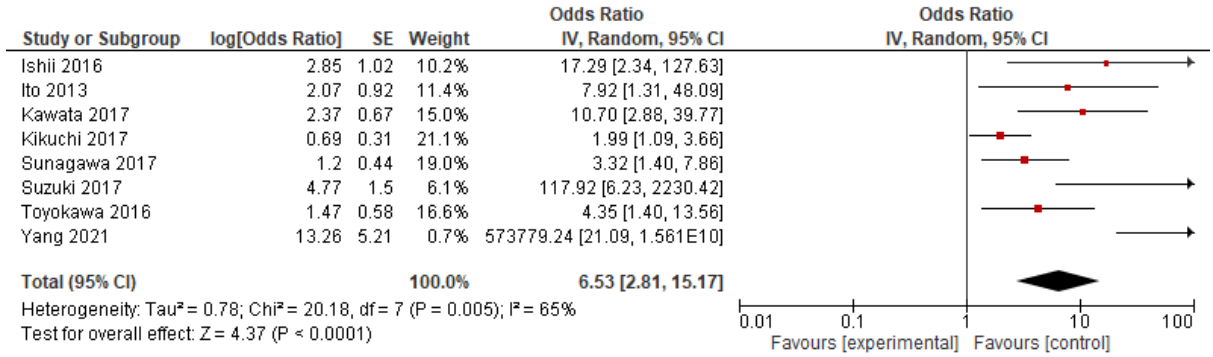

Fig. 3: Assessing the relationship between the vertical margin and LNM

Publication bias

Funnel plot has indicated the involvement of publication bias (Fig. S3).

Sensitivity analysis

The results of sensitivity analysis have shown no impact of individual studies on the outcome (S4a-e) except Fig. S4f.

Assessing the relationship between the horizontal margin and LNM

The overall estimate was found to be 0.69 [0.22, 2.14] which indicate non-significant association between the horizontal margin and LNM (Fig. 4). Further, the heterogeneity among studies was found to be 52%.

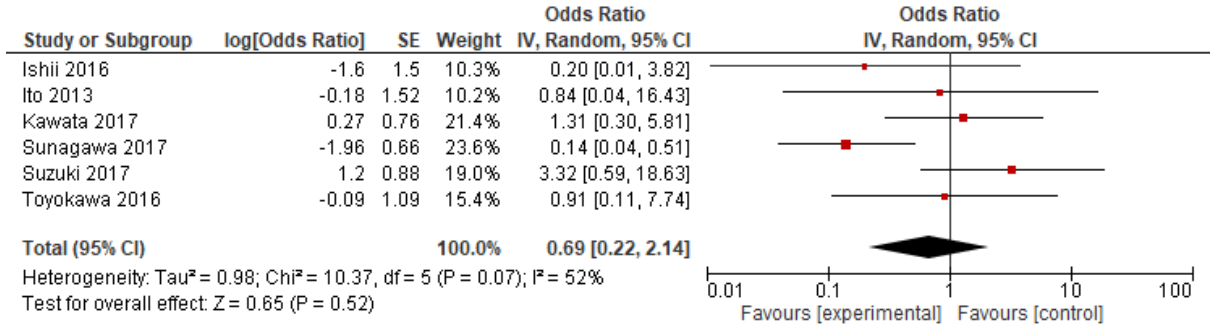

Fig. 4: Assessing the relationship between the horizontal margin and LNM

Publication bias

Funnel plot has indicated less involvement of publication bias, however, a greater number of studies are required to confirm it (Fig. S5).

Sensitivity analysis

The sensitivity analysis results have shown no impact of individual studies on the outcome (Fig. S6 a-d).

Association between lymphatic invasion and LNM

According to the description of invasion to lymph and vascular, eight papers, including 1121 individuals who endured additional surgery after endoscopic resection, were entered in this review.

The overall estimate was found to be 6.33 [1.98, 20.24] which indicate significant association between lymphatic invasion and LNM (Fig. 5). The heterogeneity among studies was found to be 91%.

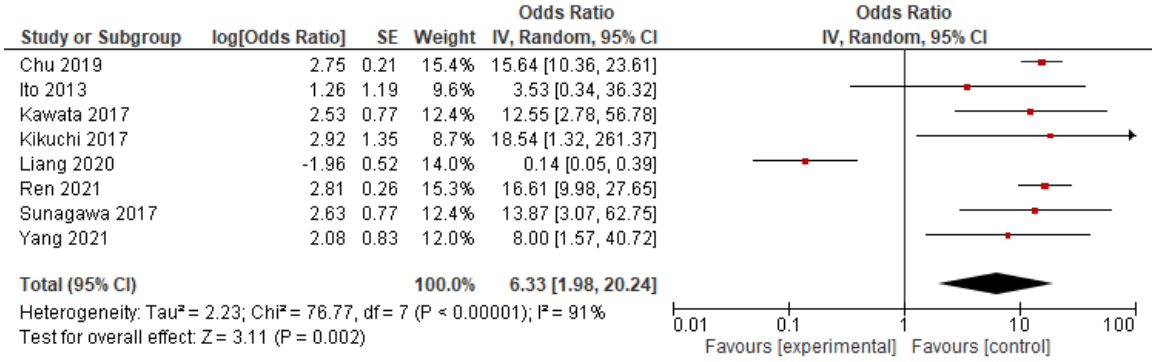

Fig. 5: Association between lymphatic invasion and LNM

Publication bias

The funnel plot has indicated less involvement of publication bias (Fig. S7).

Sensitivity analysis

The sensitivity analysis results have shown impact of individual studies on the outcome after removal of two studies 11 and 13 as shown in Fig. S8b. There was no impact on the outcome after removal of 11, 13,14,15,17 as shown in Fig. S8f.

Assessing the relationship between the vascular invasion and LNM

The overall estimate measure was found to be 3.55 [1.31, 9.58] which indicate significant association between the vascular invasion and LNM (Fig. 6). However, heterogeneity among studies was found to be high.

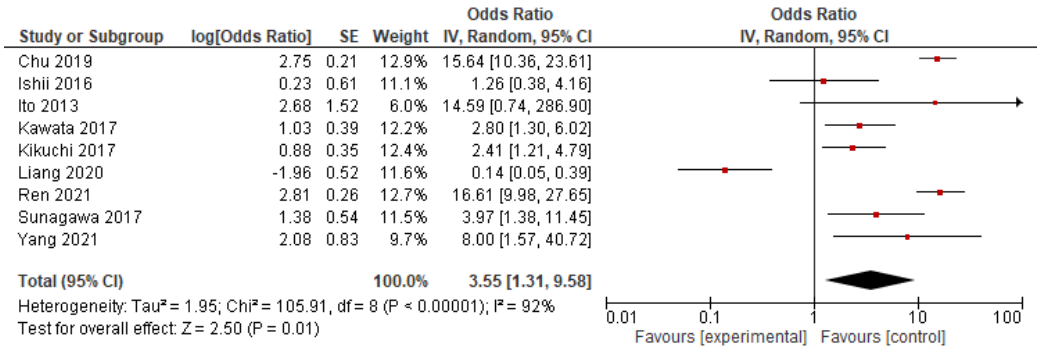

Fig. 6: Assessing the relationship between the vascular invasion and LNM

Publication bias

Funnel plot has indicated less involvement of publication bias (Fig. S9).

Sensitivity analysis

The sensitivity analysis results have indicated the impact of individual studies on the outcome (Fig. S10a-g).

Discussion

In patients who underwent additional surgery following nCER, submucosal invasion, vertical margin, and lymphatic vascular invasion were substantially linked with LNM. The infiltration of tumour cells into lymphatic vessels is regarded as the beginning of lymph node metastasis. The findings of certain investigations supported the observation of LNM and distant metastases in patients with lymphatic vascular invasion (14, 20, 36). Additionally, LNM in those with nCER was at risk for lymphatic vessel invasion (14, 19–21, 28). Therefore, a larger incidence of LNM can be seen in nCER patients as the depth of tumour invasion increases. A strong correlation between LNM and an increase in risk factors has also been found, according to the findings of various research (19, 27, 28).

The horizontal margin was not recognized as a risk factor in LNM in the current investigation. A precise identification of the vertical margin is also required in the pathological evaluation of samples taken by endoscopy because a positive vertical margin might also signify a deeper tumour invasion.

Heterogeneity among studies is one of the important parameters to be calculated in every meta-analysis. Higher the heterogeneity among studies less will be confidence on the results (37, 38). The results of current met-analysis has indicated the heterogeneity among studies. This might be due to variations among individual studies included in the current meta-analysis.

Publication bias is one of the important parameters in meta-analysis (39-41). The funnel plots of the current investigation have indicated less involvement of publication bias in most of the parameters.

There are certain restrictions. First of all, because all of the chosen studies were retrospective in nature, several confounding variables may have impacted the findings. The research population may become heterogeneous as a result of changing surgical indications in some patients. Second, because of their advanced age or the presence of other underlying conditions, some nCER patients may decide against surgery. As a result, selection bias should be taken into account.

Limitation

The study does not include the studies available in the Web of Sciences and Embase. The studies published in English language are only considered.

Conclusion

Invasion of the submucosa, lymphatic vascular tissue, and the positive vertical margin all posed a significant risk for lymph node metastases in people. The development of evidence to identify LNM predictors and support individualised treatment in nCER patients will be made possible by the data presented here. However, additional clinical investigations that are both more in-depth and comprehensive are required to validate the relationship.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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