# The incidence of lymph node metastasis in early gastric cancer according to the expanded criteria in comparison with the absolute criteria of the Japanese Gastric Cancer Association: a systematic review of the literature and meta-analysis CME

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**Background and Aims:** Japanese criteria for curative endoscopic resection of early gastric cancer initially included nonulcerated, well-differentiated mucosal lesions ≤2 cm in diameter, known as the absolute criteria. Subsequently, these indications were expanded to include larger, ulcerated, and undifferentiated mucosal lesions as well as differentiated lesions with slight submucosal invasion. Whether patients meeting the expanded criteria can be managed safely without gastrectomy and lymph node dissection has been controversial. The risk of lymph node metastasis (LNM) in patients who met the expanded criteria is a critical factor in determining the best course of management for these patients.

**Methods:** We comprehensively searched main reference databases for studies that included patients who underwent gastrectomy and lymph node dissection for early gastric cancer. A meta-analysis was conducted by using the random effects model. Relative risk reduction was used to compare the incidence of LNM in patients meeting the absolute criteria as compared with those meeting the expanded criteria.

**Results:** Twelve studies met the inclusion criteria, providing a total of 9798 patients. The incidence of LNM was 0.2% for patients who met the absolute criteria as compared with 0.7% for patients who met the expanded criteria. Analysis of the various components of the expanded criteria was conducted, revealing that the incidence of LNM for differentiated mucosal lesions ≤3 cm with ulceration and for differentiated mucosal lesions without ulceration, irrespective of size, was 16 of 2814 (0.57%), reference range (RR) 3.01; $P = .02$ and 8 of 3004 (0.27%), RR 1.69; $P = .37$, respectively, only marginally higher than the risk of LNM associated with the absolute criteria. In contrast, undifferentiated mucosal lesions ≤2 cm and differentiated lesions <3 cm with slight submucosal invasion had a significantly higher incidence of LNM in comparison with the absolute criteria (25/972 [2.6%], RR 6.79; $P = .0004$ and 8/315 [2.5%], RR 6.30; $P = .004$, respectively).

**Conclusion:** Overall, expanding the indication for endoscopic resection to include mucosal nonulcerated differentiated lesions irrespective of size and differentiated mucosal ulcerated lesions <3 cm is justified with minimal increased risk in comparison to the absolute criteria. However, expanding the indication for undifferentiated lesions ≤2 cm and differentiated lesions with slight submucosal invasion (T1b) should be balanced with the risks of surgery, given the increased risk of LNM in these patients. (Gastrointest Endosc 2018;87:338-47.)

*Abbreviations: EGC, early gastric cancer; ESD, endoscopic submucosal dissection; LND, lymph node dissection; LNM, lymph node metastasis.*

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See CME section; p. 573.


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Worldwide, gastric cancer is the fifth most common cancer and the third leading cause of cancer death (10%).[1,2] Because the diagnosis of gastric cancer often occurs late in the course of the disease, the 5-year survival rate is only 20% to 30%.[3,4] Until relatively recently, radical surgical gastrectomy with the removal of at least 15 lymph nodes was considered the only potentially curative treatment for gastric cancer.[5] However, radical surgery is associated with high morbidity and mortality rates as well as a decrease in the quality of life.[6-8]

Early gastric cancer (EGC) was defined in 1962 by the Japanese Research Society for Gastric Cancer as tumors with invasion limited to the mucosa or submucosa of the stomach, irrespective of lymph node involvement.[6,9] EGCs that are limited to the mucosa have a 2% to 5% incidence of lymph node metastasis (LNM) which increases to 10% to 25% when the disease invades the submucosa.[10,11] Over the past 3 decades, the ability to identify patients with EGC having a negligible risk of LNM has led to the development of effective minimally invasive strategies for the endoscopic cure of EGC, initially by using EMR and more recently with endoscopic submucosal dissection (ESD). With advances in screening and endoscopic resection, now more than half of the 10,000 cases of gastric cancer detected annually in Japan are EGC.[12] The 5-year survival rate for these patients is up to 99%.[13]

Critical to the effective use of endoscopic techniques for curative resection of EGC is the ability to accurately predict the risk of LNM based only on the endoscopic and histologic characteristics of a lesion. In order to estimate the risk of LNM in EGC, Gotoda et al[14] studied the prevalence of LNM in 5265 patients who underwent gastrectomy with careful lymph node dissection (LND) over a 30-year period. The overall risk of LNM in mucosal lesions was only 2.7%, whereas the risk of LNM for all submucosal lesions was 18.6%. Interestingly, the risk of LNM was 0% for mucosal differentiated lesions without ulceration irrespective of size, mucosal differentiated ulcerated lesions ≤2 cm, and poorly differentiated lesions ≤3 cm. The authors noted that lesions under 3 cm with slight submucosal invasion (<500 μm) and no lymphovascular invasion had 0% LNM, provided that an endoscopic submucosal en bloc resection was performed, with negative margins. Giving these low LNM rates, Gotoda et al[14] proposed the expanded endoscopic resection criteria (Table 1). The same group found that nonulcerated undifferentiated intramucosal lesions ≤20 mm without lymphatic-vascular involvement present a negligible risk of LNM,[15] and shortly after they published similar 5-year survival after endoscopic resection between patients who met expanded criteria versus patients who met the absolute criteria.[16] Isomoto et al[17] reported similar results in patients who underwent ESD for EGC, with 97.1% 5-year overall and 100% disease-specific survival rates. As a result, the Japanese Gastric Cancer Association recently provided expanded indications for ESD. After the introduction of expanded criteria for endoscopic resection, many studies evaluated their risk of LNM, with variable results.[18-27,31,32]

Disturbingly, some authors have reported local and distant metastases in patients who met the expanded criteria. Wang et al[27] found that the incidence of LNM for patients who met the expanded criteria was 8.7% compared with 0% for patients who met the absolute criteria. Moreover, Kang et al[22] noted LNM in 15% of patients with submucosal lesions that met the expanded criteria. The accurate incidence of LNM after the National Cancer Center expanded criteria was applied remains controversial. Some argue that endoscopic resection could result in a delay of LNM discovery and result in the delay of appropriate treatment including surgery and chemotherapy.[24,28] In contrast, others argue that a significant percentage of patients with EGC could benefit from the expanded indications for endoscopic resection to avoid the morbidity, mortality, and diminished quality of life associated with gastric resection.[7,29]

In order to better estimate the benefits of applying the expanded endoscopic resection criteria as compared with the risks of metastatic disease after a noncurative endoscopic resection, we performed a systemic review and meta-analysis investigating the incidence of LNM among patients with EGC who underwent gastric resection with node dissection.

**TABLE 1. Criteria for endoscopic resection according to the absolute and expanded indications**

| Absolute indications | Expanded indications |
|---|---|
| Clinically intramucosal, differentiated type, ≤2 cm in size, UL (-) | Intramucosal cancer, differentiated type, ≤3 cm in size, UL (+) [Ex-1]<br>Intramucosal cancer, differentiated type, >2 cm in size, UL (-) [Ex-2]<br>Intramucosal cancer, undifferentiated type, ≤2 cm in size, UL (-) [Ex-3]<br>SM1 cancer (<500 μm invasion), differentiated type, ≤3 cm in size [Ex-SM] |

*UL*, Ulcerated; *Ex-1*, expanded criteria 1; *Ex-2*, expanded criteria 2; *Ex-3*, expanded criteria 3; *SM1*, slight submucosal invasion; *Ex-SM*, expanded submucosal criteria.

## MATERIALS AND METHODS

### Definition and terms

**EGC.** A tumor with invasion limited to the mucosa or submucosa of the stomach, irrespective of lymph node involvement.

**The Japanese Gastric Cancer Association criteria (absolute criteria).** Tumors for which endoscopic resection is indicated as a standard treatment: differentiated-type adenocarcinomas without ulcerative findings, of which the depth of invasion is clinically diagnosed as T1a, and the diameter is ≤2 cm.[30]

**National Cancer Center Expanded criteria.** Expanded criteria 1. Intramucosal differentiated type, no lymphovascular invasion, with ulcer findings and tumor size ≤3 cm. Expanded criteria 2. Intramucosal differentiated type, no lymphovascular invasion, without ulcer findings and irrespective of tumor size. Expanded criteria 3. Undifferentiated type, no lymphovascular invasion, without ulcer findings and ≤2 cm in size. Expanded submucosal criteria. Submucosal lesions ≤3 cm in size, differentiated, with submucosal invasion of <500 μm.

### Search strategy

We performed a systematic and comprehensive search of major reference databases (MEDLINE, EMBASE,

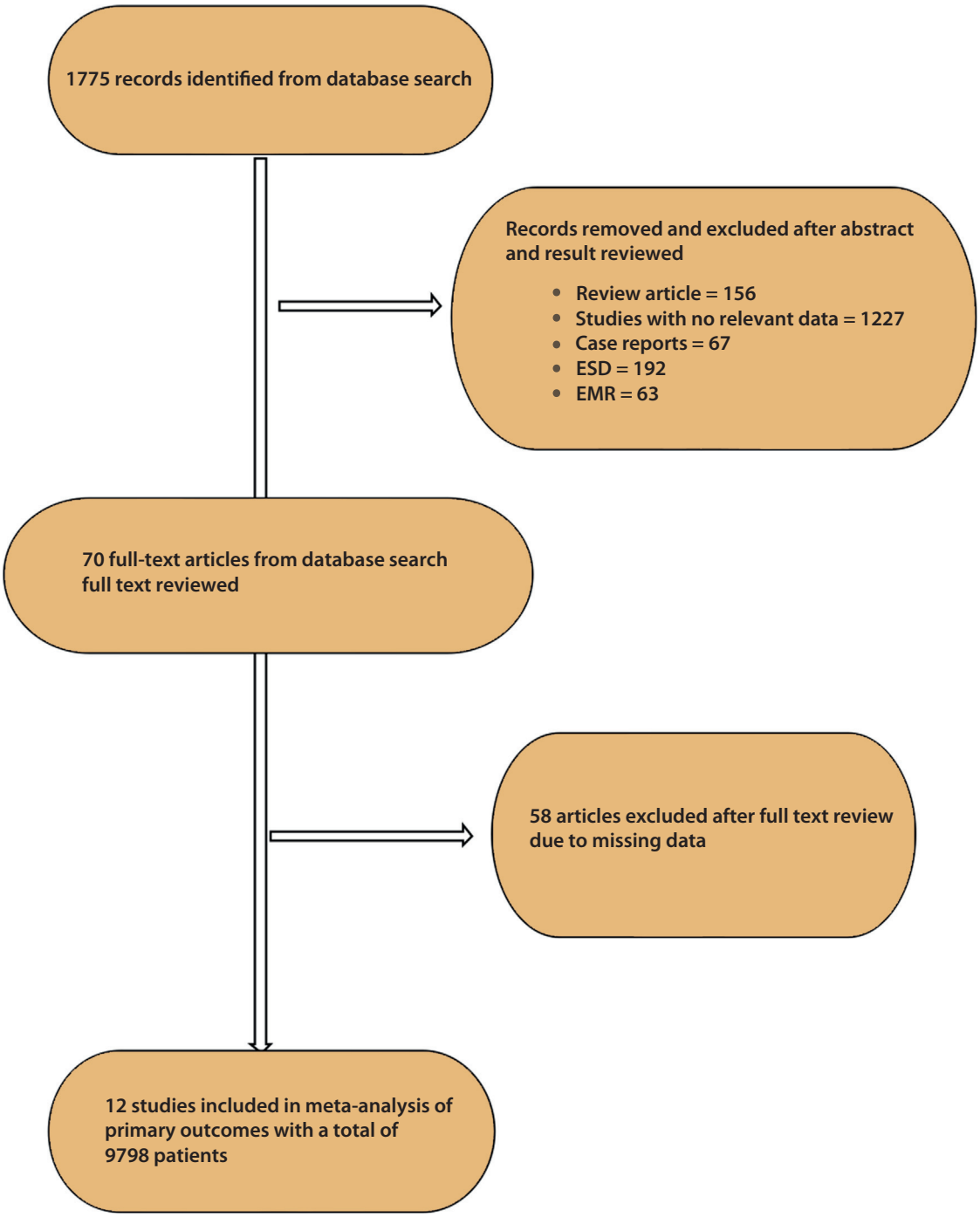


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. *ESD,* endoscopic submucosal dissection.

CINHAL) for all studies that reported the incidence of LNM in EGC, according to the absolute and expanded criteria, restricted to human studies published in English. Articles were compiled into a database, and duplicates were removed. The abstracts were then screened for relevance. Subsequently, the reference lists of relevant trials, reviews, and international guidelines were hand searched. Reference lists of the retrieved literature were cross-searched manually for additional publications.

We followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses,[31] and Meta-Analysis of Observational Studies in Epidemiology.[32] The search strategy and subsequent literature search were performed by an experienced medical reference librarian (C.D.). The search strategy was developed in Ovid MEDLINE and translated to match the subject headings and keywords for Ovid EMBASE, Cochrane database, and Scopus from inception through May 1,

**TABLE 2. Details of included studies evaluating the incidence of lymph node metastasis in patients who met the absolute and expanded criteria**

| Author | Country | Ex criteria | Ex LNM | Ex-1 | Ex-1 LNM | Ex-2 | Ex-2 LNM | Ex-3 | Ex-3 LNM | Ex-SM | Ex-SM LNM | Absolute criteria | Absolute criteria LNM | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chung[1] | Korea | 1869 | 7 | 726 | 2 | 882 | 2 | 261 | 3 | N/A | N/A | 501 | 0 | 20% |
| Gotoda[2] | Japan | 2445 | 0 | 1230 | 0 | 929 | 0 | 141 | 0 | 145 | 0 | 437 | 0 | 24% |
| Park[3] | Korea | 588 | 9 | 230 | 2 | 138 | 1 | 107 | 3 | 98 | 3 | 214 | 2 | 6% |
| Lee[4] | | 430 | 3 | 136 | 2 | 294 | 1 | 0 | 0 | N/A | N/A | 245 | 0 | 4% |
| Kang[5] | Korea | 292 | 7 | 126 | 2 | 146 | 2 | N/A | N/A | 20 | 3 | 88 | 1 | 3% |
| Choi[6] | | 2678 | 11 | N/A | N/A | N/A | | N/A | N/A | N/A | N/A | 1065 | 3 | 28% |
| Ishikawa[11] | Japan | 78 | 1 | 21 | 1 | 42 | 0 | 15 | 0 | N/A | N/A | 26 | 0 | 1% |
| Sung[16] | China | 190 | 3 | 78 | 0 | 77 | 0 | 35 | 3 | N/A | N/A | 42 | 0 | 2% |
| Takizawa[18] | | 137 | 0 | 29 | 0 | 66 | 0 | 42 | 0 | N/A | N/A | 22 | 0 | 1% |
| Wang[21] | China | 183 | 16 | 71 | 4 | 31 | 1 | 81 | 11 | N/A | N/A | 40 | 0 | 2% |
| Kim[31] | Korea | 727 | 6 | 129 | 2 | 341 | 1 | 257 | 3 | N/A | N/A | 234 | 0 | 8% |
| Jee[32] | Korea | 181 | 5 | 38 | 1 | 58 | 0 | 33 | 2 | 52 | 2 | 111 | 0 | 1% |

*Ex,* Expanded; *LMN,* lymph node metastasis; *SM,* submucosal.

2016. Search terms included *early gastric cancer, lymph node metastasis, lymph nodes recurrence, endoscopic mucosal resection, endoscopic submucosal dissection,* and *lymphovascular invasion.* Additionally, the reference lists of all articles included in the final analysis as well as in previous reviews were hand searched to ensure identification of all relevant studies.

## Selections of studies

**Inclusion criteria.** Studies (randomized, prospective observational and retrospective observational) were eligible for inclusion in the meta-analysis if they met these criteria: (1) Patients included in the study were diagnosed with EGC by histopathology, and they underwent gastrectomy with LND. (2) Sufficient data were presented on the lesion, including depth of invasion, size, ulceration, and differentiation, in order to categorize the patients into expanded criteria versus absolute criteria. (3) Adequate details were provided on the total number of patients and percentage of patients involved.

**Exclusion criteria were as follows:** (1) Publications including meeting abstracts, case reports, review articles, letters to the editor, comments, and editorials. (2) Patients without EGC but with other lesions, such as a precancerous lesion, adenoma, or metastatic gastric cancer and studies referring to patients with recurrent EGCs. (3) Insufficient data provided in the article regarding the details of the lesions to categorize them into expanded criteria versus absolute criteria. (4) Articles that did not report on the frequencies of LNM.

## Data extraction and study quality assessment

Data from included studies were independently extracted by 2 reviewers (M.M.A. and M.B.) on data collection sheets. Details extracted from each report included study design, country, year of publication, patient demographics, the incidence of LNM, the size of the lesion, and the presence of ulceration and differentiation. To avoid bias in the data extraction process, 2 investigators independently assessed study quality by using the Newcastle-Ottawa scale for cohort studies. In the case of disagreement, the third investigator made a consensus decision (M.O.).

## Data synthesis

The primary outcome of interest was the incidence of LNM in patients who underwent gastrectomy and LND for EGC according to expanded criteria versus absolute criteria.

## Statistical analysis

Meta-analysis was conducted with Review Manager (RevMan) Version 5.3.0, The Cochrane Collaboration, Copenhagen, Denmark. Relative risk was used to compare the incidence of LNM in each group. Confidence interval (CI) of 95% and a $P$ value of $< .05$ was considered significant. Heterogeneity among the studies was assessed with the chi-square test. A $P$ value of .05 was considered to be significantly heterogeneous. Heterogeneity was categorized as $I^2$ of 0% to 40%, low; 30% to 60%, moderate; 50% to 90%, substantial; and 75% to 100% considerable. Meta-analysis was to be calculated by using a random-effects model. Publication bias for the outcome of the histologically complete resection rate was detected by a funnel plot. The symmetry of the funnel plot was confirmed by the Egger test, with a $P$ value of .05. Subgroup analyses were performed to compare LNM between patients that met each indication of the expanded criteria versus the absolute criteria.

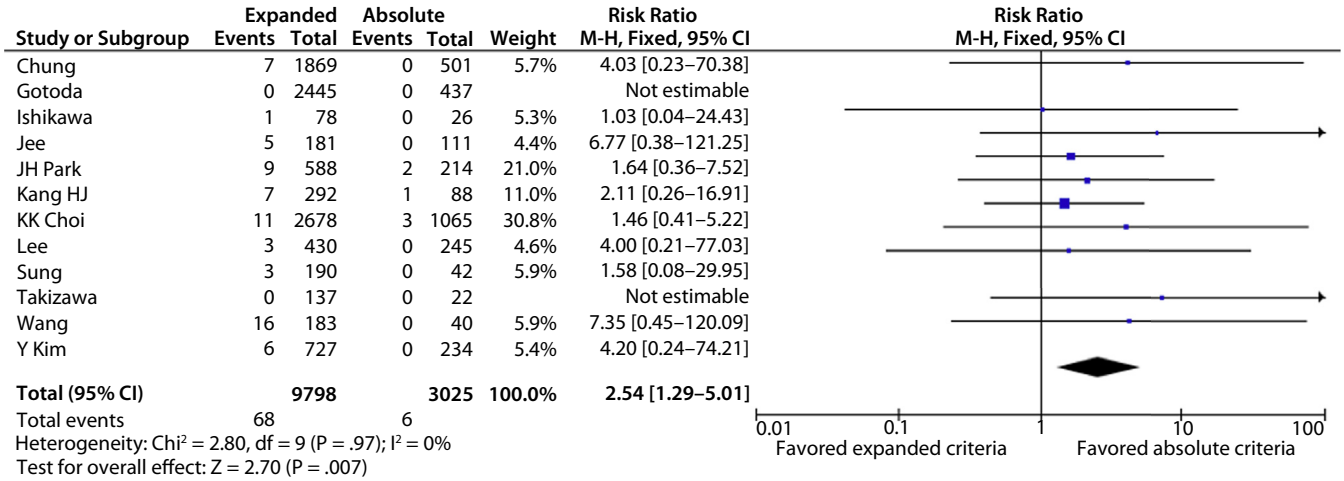


**Figure 2.** Forest plot of studies evaluating the incidence of lymph node metastasis in patients who met the absolute and expanded criteria. *M-H,* Mzantel-haenszel; *CI,* confidence interval.

## RESULTS

### Identification of studies and study characteristics

Our search yielded 1775 studies, of which 1705 were excluded after abstract or method and result sections were reviewed. A total of 70 full-text articles were reviewed. Fifty-eight articles were excluded because of missing data on lymph nodes. Twelve manuscripts, with a total of 9798 patients undergoing gastrectomy with LND were included in the final analysis. The search strategy is summarized in Figure 1. The 12 included studies (11 retrospectives and 1 prospective) originated from Japan, South Korea, and China (Table 2). There was no heterogeneity among the included studies, with an $I^2$ of 0% ($P = .97$).

### Study outcomes

In patients who underwent gastrectomy with LND, those who met the expanded criteria had a higher incidence of being diagnosed with LNM than patients who met the absolute criteria (68/9798 [0.7%] vs 6/3025 [0.2%]). The relative risk reduction when the absolute criteria were applied instead of the expanded criteria was 2.54 (1.29, 5.01) ($P = .007$) (Fig. 2).

In the subgroup analysis, the incidence of LNM in patients who met the first expanded criteria (mucosal differentiated type, no lymphatic-vessel invasion, irrespective of ulcer findings, and tumor size ≤3 cm) was slightly higher than the incidence of LNM in patients who met the absolute criteria (16/2814 [0.57%] vs 3/1960 [0.15%]). The relative risk reduction of applying the absolute criteria versus expanded criteria 1 was 3.01 (1.15, 7.85), which is statistically significant ($P = .02$) (Fig. 3).

The incidence of LNM in patients who met the second expanded criteria (mucosal differentiated type, no lymphatic-vessel invasion, without ulcer findings, and irrespective of tumor size) was similar to that of patients who met the absolute criteria (8/3004 [0.27%] vs 3/1959 [0.15%]). The relative risk reduction of applying the absolute criteria versus expanded criteria 2 was 1.69 (0.53, 5.35), which did not reach statistical significance ($P = .37$) (Fig. 4).

These results were in contrast to the third expanded criteria (undifferentiated type, no lymphatic-vessel invasion, without ulcer findings, and ≤3 cm in size). The LNM was considerably greater in patients who met the third expanded criteria in comparison to the absolute criteria (25/972 [2.6%] vs 2/1872 [0.11%]). The relative risk reduction of applying the absolute versus expanded criteria 3 was 6.79 (2.37, 19.48) ($P = .0004$) (Fig. 5). Likewise, the incidence of LNM in patients who met the expanded submucosal invasion criteria (<500 μm submucosal penetration, differentiated type, no lymphatic-vessel invasion, and ≤3 cm in size) was significantly higher than that of LNM in patients who met the absolute criteria (8/315 [2.5%] vs 3/850 [0.35%]). The relative risk reduction of applying the absolute criteria versus expanded criteria 1 was 6.30 (1.79, 22.16) ($P = .004$) (Figs. 6 and 7) (Table 3).

## DISCUSSION

To our knowledge, this is the first meta-analysis to compare the expanded criteria to the absolute criteria by using pathology findings from patients who had undergone a total gastrectomy with LND. We found that the rate of LNM in all patients who met the expanded criteria was slightly higher than that of patients who met the absolute criteria: 0.7% versus 0.2%. Relative risk reduction after applying the absolute criteria versus the expanded criteria was 2.54 (1.29, 5.01) ($P < .007$). Interestingly, the subgroup analysis of each of the criteria of the expanded indications, undifferentiated mucosal lesions and submucosal lesions, carries the highest risk of LNM when compared

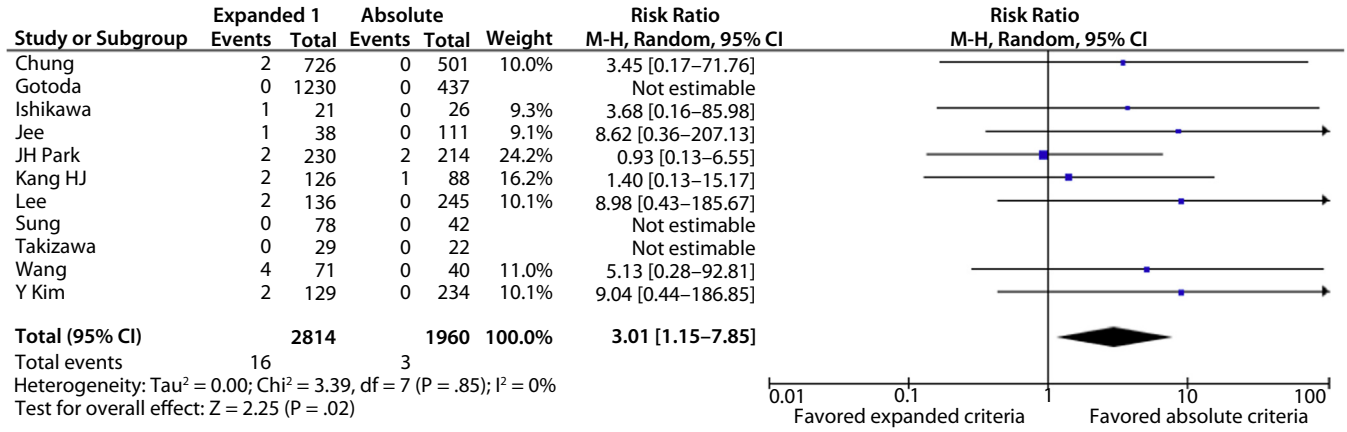


**Figure 3.** Forest plot of studies evaluating the incidence of lymph node metastasis in patients who met the absolute and the first expanded criteria. *M-H,* Mzantel-haenszel; *CI,* confidence interval.

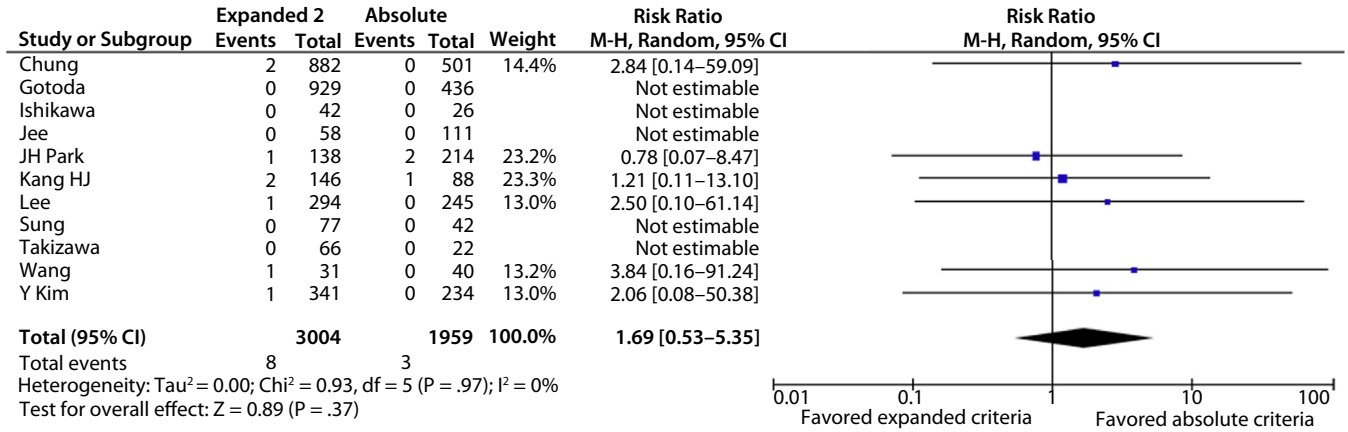


**Figure 4.** Forest plot of studies evaluating the incidence of lymph node metastasis in patients who met the absolute and the second expanded criteria. *M-H,* Mzantel-haenszel; *CI,* confidence interval.

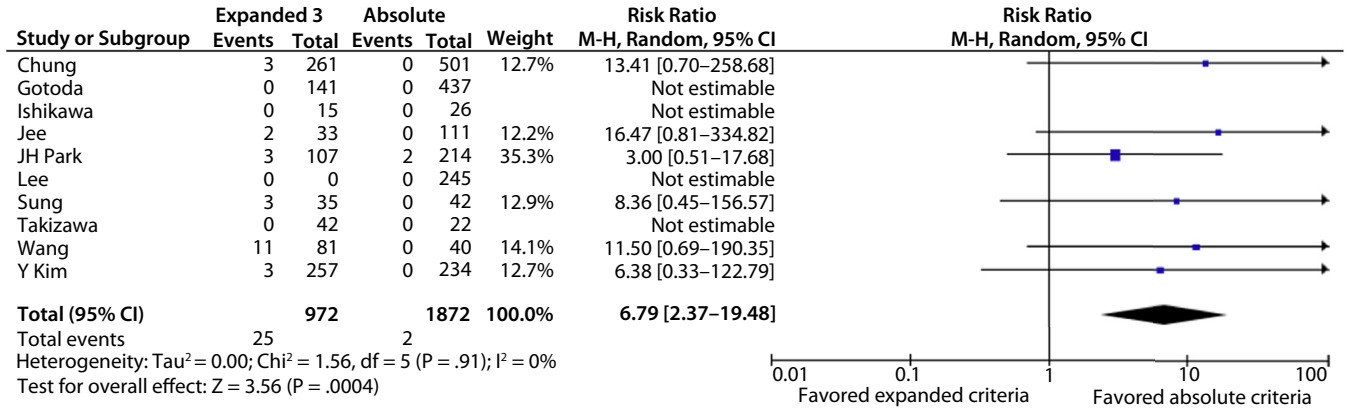


**Figure 5.** Forest plot of studies evaluating the incidence of lymph node metastasis in patients who met the absolute and the third expanded criteria. *M-H,* Mzantel-haenszel; *CI,* confidence interval.

with the absolute criteria. These were in contrast to the mucosal differentiated ulcerated lesions ≤3 cm and mucosal differentiated nonulcerated lesions irrespective of size, because these lesions had a minimal additional risk of LNM when compared with the absolute criteria. In fact, nonulcerated mucosal lesions of any size appear to have no statistically increased risk of LNM over nonulcerated lesions measuring ≤2 cm.

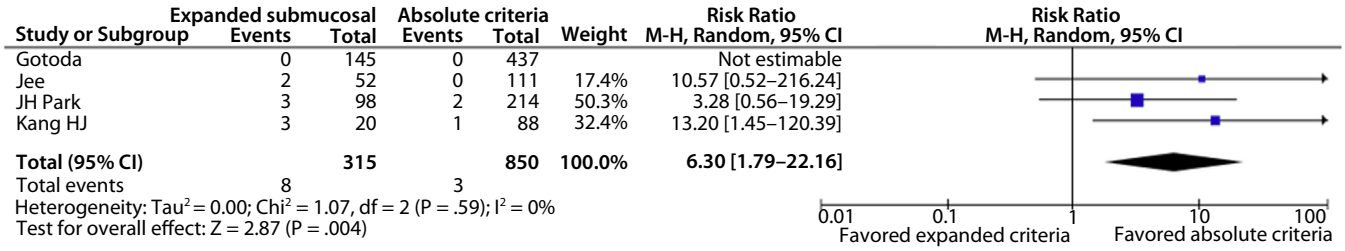


**Figure 6.** Forest plot of studies evaluating the incidence of lymph node metastasis in patients who met the absolute and the expanded criteria for submucosal lesions. *M-H,* Mzantel-haenszel; *CI,* confidence interval.

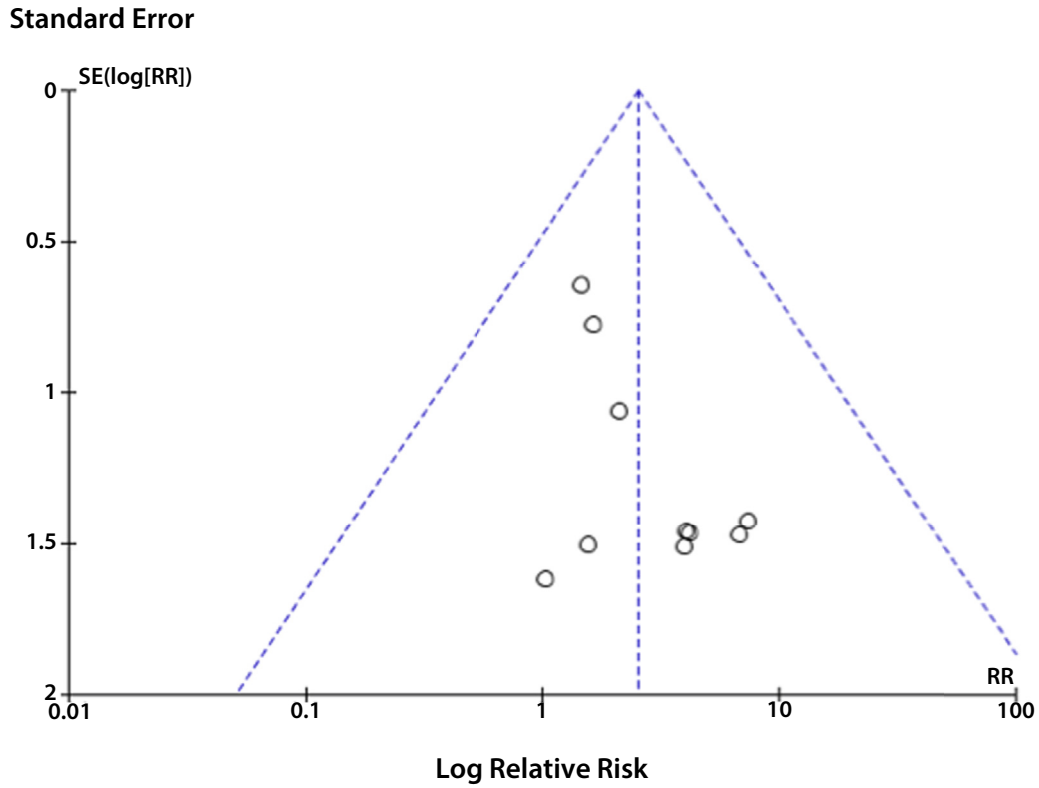


**Figure 7.** Funnel plot of standard error by log relative risk. *SE,* standard error; *RR,* reference range.

In concordance with our findings, a recently published study by the Japan Clinical Oncology Group (JCOG0607) provides confirmatory evidence that expanding the ESD criteria to include intestinal-type EGC measuring >2 cm and ulcer-positive differentiated lesions <3 cm is both safe and effective, arguing that ESD should now be the standard of care for these patients, rather than surgery. None of the patients who met curative resection criteria in this cohort had a recurrence of cancer, and the 5-year overall survival rate was 97%. The success rate for en bloc resection was 99.1%, but gastrectomy was required in 28% of the cohort because of failure to meet the curative resection criteria.[33]

ESD use under the expanded criteria has become widely accepted, with higher 5-year survival rates and lower adverse events rates as compared with surgery.[34] However, ESD is still classified as an investigational procedure under 2010 and 2015 Japanese guidelines for gastric cancer treatment. A significant challenge in applying the expanded criteria in practice is the imperfect diagnostic and staging accuracy of endoscopic optical diagnosis before resection.[35,36] Despite a detailed and thorough endoscopic examination, visually enhanced with chromic dyes and magnification, or with the addition of EUS, it is not always possible to predict accurately whether the lesion has invaded the submucosa or whether the lesion will be amenable to endoscopic resection under the expanded indications.[37-42] Ultimately, a careful pathology examination of an en bloc resection specimen is the only reliable way to determine whether endoscopic resection was likely to have been curative. According to the current guidelines, a noncurative resection after ESD generally should be managed with a radical gastrectomy

**TABLE 3. Summary of the incidence of LNM and RR reduction when the expanded indication was applied instead of the absolute indication**

| | Patients with LNM, no. (%) | Total no. of patients | RR | CI | *P* value |
|---|---|---|---|---|---|
| Absolute indication | 6 (0.2%) | 3025 | | | |
| Expanded indication | 68 (0.69%) | 9798 | 2.54 | 1.29-5.01 | .007 |
| Expanded indication-1 | 16 (0.57%) | 2814 | 3.01 | 1.15-7.85 | .02 |
| Expanded indication-2 | 8 (0.27%) | 3004 | 1.69 | 0.53-5.35 | .37 |
| Expanded indication-3 | 25 (2.6%) | 972 | 6.79 | 2.37-19.48 | .0004 |
| Expanded indication-SM | 8 (2.5%) | 315 | 6.30 | 1.79-22.16 | .004 |

*LMN,* Lymph node metastasis; *RR,* relative risk; *CI,* confidence interval; *SM,* submucosal.

with LND.[43] However, several reports indicate that LNM is found in only 5% to 10% of patients who undergo radical surgery, suggesting that >90% of the operations in these patients may be unnecessary.[44-49] Future research is fundamental in identifying the 10% of patients who do not meet the expanded indication and will benefit the most from radical surgery. A recent report by Hatta et al[49] demonstrated that ESD without additional treatment appears to be an acceptable option for patients at low risk for LNM, according to a novel scoring system.

Given the promising results of adjuvant chemotherapy[50,51] the National Comprehensive Cancer Network and the European Society of Medical Oncology[52] advise using adjuvant chemotherapy in patients with T1 (early gastric cancer) and node-positive disease. Whether neoadjuvant chemotherapy plus ESD is a beneficial strategy for patients with EGC and moderate to high risk of LNM is yet unknown.

The strength of our study involves the compilation of data from many different institutions, providing a large sample size. Furthermore, we performed a subgroup analysis for each of the criteria of the expanded indications and compared it with the absolute indications to determine which components are most strongly associated with a risk of LNM. Nevertheless, our study has several limitations. First, the generalizability of the results may be limited because all of the included studies were from Asian countries. Second, because of the small number of studies (mainly retrospective), we were not able to perform a reliable publication bias analysis. Third, there was heterogeneity between the included studies in the technique of LND because some used D1 dissection (perigastric lymph node stations 1-6) and others used D2 dissection (all D1 lymph nodes in addition to nodes along the left gastric, common/proper hepatic artery, celiac axis, and splenic artery). However, D2 dissection appears to offer no significant survival benefit over D1 LND.[35,36] Fourth, our search included publications in English only. Fifth, it is important to note that the preparation of gastrectomy specimens for pathology assessment is not the same as for ESD specimens. In Japan, gastrectomy specimens are sectioned every 1 cm, whereas ESD specimens are sectioned every 2 mm. Thus, ESD specimens may provide a more accurate assessment of histologic risk factors for LNM—such as lymphovascular invasion or deep submucosal invasion—which could be missed in larger gastrectomy specimens. Consequently, predictions regarding the risk of LNM that are based on data derived from gastrectomy specimens may lead to a falsely elevated estimation of the risk of LNM than would actually be present in patients undergoing a curative endoscopic resection for EGC, based on 2-mm pathology sections.

In summary, our meta-analysis of a large data set from surgically resected specimens suggests that the various components of the expanded criteria do not carry equal prognostic significance. Expanding the indications for endoscopic resection to include differentiated mucosal lesions regardless of size as well as ulcerated lesions $\leq$3 cm appears to add little or no additional risk for LMN, in comparison to the absolute criteria. However, with poorly differentiated or undifferentiated EGC and with differentiated EGC having slight submucosal invasion (<500 μm), we found that the risk of nodal metastasis was significantly increased as compared with the absolute criteria. Although the benefit of ESD likely still outweighs the risk of surgery in many patients meeting the expanded criteria,[53-56] the increased risk of LNM in patients with undifferentiated and submucosally invasive EGC should be considered when one compares the relative risks of subsequent gastrectomy and LND versus frequent surveillance with imaging studies in patients who have undergone ESD for early gastric cancer.

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