SYSTEMATIC REVIEW

THE ROLE OF LYMPH NODE METASTASIS IN EARLY GASTRITIS INDIVIDUALS FOLLOWING NONCURATIVE ENDOSCOPIC RESECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Recent studies suggest that individuals who underwent noncurative endoscopic resection for gastric cancer may require additional surgery. We conducted a comprehensive systematic review and meta-analysis to investigate the risk of lymph node metastasis in these cases. **Methods:** We comprehensively examined relevant literature by extensively reviewing electronic databases such as PubMed, Cochrane Library, and Google Scholar. Subsequently, we analyzed clinicopathological outcomes and calculated pooled odds ratios and 95 percent confidence intervals using diverse effects models. **Results:** This analysis included 12 papers with 4808 individuals who underwent additional surgery after noncurative endoscopic resection for early gastric cancer. The results indicated significant associations between lymph node metastasis and submucosal invasion (Odd ratio 2.04, 95% (CI): 1.58–2.63, I 2 = 88.7%; p<0.001), vertical margin (Odd ratio 6.11, 95% (CI): 1.94–19.23, I 2 = 0%; p<0.001), lymphatic invasion (Odd ratio 10.02, 95% (CI): 7.57–13.27, I 2 = 92%; p<0.000), and vascular invasion (Odd ratio 7.11, 95% (CI): 5.49–9.22, I 2=92%; p<0.000). **Conclusion:** When choosing factors for surgical treatment, it is essential to thoroughly consider the invasion of lymph nodes, vascular system, submucosa, and positive vertical margin.

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

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INTRODUCTION

Gastric cancer is a prevalent malignant disease worldwide.[1] However, due to advancements in diagnostic techniques, such as screening endoscopies, the early detection of the disease has become more feasible. Consequently, more patients are diagnosed early through clinical symptoms and screenings.[2]

Doctors usually suggest a minimally invasive resection for patients with early gastric cancer (EGC) who have a lower risk of lymph node metastasis (LNM). Doctors have recently considered endoscopic submucosal dissection (ESD) as a treatment choice for lymph metastasis in these patients.[3–5]

Determining the extent of tumour invasion and lymph vessel involvement can be difficult through this method. As a result, noncurative endoscopic resection (nCER) is often recommended for patients with early gastric cancer (EGC) who have received ESD therapy.[6–8] Patients who undergo nCER are generally advised to have additional gastrectomy with adequate lymphadenectomy as a precaution against the risk of lymph node metastasis.[9,10] However, recent studies have shown that a small percentage of patients, ranging from 5% to 19%, may require further surgery to address lymph node metastasis.[11–22] Therefore, it is crucial to be aware of this possibility when making treatment decisions.

Studies suggest that not all cases of nCER lead to tumour recurrence and cancer-related deaths. For older patients, short-term endoscopy surveillance could be a viable alternative to invasive surgery.[8,23–25]

Identifying the risk factors associated with LNM is crucial to avoid unnecessary additional surgery. Age, tumour size, vascular/lymphatic and submucosa invasion, positive vertical margin, tumour location, and macroscopic findings in nCER patients are significant indicators of lymph node metastasis, as reported in available studies.[10,12–16,21,26–26]

Despite conflicting data and limited sample sizes, we conducted a review to determine the correlation between clinical outcomes and metastasis to lymph nodes. Unfortunately, there is no agreement yet on the potential risk factors involved.

Study design

Our research involved thoroughly searching published literature on PubMed, Cochrane Library, and Google Scholar databases using a thematic search strategy. We also screened related sources to identify associated studies. Our search focused on MeSH terms like endoscopic dissection, noncurative resection, surgery, metastasis of lymph nodes, and early gastric cancer. However, we were limited to papers published in English due to language constraints.

Criteria

In this meta-analysis, we assessed individuals with early gastric cancer who underwent endoscopic submucosal dissection and were categorized as non-curative endoscopic resection (nCER) patients based on treatment guidelines. We included patients with additional surgery with lymphadenectomy and had their removed samples pathologically evaluated for lymph nodes. The patients were then divided into two groups after undergoing other surgery following nCER: those who tested negative for lymph node metastasis (LNM) and those who tested positive. The studies ultimately analyzed the risk factors associated with LNM for both groups of patients.

Extraction of Data

Two researchers evaluated the chosen paper based on established criteria for inclusion and exclusion. Both researchers independently extracted data, including author, publication year, sample size, age, rate of lymph node metastasis, and overall, 5-year survival rate. A third researcher resolved any discrepancies.

Based on the papers, we have summarized the clinicopathological outcomes, including the depth of tumour invasion, lymph and vascular invasion, and the vertical and horizontal margin.

To assess the methodological quality of the papers, the Newcastle-Ottawa Quality Assessment Scale (NOS) was utilized, and two researchers independently evaluated the studies.[29] The studies included were given points, and those that scored above seven were deemed high quality.

Statistical analysis

We analyzed categorical outcomes using odds ratio (OR) and 95% confidence intervals (CI). Heterogeneity was evaluated using Cochran's Q test and I2 statistic. We used forest plots to determine OR and 95% CI and a funnel plot to check for potential publication bias. All statistical analyses were conducted using Stata 14.0 software, and a P value of less than 0.05 was considered statistically significant.

RESULTS

Search strategy

A flow chart was created in figure1 to guide the literature search process. After implementing the search strategy, a total of 269 potentially relevant studies were found through electronic databases and manual searches. After screening 175 articles, 94 remained for evaluation. The remaining articles were thoroughly evaluated, with all irrelevant articles being removed. Only 12 studies met the necessary criteria for inclusion in the review, with 4,808 individuals with EGC undergoing additional surgery after endoscopic resection.[10–19,21,22] All selected papers were retrospective and the principal characteristics of the selected articles were assessed for adequate criteria and inclusion into Table-1.

Risk factors correlated to LNM.

The study analyzed 11 reports involving 4696 individuals to understand the correlation between tumour invasion depth and lymph node metastasis. The findings, depicted in Figure-2, indicated that individuals with a submucosal invasion of over 500 mm had a significantly higher risk of lymph node metastasis (OR 2.04, 95% CI 1.58–2.63, $p<0.001$; I 2 = 88.7%).

Based on eight studies involving 2378 individuals, it has been found that a positive vertical margin is a risk factor for metastasis to lymph nodes in patients with noncurative endoscopic resection. Similarly, six studies, including 1594 patients, have shown that the horizontal margin also impacts metastasis to lymph nodes. The results indicated that a positive vertical margin could increase the risk of metastasis to lymph nodes (Odd ratio 6.11, 95% (CI) 1.94–19.23, I 2= 0%, $p<0.001$). These findings are illustrated in Figure-3, although the evaluation of the horizontal margin did not confirm the same data (Odd ratio 1.06, 95% (CI) 0.49-2.26, I 2 =0%, $p<0.48$) (Figure-4).

This review included eight papers with 1121 individuals who underwent additional surgery after endoscopic resection. According to the analysis of invasion to lymph and vascular, the data

showed that both invasions to lymph (Odd ratio 10.02, 95% (CI) 7.57–13.27, I 2 = 92%, p<0.000) and vascular (OR 7.11, 95% (CI) 5.49–9.22, I 2=92%, p<0.000) were significantly associated with a higher risk of metastases to lymph nodes (Figures-5 & 6).

Bias

The funnel plots in Figure 7 do not show any significant asymmetry, indicating the absence of bias.

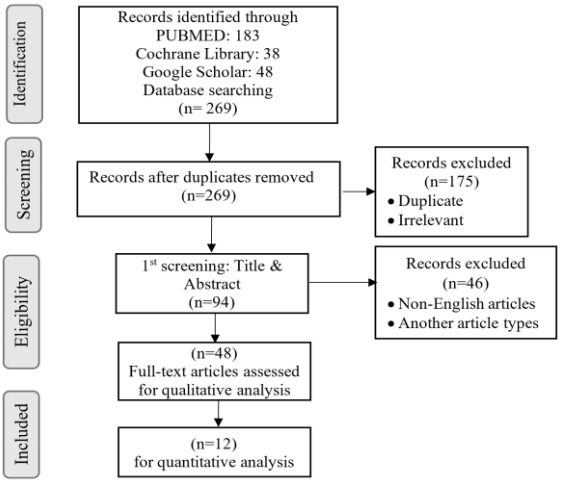

Figure-1: Flow charts for the selected studies in the present review

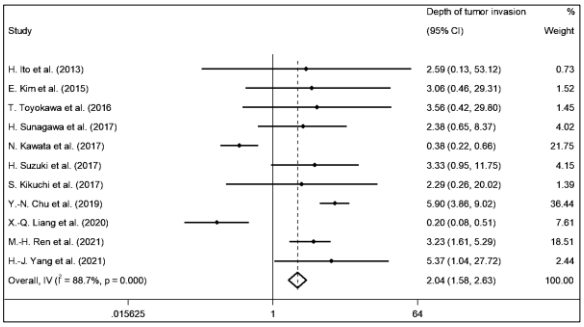

Figure-2: Assessing the relationship between the depth of tumour invasion and LNM

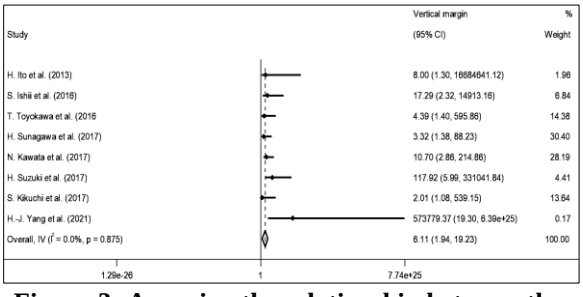

Figure-3: Assessing the relationship between the vertical margin and LNM

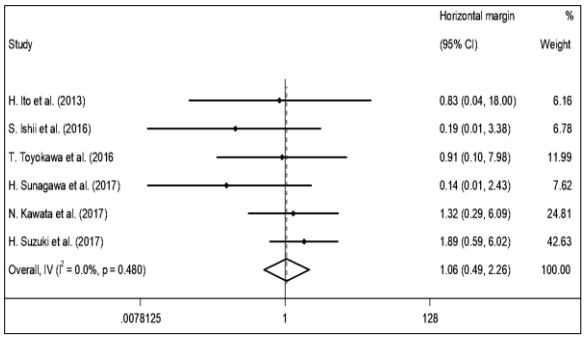

Figure-4: Assessing the relationship between the horizontal margin and LNM

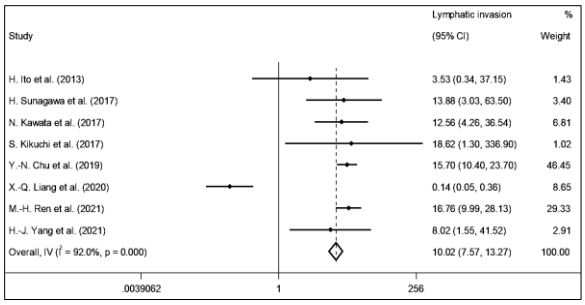

Figure-5: Assessing the relationship between the lymphatic invasion and LNM

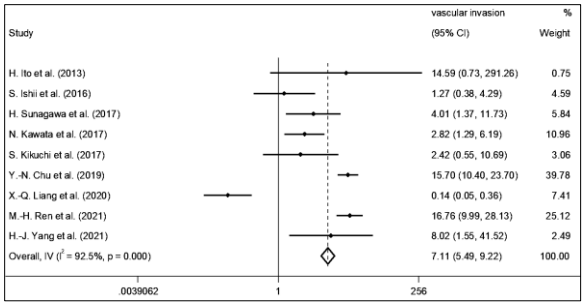

Figure-6: Assessing the relationship between the vascular invasion and LNM

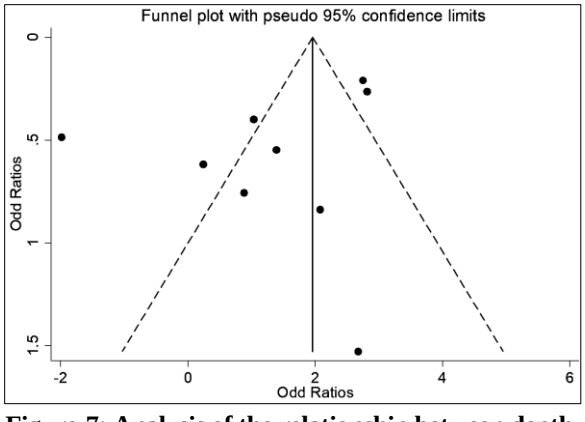

Figure-7: Analysis of the relationship between depth of tumour invasion and LNM by Funnel plot.

Table-1: Summarized characteristics of selected studies

			participants		Age (mean± SD)	Lymphatic metastasis%	5-year survival rate
			surgery group	follow-up group	surgery group		
Ito *et al*.	2013	41	41	-	67.7 (46–83)	9.8	-
Kim *et al*.	2015	274	194	80	69.4 (42–86)	5.7	94.3
Ishii *et al*.	2016	112	112	-	67 (40–87)	10.7	94.7
Toyokawa *et al*.	2016	167	100	67	69 (63–73)	9.0	-
Sunagawa *et al*.	2017	200	200	-	68 (43–81)	7.5	-
Kawata *et al*.	2017	506	323	183	69 (37–89)	9.3	90
Suzuki *et al*.	2017	568	356	212	Not reported	5.3	94.7
Kikuchi *et al*.	2017	150	73	77	68.8	11	85.0
Chu *et al*.	2019	1262	182	1080	60 (43-81)	14.4	96
Liang *et al*.	2020	203	203	-	54 (22-84)	19.7	94.7
Ren *et al*.	2021	691	691	-	61 (38-80)	16.5	95
Yang *et al*.	2021	634	270	364	60.1±10.4	9.6	95

DISCUSSION

Endoscopic submucosal dissection (ESD) has shown promising results in treating patients with early gastric cancer (EGC).[30–32] However, there may be limitations in assessing certain clinical pathological features, such as tumour invasion depth, through methods like endoscopy, ultrasound, and biopsy before the procedure. In some cases, ESD may result in noncurative resection (nCER), which may require additional gastrectomy and lymphadenectomy to prevent metastasis to lymph nodes.[33] The question remains whether additional surgery is beneficial for nCER patients. While some studies suggest that further surgery after nCER can improve survival rates[10,34,35], others propose endoscopy and close monitoring as viable alternatives for patients who are not eligible for surgery[8,23–25].

It is essential to predict the likelihood of lymph node metastasis (LNM) before performing additional surgery on patients with nCER to avoid unnecessary procedures. However, a definitive conclusion cannot be confidently reached due to the small sample size in previous studies assessing the impact of various factors on LNM. To address this, our current study conducted a meta-analysis to identify potential risk factors for LNM in patients with nCER.

The results showed that submucosal invasion, vertical margin, and lymphatic vascular invasion were significantly linked to LNM in patients who underwent additional surgery after nCER. The invasion of tumour cells into lymphatic vessels is regarded as the initial phase of metastasis to lymph nodes. Studies have shown that LNM and distant metastasis are more likely to occur in those with lymphatic vessel invasion.[14,20,36] Additionally, lymphatic vessel invasion has been identified as a hazard for LNM in nCER patients.[14,19–21,28] As a result, patients with a deeper level of tumour invasion have a higher risk of LNM. Furthermore, studies indicate a significant correlation between LNM and increased risk factors.[19,27,28]

According to the study, the horizontal margin was not a risk factor for LNM. However, a positive vertical margin may suggest a deeper tumour invasion. Therefore, pathological evaluation of samples removed by endoscopy should include an accurate diagnosis of the vertical margin.

There are certain limitations to consider. Firstly, it's important to note that all of the studies chosen were retrospective, which could have influenced the results by some confounding factors. Additionally, the indications for additional surgery among certain patients may have changed, leading to heterogeneity in the study population. Secondly, it's worth noting that some nCER patients may opt not to undergo surgery due to their advanced age or pre-existing medical conditions. As a result, it's crucial to consider the potential for selection bias.

In conclusion, according to the study's findings, individuals who experienced the invasion of the submucosa, lymphatic vascular, and a positive vertical margin were at significant risk for lymph node metastasis. We anticipate that this data will provide evidence to identify predictors of LNM and aid in tailoring treatment for individuals with nCER.

Conflicting Interest:

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial or non-financial interest in this manuscript's subject matter or materials

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