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REVIEW ARTICLE

The incidence of lymph node metastasis in submucosal early gastric cancer according to the expanded criteria: a systematic review

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Abstract

Background For successful endoscopic treatment of early gastric cancer (EGC), absolute criteria for a curative en bloc resection were initially established to include predominantly differentiated mucosal lesions ≤ 2 cm in diameter without ulceration. These indications were subsequently expanded to include larger, ulcerated, and predominantly undifferentiated mucosal lesions. In addition, differentiated type adenocarcinomas ≤ 3 cm with slight submucosal invasion of < 500 µm (pT1b1) are regarded as "curative" under the expanded criteria. However, data derived from studies of surgical specimens in patients with pT1b1 EGC have yielded varying rates of lymph node metastasis (LNM).

Method A systemic review was conducted using the pooled analysis to calculate the incidence of LNM in pT1b1 EGC, and to investigate whether using a cut-off value of < 300 µm would decrease the risk of LNM in patients with submucosal EGC.

Results Nineteen articles were included. 1507 patients with pT1b1 EGC met the expanded indications. The incidence of LNM was 3% (45 out of 1507 patients). In a subgroup analysis of three studies, there was no significant difference in the LNM between pT1b EGC < 300 µm and < 500 µm [3/121(2.5%) vs. 5/180 (2.8%)] (OR 0.89, 95% CI 0.22–3.54).

Conclusion Overall, expanding the indications for endoscopic resection of EGC to include lesions ≤ 3 cm T1b1 is associated with a potential risk of LNM of 3%. In countries outside of Japan, we found a slightly higher risk of LNM (4.0%). These estimates of LNM should be incorporated into decisions regarding further management of patients with EGC ≤ 3 cm who are found to have slight submucosal invasion (< 500 µm) in an ESD specimen. Standardization of specimen handling and histological evaluation is essential if the Japanese results of endoscopic treatment for EGC are to be successfully applied in other parts of the world.

Keywords Foregut · Esophagus and stomach · Surgery/interventions · Malignant gastric diseases

Worldwide, gastric cancer is the fifth most common cancer and the third leading cause of cancer death (10%) [1, 2]. Traditionally, radical surgical gastrectomy with the removal of at least 15 lymph nodes was the only potentially curative treatment for early gastric cancer (EGC) [3]. However, radical surgery is associated with significant morbidity and mortality, as well as a decrease in the quality of life [4–6]. Endoscopic submucosal dissection (ESD) offers an efficacious alternative to gastrectomy for certain EGCs, using a minimally invasive technique that is associated with lower morbidity and mortality than traditional surgery. Several studies have reported an incidence of lymph node metastasis (LNM) in the range of 5–10% among patients undergoing radical surgery for EGC, suggesting that over 90% of surgery could potentially be avoided if a curative endoscopic resection could be accurately predicted based on the histopathology of an ESD specimen [7–12].

The incidence of LNM in EGC is significantly higher when submucosal (SM) invasion is present, as compared to the incidence of LNM in gastric cancers that are limited to the mucosa (0–25% vs. 2–5% respectively) [13, 14]. In

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1997, Omote et al. reported that differentiated SM EGC with < 500 µm invasion had a 0% rate of LNM [15]. Three years later, Gotoda et al. reported 0% risk of LNM for lesions under 3 cm in diameter with slight SM invasion (< 500 µm) and no lymphovascular invasion, as compared to 18.6% for all ECG with SM invasion [16]. In 2016, the Japan Gastroenterological Endoscopy Society (JGES), in collaboration with the Japanese Gastric Cancer Association (JGCA) expanded the indications for ESD beyond the initial absolute criteria (Table 1) [17]. Following the introduction of these expanded (Ex) criteria for ER, many studies have re-evaluated the risk of LNM in EGC meeting the expanded criteria, with variable results [16, 18–35].

Our recent meta-analysis comparing the expanded indication to the absolute indication found that the risk of LNM was significantly higher for differentiated SM cancer with < 500 µm invasion (2.5%) compared to when the absolute criteria were met (0.2%), with a relative risk of 6.3 (CI 1.79–22.16) [36]. Even though the overall results of applying the expanded indication for SM EGC have been promising in terms of overall survival and disease-specific survival after ESD for EGC, our recent meta-analysis demonstrated that the highest risk of LNM was in gastrectomy specimens with limited SM invasion, meeting the expanded criteria. This raises the question of whether there may be a critical and safer cut-off value for tumor invasion of T1b lesions that would potentially have a lower risk of LNM than the current expanded criterion of 500 µm. Few reports have investigated the incidence of LNM using a cut-off of < 300 µm invasion in the SM [20, 21, 52]. It is unknown whether using a cut-off value of < 300 µm of SM invasion would potentially decrease the risk of LNM for SM EGC in patients undergoing endoscopic resection.

We performed a systemic review that included all relevant published reports of patients who underwent gastric resection with lymph node dissection for EGC who were found to have SM invasion (T1b), and who met the expanded criteria. Furthermore, we performed a meta-analysis to compare the incidence of LNM for SM cancers fitting the Ex criteria with < 300 µm versus 500 µm of SM invasion.

Materials and methods

Search strategy

We performed a systematic and comprehensive search of major reference databases (MEDLINE, EMBASE, CINAHL) for all studies that reported the incidence of LNM in EGC, according to the SM-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 (PRISMA) [37]. 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 December 10, 2017. Search terms included "EGC," ''LNM," "ESD," "SM invasion." Additionally, the reference lists of all of the articles included in the final analysis, as well as previous review papers, were hand-searched to ensure identification of all relevant studies.

Selections of studies

Inclusion and exclusion criteria

Studies (randomized, prospective observational, and retrospective observational) were eligible for inclusion in the meta-analysis if they met these following criteria: (1) patients included in the study were diagnosed with SM EGC by histopathology, and underwent gastrectomy with LND (without preceding ESD); (2) sufficient data were provided regarding the lesion's depth of invasion, size, ulceration, and degree of differentiation, in order to categorize the patients into absolute and expanded criteria; and (3) adequate details

Table 1 Curative resection criteria for endoscopic resection according to the absolute and the expanded indications [17]

Expanded indications	Absolute indications
En bloc resection, negative horizontal margin, negative vertical margin, no lymphovascular infiltration, and • Tumor size > 2 cm, histologically of differentiated type, pT1a, ulceration (−) • Tumor size ≤ 3 cm, histologically of differentiated type, pT1a, ulceration (+) • Tumor size ≤ 2 cm, histologically of undifferentiated type, pT1a, ulceration (−) • Tumor size ≤ 3 cm, histologically of differentiated type, pT1b1 (SM1, < 500 microns from the muscularis mucosa)	En bloc resection, Tumor size ≤ 2 cm, histologically of differentiated type, pT1a, negative horizontal margin, negative vertical margin, and no lymphovascular infiltration

were provided on the total number of patients and the percentage of patients diagnosed with LNM.

Data extraction and study quality assessment

Data from included studies were independently extracted by two 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, the presence of ulceration, and the degree of tumor differentiation. To avoid bias in the data extraction process, two investigators independently assessed study quality using the Newcastle–Ottawa scale for cohort studies. In the case of disagreement, the third investigator made a consensus decision (M.O.).

Statistical analysis

The data analysis was performed using Review Manager 5.3 software (Cochrane Collaboration). Statistical analysis for LNM between SM invasion < 300 μm and SM invasion < 500 μm was performed using the odds ratio (OR) as the summary statistic [with a corresponding 95% confidence interval (CI)].

Results

Identification of studies and study characteristics

Our search yielded 5499 studies, of which 5332 studies were excluded after review of the abstract, methods, and result sections. A total of 148 full-text articles were then reviewed; 148 articles were excluded due to missing data on LNM (Fig. 1).

Study outcomes

Studies characteristics

Among 19 studies that provided adequate information, we identified 1507 patients who met the expanded criteria for SM lesions. These comprised two prospective and 17 retrospective studies from Japan, Korea, Brazil, Taiwan, and China. Three studies reported outcome data based on the degree of SM invasion classified as < 300 μm and < 500 μm, along with parameters of expanded criteria, while 16 studies reported LNM for EGC with variable degrees of SM invasion extending beyond the expanded criteria. Ten studies reported data on macroscopic tumor type [15–24, 26–28, 43, 44], while eight studies reported data regarding Lauren classification of the tumor [16, 17, 20, 23, 24, 26, 43, 44].

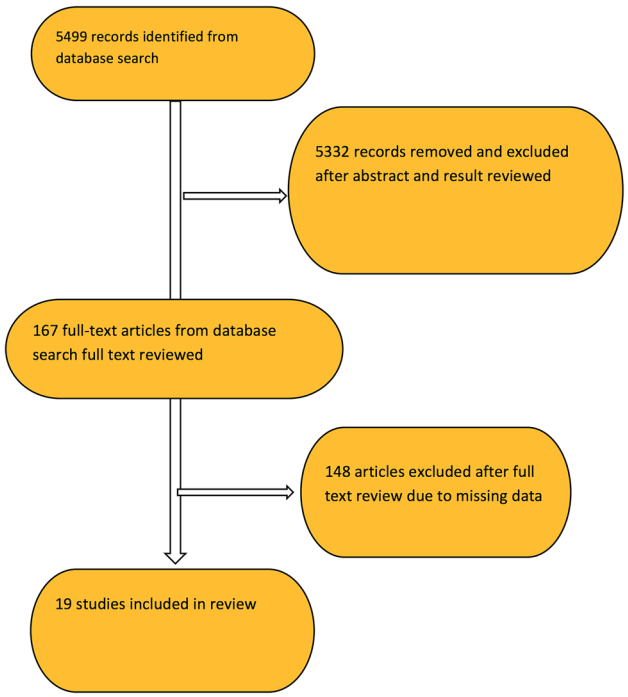

Fig. 1 PRISMA flowchart

Pooled data for all the SM lesions

The incidence of LNM varied from 0 to 15%. The aggregate incidence of LNM was 45 out of 1507 patients (3%) (Table 2; Fig. 2). In a subgroup analysis of three studies, there was no significant difference in the prevalence of LNM between SM EGC < 300 μm and < 500 μm [3/121(2.5%) vs. 5/180 (2.8%)] (OR 0.89, 95% CI 0.22–3.54) (Table 3; Fig. 3).

All studies from Japan, comprising 389 patients, reported a 0% incidence of LNM. Excluding the Japanese papers, the rate of LNM in the remaining countries was 45/1118 (4.0%).

Discussion

Our systemic review demonstrated that the rate of LNM for patients who met the curative resection criteria for SM lesions was (3%). This estimate of the risk of LNM in SM EGC differs from our previously published meta-analysis, which included only three studies that provided information on the absolute criteria, and on other estimates based on far fewer patients [36].

Curative treatment of EGC with ESD mandates the absence of LNM, which is crucial for long-term survival. Lesions removed *en bloc* with ESD that are found on histopathology to meet the curative criteria are generally considered cured; nodal metastasis is extremely uncommon in

Table 2 Details of included studies evaluating the incidence of lymph node metastasis according to the submucosa-expanded criteria

Author name	Year	Design	Country	Total EX-SM	EX-SM with LNM	%
Omote et al. [15]	1997	Retrospective	Japan	31	0	0
Gotoda et al. [16]	2000	Retrospective	Japan	145	0	0
Gotoda et al. [22]	2001	Retrospective	Japan	117	0	0
Nakahara et al. [23]	2004	Retrospective	Japan	7	0	0
Jee et al. [24]	2009	Prospective	Korea	52	2	4
Hanaoka et al. [25]	2009	Retrospective	Japan	41	0	0
Kang et al. [26]	2010	Retrospective	Korea	20	3	15
Kim et al. [27]	2012	Retrospective	Korea	49	2	4
Lee et al. [28]	2013	Retrospective	Korea	105	4	4
Tae et al. [21]	2015	Retrospective	Korea	46	1	2
Eom et al. [20]	2015	Retrospective	Korea	103	4	4
Park et al. [29]	2015	Retrospective	Korea	113	3	3
Choi et al. [34]	2015	Retrospective	Korea	80	5	6
Kim et al. [56]	2016	Prospective	Korea	281	7	2
Sekiguchi et al. [32]	2016	Retrospective	Japan	48	0	0
Feng et al. [33]	2016	Retrospective	China	137	9	7
Pereira et al. [18]	2017	Retrospective	Brazil	22	3	14
Fang et al. [19]	2015	Retrospective	Taiwan	8	1	13
Choi et al. [35]	2011	Retrospective	Korea	102	1	1
Total				1507	45	3

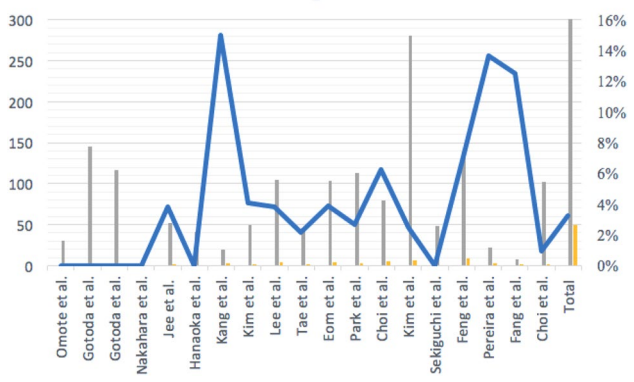

Fig. 2 Studies that investigated the incidence of LNM according to the expanded indication; left axis is the number of patients and right axis is the incidence of lymph node metastasis in each study

these EGCs. In contrast, lesions found to meet the expanded criteria are considered potentially curable with ESD, but the decision as to whether to recommend further surgery is dependent on the risk of nodal metastasis.

There are several risk factors associated with an increased rate of LNM. Among those, the lymphovascular invasion is a primary factor associated with increased risk of LNM. Previous studies have shown that LNM strongly correlates with the depth of tumor invasion. This was thought to be due to the presence of larger diameter lymphatic vessels in the deeper third of the lamina propria, and the progressive increase in diameter as these vessels go deeper into the submucosal layer, where the lymphatic network is richer [38–40].

In our review, we included studies that defined the depth of SM invasion by the actual length measured by the pathologist, and all studies included patients who underwent gastrectomy with LN dissection. Working with a complete resection specimen, it is possible for the pathologist

Table 3 Details of included studies evaluating the incidence of lymph node metastasis for submucosal gastric cancer with < 300 µm invasion

			Number pf patient with 300 m	LNM *n* (%)	Number pf patient with SM 500 m	LNM *n* (%)
Eom et al. [20]	2015	Korea	78	3 (3.8)	103	4 (3.9)
Tae et al. [21]	2015	Korea	27	0	46	1 (2.2)
Omote et al. [15]	1997	Japan	16	0	31	0

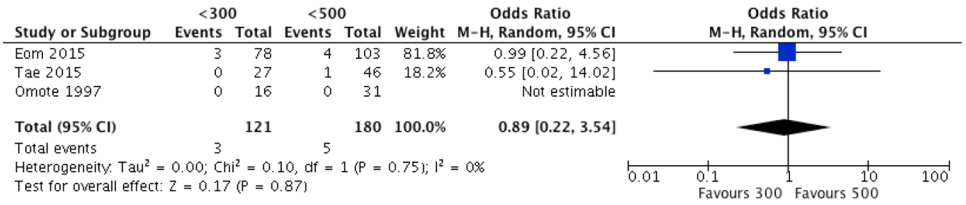

Fig. 3 Forest plot comparing the incidence of LNM in patients with SM EGC with < 300 μm invasion to patients with < 500 μm invasion

to measure the SM invasion and determine if it is limited to 500 μm or 300 μm. Moreover, they can categorize SM invasion into upper-third (sm1), middle-third (sm2), and lower-third (sm3) subgroups, which can only be applied to surgically resected specimens (but not ESD specimens, as the latter do not contain the full thickness of the submucosa).

The differences in the incidence of LNM among the studies included in this review were considerable. Several studies reported a 0% incidence of LNM, including all of the studies from Japan, whereas other studies reported an incidence as high as 15% [18, 19, 26]. We suspect that these differences are most likely explained by diverse tissue handling techniques in different countries, as the standards for sectioning and measuring SM invasion, and pathologist experience, differ significantly around the world [17, 41] (personal communication with several authors from Japan, Taiwan, Hong Kong, China, and Korea and with GI pathologists in the US). Japanese surgeons and pathologists usually section a specimen more meticulously (about 1 cm width) which may increase the probability of detecting deep SM invasion as compared to other countries, where the specimen is often sectioned in one line, which may underestimate the depth of tumor invasion. Another plausible explanation for variations in LNM incidence could involve different tumor characteristics in the countries studied, e.g., varying sites of cancer development within the stomach or differing histological types. However, the data necessary to address these possibilities were not provided in the included publications.

Kim et al. in their study compared two different measurement techniques to assess tumor penetration and assessed their significance on LNM. One method measured the depth of invasion from the lowest point of the muscularis mucosa to the deepest point of the tumor while the second method involved measuring the lowest point of an imaginary line in continuity with the adjacent muscularis mucosa to the deepest tumor penetration. They demonstrated that different methods of assessing tumor invasion led to variable results [42]. Standardization of the method to determine SM invasion is crucial if the JGCA-expanded criteria are to be applied successfully outside of Japan [46].

We hypothesized that less SM invasion would be associated with a lower risk of LNM. In our meta-analysis, we examined the effect of a different cut-off for SM cancer invasion (300 μm vs. 500 μm) to assess if it could potentially reduce the risk of LNM. Interestingly, limiting the expanded indication from 500 to 300 μm SM invasion did not decrease the incidence of LNM. These findings imply that any degree of SM invasion can be associated with nodal metastasis. Our results should be interpreted with caution due to the small sample size.

To date, there is no single modality that can reliably predict LNM in SM EGC. ESD utilization has become widely accepted for EGC in eastern Asia [43]. Despite advances in optical diagnosis, chromoendoscopy, and the use of endoscopic ultrasound, it is often difficult to accurately predict the depth of SM invasion prior to resection [44–51]. Ultimately, a detailed and accurate pathological examination of an *en bloc* resection specimen is the only reliable way to determine if ESD was curative. In the event that the ESD was non-curative, then a radical gastrectomy with lymph node dissection should be considered [52]. In this regard, it is important to clarify whether shallow SM cancer invasion should be included in the curative resection criteria. The largest multicenter study from Japan compared patients with non-curative ESD who either underwent gastrectomy with LND dissection or conservative follow-up. This study showed comparable 5-year disease-specific survival between the gastrectomy group and the follow-up group. Recurrence was observed in 1.3% in the surgery group compared to 3.1% in the follow-up group. However, when a relapse was discovered in the follow-up group, it was more likely to involve a distant lymph node or an organ metastasis (78.6%) than a regional lymph node (21.4%). This suggests a more aggressive pattern of recurrence and difficulties of salvage surgery in non-curative ESD and casts doubt on the value of frequent surveillance imaging studies in hopes of detecting an early, potentially resectable local relapse [53].

The major strength of this review is that it combines a large number of patients from diverse locations, allowing for a more accurate estimate of the incidence of LNM for SM EGC meeting the expanded indication. Furthermore, our review demonstrated a significant difference in the reported LNM between Japanese and non-Japanese centers. Our study had several limitations. Since all included patients with SM EGC met the expanded indication, other potential confounders could not be reliably extracted to perform subgroup analyses for lesions based on other features such as size, location, and degree of differentiation. Second, the small sample size of the included studies in the meta-analysis compared 500–300 μm SM invasion. Third,

the lack of standardization of tissue handling by pathologists could explain the heterogeneity between some of the studies. Finally, LNM rate could have been overestimated due to underestimated depth of tumor invasion in surgical pathologic evaluation. The preparation of gastrectomy specimens for pathology assessment is often not the same as it is 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 lymphovascular invasion that could necessitate further surgical management, whereas this information could be missed in larger gastrectomy specimens.

In summary, the risk of LNM for differentiated EGC ≤ 3 cm with SM invasion of < 500 μm was not negligible (3%). While the benefit of ESD likely still outweighs the risk of surgery in many patients meeting the expanded criteria for SM EGC [30, 34, 54, 55], the relatively higher risk of LNM in patients with SM EGC should be considered when weighing the risks and benefits of surgery. In countries outside of Japan, where a gastric ESD specimen may not be handled with the same methodology as in Japan, a slightly higher risk of LNM should be expected. Accordingly, better standardization of specimen handling and histological evaluation will be necessary if the Japanese criteria for curative ESD resection of EGC are to be successfully applied outside of Japan.

Compliance with ethical standards

Disclosures Dr. Ian S. Grimm is a consultant at Boston Scientific. Mohamed M. Abdelfatah, Mohamed Barakat, Mohamed O. Othman, and Noriya Uedo declare that they have no conflict of interest or financial ties to disclose.

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