

## Original Article



# Evaluation of Submucosal or Lymphovascular Invasion Detection Rates in Early Gastric Cancer Based on Pathology Section Interval

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## ABSTRACT

**Purpose:** The guidelines for pathological evaluation of early gastric cancer (EGC) recommend wider section intervals for surgical specimens (5–7 mm) than those for endoscopically resected specimens (2–3 mm). Studies in surgically resected EGC specimens showed not negligible lymph node metastasis risks in EGCs meeting the expanded criteria for endoscopic submucosal dissection (ESD).

**Materials and Methods:** This retrospective study included 401 EGC lesions with an endoscopic size of  $\leq 30$  mm detected in 386 patients. Pathological specimens obtained by ESD or surgery were cut into 2-mm section intervals for reference. Submucosal or lymphovascular invasion (LVI) was evaluated arbitrarily in 4- or 6-mm section intervals. McNemar's tests compared the differences between submucosal and LVI.

**Results:** Submucosal invasion was detected in 29.2% (117/401) and LVI in 9.5% (38/401) at 2-mm interval. The submucosal invasion detection rates in 4-mm intervals decreased to 88.0% or 90.6% (both  $P < 0.001$ ), while the LVI detection rates decreased to 86.8% or 57.9% ( $P = 0.025$  and  $P < 0.001$ , respectively). In 6-mm intervals, the submucosal and LVI detection rates decreased further to 72.7–80.3% ( $P < 0.001$  for all three sets) and 55.3–63.2% ( $P < 0.001$  for all three sets), respectively. Among 150 out-of-indication cases at 2-mm interval, 4–10 (2.7%–6.7%) at 4-mm intervals, and 10–17 (6.7%–11.3%) at 6-mm intervals were misclassified as lesions meeting the curative resection criteria due to the underestimation of submucosal or LVI.

**Conclusions:** After ESD, the 2-mm wide section interval was suitable for the pathological evaluation of focal submucosal or LVI. Thus, if an EGC lesion meets the expanded criteria for the ESD specimen pathological evaluation, it could be safely followed up.

**Keywords:** Stomach neoplasm; Endoscopic submucosal dissection; Submucosal invasion; Lymphovascular invasion

## INTRODUCTION

Endoscopic resection is a standard treatment for early gastric cancer (EGC), which has minimal risk of lymph node metastasis [1–3]. Current endoscopic resection criteria for EGC

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#### Author Contributions

Conceptualization: C.I.J.; Data curation: K.M.C., L.J.Y., K.C.G., E.B.W., Y.H.M., R.K.W., K.Y.W., C.I.J.; Formal analysis: K.Y.I., K.M.C., C.I.J.; Writing - original draft: K.Y.I., C.I.J.; Writing - review & editing: K.Y.I., K.M.C., C.J.E., L.J.Y., K.C.G., E.B.W., Y.H.M., R.K.W., K.Y.W., C.I.J.

#### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

are based on a previous study that evaluated the incidence of lymph node metastasis in a large number of surgically resected EGC specimens [4]. Endoscopic resection criteria were proposed for EGC lesions with no lymph node metastasis [4]. However, several studies suggested that lymph node metastasis risks were not negligible, especially in EGC lesions meeting the expanded criteria [5-7]. A meta-analysis of 12 studies including patients with EGC who underwent surgery showed that lymph node metastasis risk was significantly higher in lesions meeting the expanded criteria (relative risk, 2.54; 95% confidence interval, 1.29–5.01) than those in the absolute criteria [8]. In addition, extra-gastric recurrences have been reported after curative endoscopic resection of EGCs, especially in cases with minute submucosal invasion [9,10] or missed lymphovascular invasion (LVI) in the resected specimen [11].

Submucosal and LVI are significant risk factors associated with lymph node metastasis in EGC [4,12]. Recommended guidelines for section intervals in pathological evaluations were 5- to 7-mm intervals for surgical specimens and 2- to 3-mm intervals for endoscopic resection specimens [3,13,14]. However, the submucosal or LVI could be detected in a very focal area of the resected specimens [11,15,16]. Thus, the focal submucosal or LVI might be missed in surgically resected specimens because of wider section intervals.

In the present study, we aimed to evaluate whether the submucosal and LVI detection rates are affected by the width of the section intervals used in the pathological examination.

## MATERIALS AND METHODS

### Patients

This retrospective study included 414 patients with 429 EGC lesions with an estimated size of 30 mm or less as determined by diagnostic endoscopy. The EGC lesions were treated by endoscopic submucosal dissection (ESD) or surgical resection at the National Cancer Center, Korea, from April 2012 to December 2013. Patients with noninvasive carcinoma and those with tumor invasion in the proper muscle on final pathological evaluations were excluded. The baseline demographic data and tumor characteristics were obtained from the medical records of patients.

The Institutional Review Board of the National Cancer Center, Korea (IRB number: NCC2016-0060), approved this study, and the requirement for informed consent waived.

### EGC Treatment

ESD was performed in patients with EGC who clinically met the clinical absolute indication criteria for endoscopic resection following the gastric cancer treatment guidelines [1,2]. EGC cases that met the clinically expanded indication, the choice of ESD vs. surgery were determined after a thorough review of the cases in multidisciplinary conferences. The ESD procedure details were as described earlier [17]. The surgical treatment included laparoscopic or robot-assisted radical gastrectomy with lymph node dissection. The extent of lymph node dissection was D1+ or more following the gastric cancer treatment guidelines [2].

### Pathological evaluations

The resected EGC specimens from ESD and surgery were stretched and pinned on a flat board and fixed in 10% buffered formalin solution. The samples were sliced serially at 2-mm

Submucosal and Lymphovascular Invasion according to Section Interval

intervals parallel to the reference cutting line in the center of the specimen. Each 2-mm interval sections were numbered serially from the proximal to the distal end [13].

The pathological findings of the presence of submucosal and LVI in the 2-mm sections served as the reference (Fig. 1A). The 4- and 6-mm interval sections were used to evaluate detection rates in wider interval sections. The pathological findings in the 4-mm interval sections were evaluated in even (2n) or odd (2n+1) numbered sets (Fig. 1B). Evaluation of the 6-mm interval sections was performed in three sets (3n, 3n+1, or 3n+2 numbered section sets) (Fig. 1C). The results were evaluated by a pathologist specializing in gastric cancer (MC Kook). Tumor histologic types were classified following the World Health Organization classification system [18] and categorized into differentiated and undifferentiated histologic types following the gastric cancer treatment guidelines [2].

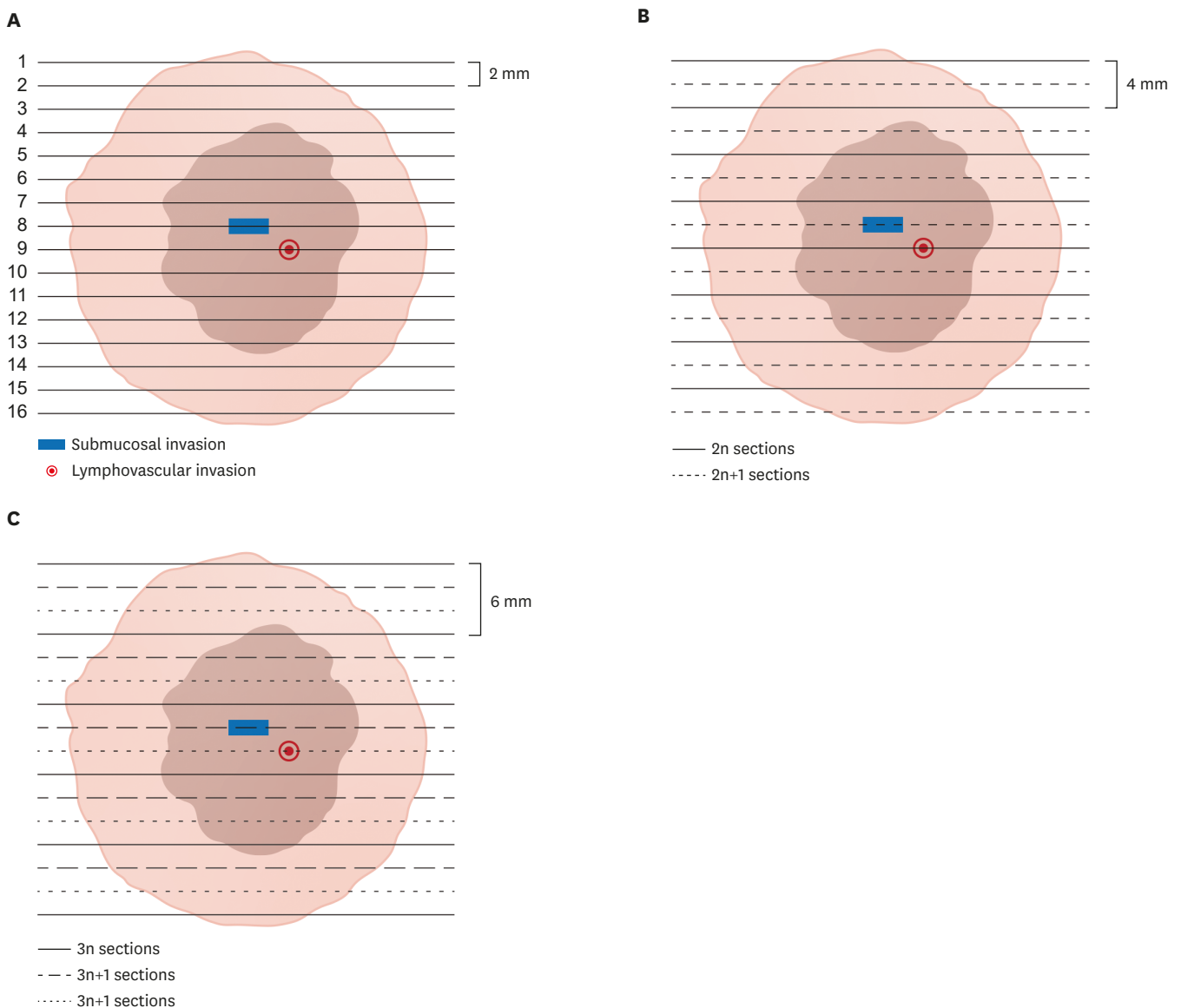


Fig. 1. Section cut and reconstruction of a resected specimen. Light brown color indicates the resected specimen, while dark brown color indicates the tumor area. (A) Reference 2-mm section interval. (B) Two 4-mm section interval sets. (C) Three 6-mm section interval sets.

### Study outcomes

Primary outcome variables were differences in submucosal and LVI detection rates in the wider interval (4- and 6-mm) compared to 2-mm interval sections. Secondary outcomes were changes in final pathological curability criteria for endoscopic resection using wider intervals.

The absolute criteria were as follows: mucosal tumors, differentiated histologic type, and tumor sizes of  $\leq 2$ -cm without ulceration, and LVI. The expanded criteria were as follows: 1) mucosal tumors, differentiated histologic type, and tumor sizes of  $> 2$ -cm without ulceration (criteria I); 2) mucosal tumors, differentiated histologic type, and tumor sizes of  $\leq 3$ -cm with ulceration (criteria II); 3) mucosal tumors, undifferentiated histologic type, and tumor sizes of  $\leq 2$ -cm without ulceration (criteria III); or 4) tumors with minute submucosal invasion ( $< 500$   $\mu\text{m}$  from the muscularis mucosae), differentiated histologic type, and tumor sizes of  $\leq 3$ -cm (criteria IV). All tumors meeting the expanded criteria should have no LVI [1,2]. EGC lesions that did not meet the expanded criteria were defined as out-of-indication cases.

### Statistical analysis

Continuous variables are described as median with interquartile range (IQR) or mean with standard deviation, while categorical variables as percentages. The McNemar's tests were used to compare differences in submucosal and LVI between 2-mm and wider interval sections (4- or 6-mm intervals). Changes in curability criteria for endoscopic resection according to section intervals, were compared using the McNemar-Bowker's symmetry tests [19]. P-values of  $< 0.05$  were considered significant. All data were analyzed using STATA 13.1 (StataCorp, College Station, TX, USA).

## RESULTS

### Baseline characteristics

We excluded 14 muscle-invasive and 14 non-invasive carcinoma cases as diagnosed by pathological evaluation of the 429 EGC lesions from 414 patients. A total of 401 EGC lesions from 386 patients who underwent ESD or surgery were included in our study. Among them, 280 EGC lesions from 265 patients, and 121 EGC lesions from 121 patients were treated by ESD and surgical resection, respectively (Fig. 2).

The baseline patient data and tumor characteristics evaluated in 2-mm interval sections are presented in Table 1. The median age of the included patients was 63 years (IQR, 54–72 years). In the reference 2-mm interval sections, we detected the submucosal invasion in 117 cases (29.2%), while the LVI was detected in 38 cases (9.5%). Among the 117 submucosal invasion cases, 24 cases (20.5%) were identified in one section, 23 cases (19.7%) in two sections, and 70 cases (59.8%) in three or more sections. Of the 38 LVI cases, 18 cases (47.4%) were detected in one section, 7 cases (18.4%) in two sections, and 13 cases (34.2%) in three or more sections.

### Detection rates of submucosal invasion based on section intervals

Compared to the 100% detection rates of the 117 submucosal invasive EGC cases in the reference 2-mm interval section, the detection rates of submucosal invasion in the 4-mm interval sections decreased significantly to 88.0% in even-numbered (2n) sections, and 90.6% in odd-numbered (2n+1) sections (both  $P < 0.001$  by McNemar's test, each compared to the reference 2-mm interval). The submucosal invasion was detected in 78.6% (92/117) of cases, consistently in both sets of the 4-mm interval sections.

Submucosal and Lymphovascular Invasion according to Section Interval

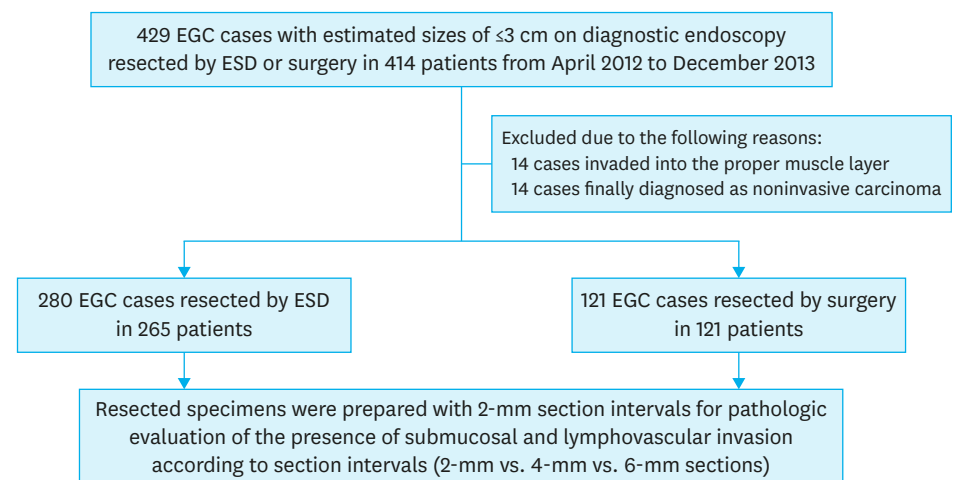
**Table 1.** Patient and tumor characteristics

Characteristics	Total	Treatment	
		ESD	Surgery
<b>Patient characteristics</b>			
No. of patients	386	265	121
Age (yr)	63 (54–72)	66 (58–74)	55 (50–65)
Sex			
Female	122 (31.6)	72 (27.2)	50 (41.3)
Male	264 (68.4)	193 (72.8)	71 (58.7)
No. of EGC lesion			
One	372 (96.4)	251 (94.7)	121 (100)
Two	13 (3.4)	13 (4.9)	0 (0)
Three	1 (0.3)	1 (0.4)	0 (0)
<b>Tumor characteristics</b>			
No. of tumors	401	280	121
Tumor location			
Upper third	23 (5.7)	13 (4.6)	10 (8.3)
Middle third	165 (41.2)	91 (32.5)	74 (61.2)
Lower third	213 (53.1)	176 (62.9)	37 (30.6)
Tumor size (cm)	1.96±1.09	1.82±1.07	2.28±1.07
Tumor histology			
Differentiated type	315 (78.6)	274 (97.9)	40 (33.1)
Undifferentiated type	86 (21.5)	6 (2.1)	81 (66.9)
Ulcer finding			
Absence	241 (60.1)	182 (65.0)	59 (48.8)
Presence	160 (39.9)	98 (35.0)	62 (51.2)
Tumor depth			
Mucosa	284 (70.8)	215 (76.8)	69 (57.0)
Submucosa	117 (29.2)	65 (23.2)	52 (43.0)
Submucosa <500 μm	47 (11.7)	30 (10.7)	17 (14.1)
Submucosa ≥500 μm	70 (17.5)	35 (12.5)	35 (28.9)
LVI			
Absence	363 (90.5)	260 (92.9)	103 (85.1)
Presence	38 (9.5)	20 (7.1)	18 (14.9)
Lymph node metastasis*			
Absence	394 (98.3)	-	114 (94.2)
Presence	7 (1.7)	-	7 (5.8)

Pathology evaluation findings from 2-mm interval sections were presented. Values are presented as number of patients (%), median (interquartile range), or mean±standard deviation.

EGC = early gastric cancer; ESD = endoscopic submucosal dissection; LVI = lymphovascular invasion.

\*Status of lymph node metastasis was evaluated only in patients with EGC who underwent resection.



**Fig. 2.** Study flow.

EGC = early gastric cancer; ESD = endoscopic submucosal dissection.

**Table 2.** Submucosal and LVI detection rates in 401 EGC lesions according to section intervals of resected specimen

Variables	Submucosal invasion		LVI	
	No. (%)	P*	No (%)	P*
Reference 2-mm interval section	117 (100.0)	-	38 (100.0)	-
4-mm interval section				
2n	103 (88.0)	0.0002	33 (86.8)	0.0253
2n+1	106 (90.6)	0.0009	22 (57.9)	0.0001
Detected in all sections	92 (78.6)	-	17 (44.7)	-
6-mm interval section				
3n	90 (76.9)	<0.0001	21 (55.3)	<0.0001
3n+1	94 (80.3)	<0.0001	22 (57.9)	0.0001
3n+2	85 (72.7)	<0.0001	24 (63.2)	0.0002
Detected in all sections	61 (52.1)	-	9 (23.7)	-

LVI = lymphovascular invasion; EGC = early gastric cancer

\*P-values calculated using McNemar's test compared to results from the reference 2-mm interval sections.

In the 6-mm sections, the detection rates decreased further to 76.9% in 3n-, 80.3% in 3n+1, and 72.7% in 3n+2 sections (all three  $P < 0.001$  by McNemar's test, as compared with the reference 2-mm interval). In 52.1% (61/117) of cases, the submucosal invasion was detected consistently in all three sets of the 6-mm interval sections (**Table 2**).

### Detection rates of LVI according to section intervals

LVI was present in 38 EGC cases (100%) in the reference 2-mm interval sections. In the 4-mm sections, the detection rates were 86.8% in 2n ( $P = 0.025$  by McNemar's test), and 57.9% in 2n+1 sections ( $P < 0.001$  by McNemar's test). LVI was detected consistently in only 44.7% (17/38) of cases in both 4-mm interval sets (**Table 2**).

In the 6-mm sections, the detection rates decreased further to 55.3%, 57.9%, and 63.2% in 3n, 3n+1, and 3n+2 sections, respectively, (all  $P < 0.001$  by McNemar's test, each compared to the reference sections). LVI was detected consistently only in 23.7% (9/38) of cases in all three 6-mm interval sets (**Table 2**).

### Curability criteria distribution following the section interval width

In the reference 2-mm interval sections, 102 (25.4%) EGC cases met the absolute criteria, while 149 (37.2%) met the expanded criteria. The remaining 150 cases (37.4%) were classified as out-of-indication cases (**Supplementary Fig. 1A**).

In the 4-mm interval sections, misclassification of the curability criteria was noted for seven cases (1.7%, 7/401 cases) in even-numbered (2n) sections. Of these, three cases were misclassified from expanded criteria to absolute criteria due to missed detection of submucosal invasion (**Table 3**). Due to the missed detection of submucosal or LVI, four (2.7%, 4/150) out-of-indication cases were misclassified as curative resection cases. Changes in the curability criteria were not significant in even-numbered sections compared to the reference interval ( $P = 0.101$  by McNemar-Bowker's symmetry test). In the odd-numbered (2n+1) sections, curability criteria were misclassified in 13 cases (3.2%, 13/401 cases). Among the 150 out-of-indication cases in the 2-mm interval sections, ten (6.7%) were misclassified as curative resection cases due to the missed detection of submucosal (2 cases) or LVI (8 cases) (**Table 3**). Compared to the 2-mm interval sections, the curability criteria distributions changed significantly ( $P = 0.043$  by McNemar-Bowker's symmetry test) (**Supplementary Fig. 1A**).

In the 6-mm interval sections, the curability criteria for 16 cases (4.0%, 16/401 cases) were misclassified in 3n, 14 (3.5%, 14/401 cases) in 3n+1, and 19 (4.7%, 19/401 cases) in 3n+2

## Submucosal and Lymphovascular Invasion according to Section Interval

**Table 3.** Misclassification in wide interval sections compared the 2-mm interval sections for endoscopic resection criteria

Variables	Section intervals				
	4-mm interval		6-mm interval		
	2n	2n+1	3n	3n+1	3n+2
Expanded criteria in 2-mm interval sections (n=149)					
Change from expanded to absolute criteria	3/149 (2.0)	3/149 (2.0)	6/149 (4.0)	4/149 (2.7)	2/149 (1.3)
Missed submucosal invasion	3	3	6	4	2
Out-of-indication cases in 2-mm interval sections (n=150)					
Change from out-of-indication to absolute criteria	1/150 (0.7)	2/150 (1.3)	4/150 (2.7)	2/150 (1.3)	5/150 (3.3)
Missed submucosal invasion	1	1	3	1	4
Missed LVI	0	1	1	1	1
Change from out-of-indication to expanded criteria	3/150 (2.0)	8/150 (5.3)	6/150 (4.0)	8/150 (5.3)	12/150 (8.0)
Missed submucosal invasion	1	1	3	2	7
Missed LVI	2	7	3	6	5

LVI = lymphovascular invasion.

sections compared to the reference 2-mm interval sections (**Supplementary Fig. 1B**). The distribution of curability criteria changed significantly in all three section numbers in the 6-mm interval ( $P=0.003$  for 3n,  $P=0.008$  for 3n+1, and  $P=0.002$  for 3n+2 sections by McNemar-Bowker's symmetry test). Compared to the 150 out-of-indication cases at 2-mm interval, ten (6.7%, 10/150) to 17 (11.3%, 17/150) cases were misclassified from non-curative resection to curative resection cases in the 6-mm intervals due to the undetected submucosal invasion or LVI (**Table 3**).

### Misclassification of endoscopic resection criteria in cases with lymph node metastasis

Lymph node metastasis was detected in seven (1.7%) of 121 surgically treated patients. In the reference 2-mm interval sections, all seven patients had out-of-indication tumors, and one patient misclassified as meeting the expanded criteria in both 4- and 6-mm interval sections due to missed LVI.

## DISCUSSION

The current guidelines for the pathologic evaluation of EGC lesions recommend different section intervals: 2–3-mm intervals for endoscopic resection, and 5–7-mm intervals for surgical specimens [3,13,14]. We speculated that wide resection interval in surgical specimens might affect the detection of lymph node metastasis risk factors. In this study, pathological evaluation of endoscopically or surgically resected 401 EGC lesions was performed using 2-mm interval sections as a reference following the specimen handling guidelines for endoscopic resection. For wide interval sections, we arbitrarily chose 4- and 6-mm sections, and the risk of missed submucosal and LVI detection was high. Thus, the under-detection of submucosal and LVI in wider interval sections might result in the misclassification of curability criteria for endoscopic resection of EGC.

LVI is the most important risk factor for lymph node metastasis in patients with EGC [4,12,20]. The rate of lymph node metastasis of 25.7%–32.1% observed in patients exhibiting LVI was much higher compared to those without LVI (1.5%–2.3%) [4,20,21]. The LVI might be very focal, and the distribution of lymphatic vessels varies according to tumor depth and histologic types [16]. LVI prediction methods before endoscopic resection are not yet available, and detection of LVI could be missed even after pathologic evaluation of endoscopically resected specimens at 2-mm interval [11]. We found that 47.4% (18 of the

38 cases) of LVI cases were focal, and detected only in one section of the reference 2-mm interval. Thus, LVI detection rates decreased significantly in wide interval sections, and the detection rates in all section sets were consistently lower at 4-mm (44.7%, 17 of the 38 cases) and 6-mm intervals (23.7%, 9 of the 38 cases). Wider interval sections recommended for surgical specimens method could result in frequent under-detection of LVI. Due to the under-detection of LVI in wider interval sections, misclassification of curability criteria might occur in patients undergoing ESD.

Submucosal invasion is another important risk factor for lymph node metastasis in patients with EGC [4,12]. Similar to the LVI, the very focal submucosal invasion might be detected frequently in EGC lesions. In a study investigating lymph node metastasis risk in patients with minute submucosal EGC (submucosal invasion depth  $\leq 500$   $\mu\text{m}$ ), the width of the submucosal invasion was 1-mm or less in 188 of the 278 patients (67.6%) [15]. In our study, 20.5% (24/117) of submucosal invasion cases were detected only in one of the reference 2-mm interval sections. The submucosal invasion was detected consistently in 92 of the 117 (78.6%) cases in both 4-mm interval section sets and 61 of the 117 (52.1%) cases in all three 6-mm interval section sets. These findings suggest the possibility that the curability criteria after endoscopic resection of EGC cases could be misclassified from non-curative to curative resection if the section intervals of EGC specimens are wider than those recommended for endoscopically resected specimens. Further studies are needed to determine whether the deepest portion of submucosal invasion (especially deeper than 500  $\mu\text{m}$ ) is detectable in wider (4- and 6-mm) interval sections.

Studies from countries outside of Japan have reported that lymph node metastasis rates were not negligible, especially in patients with EGC who met the expanded criteria [5-7,22]. Chung et al. [5] found that lymph node metastasis rates were 0.23%–1.15% in patients with mucosal EGC meeting the expanded criteria. Kim et al. [6] also reported the incidence rates for lymph node metastasis of 0.29%–1.55% in patients with mucosal EGC who met the expanded criteria. Western studies reported higher lymph node metastasis rates in patients with EGC who met the expanded criteria, and the reported lymph node metastases were 7.5% and 2.9% in the US and Brazilian studies, respectively [7,22]. A recent systematic review reported a higher lymph node metastasis rate (4.0%) in minute submucosal lesions meeting the expanded criteria in studies conducted outside of Japan [23]. They emphasized the standardization of specimen processing and histological evaluation so that the Japanese study results could apply to other countries [23]. Our results indicated that the differences in pathology specimen processing could explain the incidence rate discrepancies in lymph node metastasis between studies.

Our study results showed that the risk of misclassification of the final pathology curability criteria for endoscopic resection of EGC was higher in wider interval sections compared to the 2-mm interval sections. Nearly 6.7% of non-curative cases and 11.3% of non-curative cases identified from 4- and 6-mm interval sections, respectively, were misclassified as meeting the final curability criteria and thus were indicated for curative resection. Moreover, among the seven lymph node metastasis cases classified as out-of-indication EGCs based on 2-mm interval sections, one was erroneously classified as a lesion meeting the expanded criteria in wider intervals. Thus, the current criteria for the endoscopic resection should be updated to using pathology data obtained from 2-mm interval surgical specimen sections for evaluating the risk factors for lymph node metastasis. However, surgically resected specimen processing at 2-mm interval sections is not cost-effective because lymph node metastasis is assessed in all patients.



Currently, endoscopic resection for EGC meeting the expanded criteria is performed routinely in selected patients [1-3]. Long-term outcomes after curative resection of endoscopic resection in patients meeting the expanded criteria were as favorable as in those who met the absolute criteria [24-26]. The long-term overall survival rates of patients who underwent endoscopic resection were not different compared to those who underwent surgery for EGC meeting the curative resection criteria reported in studies performed using the propensity score matching [27-30]. Thus, if a lesion met the absolute or expanded criteria after pathological evaluation of a 2-mm interval ESD specimen section, it should be considered as a curative resection case since a thorough risk factor evaluation was undertaken.

There are several limitations to our study. First, selection bias might exist due to the inclusion of lesions with an endoscopic size of 3-cm or less. Second, we included patients who underwent endoscopic resection, and lymph node metastasis was evaluated only in patients who underwent surgery. Third, we could not assess long-term clinical outcomes, including overall mortality and cancer recurrence based on changes in section intervals due to this being a cross-sectional study. Fourth, the underestimation of lymphovascular or submucosal invasion in 4- and 6-mm interval sections might not affect decision making for additional chemotherapy of patients who underwent surgery since lymph node metastasis in the resected lymph nodes was assessed. Finally, the pathological evaluation of all study specimen was conducted with 2-mm interval sections. Hence, the detection rates for the lymphovascular and submucosal invasion could not be determined using a 3-mm interval sections as recommended by the ESD specimen handling guidelines [3,14].

In conclusion, wide interval sections recommended for surgical specimen handling might underestimate lymphovascular and submucosal invasion. This finding might explain the increased risk of lymph node metastasis in EGC lesions meeting the expanded criteria reported in the literature, which investigated lymph node metastasis risk using surgically resected specimens. Thus, if an EGC lesion meets expanded criteria after the pathological evaluation of ESD specimens, the lesion can be safely followed up.

## SUPPLEMENTARY MATERIAL

### Supplementary Fig. 1

Comparison of the curability criteria distribution according to the section intervals. (A) Curability criteria between 2-mm section interval and 4-mm section interval. (B) Curability criteria between 2-mm section interval and 6-mm section interval.

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