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ORIGINAL ARTICLE

Evaluation of the widths of the mucosal strips in pathological examination of specimens of endoscopic submucosal dissection for early gastric cancer

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Abstract

Background Endoscopic submucosal dissection (ESD) is the standard treatment for early gastric cancer in Japan. Pathological evaluation of ESD specimens is considered essential to determine if additional gastrectomy is necessary. Usually, specimens resected by ESD are sliced into 2–3 mm wide sections, and each section is examined for depth of tumor and lymphovascular invasion. Nevertheless, in most cases of additional gastrectomy, lymph node metastasis is not present. Given that there are few-studies on how clinical-decisions based on the pathologic-evaluation-method, in particular the specimen cut-width, influence patient outcomes, we retrospectively evaluated whether reducing the number of cuts to one-half or one-third would result in underestimation of the real need for additional surgery. The effect of the actual cut-width on recommended treatment (referral to operation) and patient-outcomes was also assessed.

Methods Pathological records of 498 lesions from 439 patients were reviewed and re-evaluated. All pathological descriptions are based on the gastric cancer classification system of the Japanese Gastric Cancer Association, 15th edition.

Results In 5.8% and 8.5% of the total specimens, underdiagnosis of tumor-depth and lymphovascular invasion occurred when the number of sections was reduced to one-half and one-third, respectively. Significantly more submucosal invasions were found in the group in which the cut-with was between 3 and 4 mm than in the group in which the cut width was less than 3 mm.

Conclusion Evaluation of the appropriate cut-width is important and should be discussed from the standpoint of labor costs and lost opportunities to search for molecular markers in ESD materials.

Keywords Pathology practice · Early gastric cancer · Endoscopic mucosal resection

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Introduction

In Japan, endoscopic submucosal dissection (ESD) is the standard treatment for early gastric cancer (EGC). The absolute indications for ESD are clinically diagnosed intramucosal carcinoma and differentiated adenocarcinoma of (i) any size, without ulceration or (ii) 3 cm or less in size, with ulceration [1, 2]. In addition, undifferentiated adenocarcinoma of 2 cm or less, without ulceration, is also accepted as an extended indication for ESD [3]. Specimens from patients who had undergone ESD were sliced into 2- to 3-mm wide sections, and each section was examined through microscopy to determine the depth and lymphovascular invasion of the cancer. This is the currently prevailing practice, which was developed based on the historical dataset of resected stomach and dissected lymph nodes in actual cases of early

gastric cancer. In practice, clinicians recommend further gastrectomy when the results of the pathological examination of specimens collected through this procedure reveals lymphovascular permeation of the tumors. However, a serious issue arises; that is, subsequent gastrectomy based on this initial assessment of the pathology does not actually result in detection of any lymph node metastasis. It can be assumed, therefore, that the conventional practice leads to many unnecessary surgeries as well as cases in which lymph node metastasis had not been detected; in other words, a more intense scrutiny of the tissue samples might have saved life. This dilemma is often referred to as the "trolley problem" [4], in which the question is raised of whether it is ethical to subject many patients to overdiagnosis and (possibly) unnecessary surgery to save a relatively small subset of high-risk patients.

The aforementioned conventional practice of pathological examination became routine work in pathology laboratories in Japan when EMR, the predecessor of ESD, was introduced, and the number of sections currently required for pathology examination overwhelmingly increased with the increase in clinical indication of endoscopic surgery. Multi-institutional studies of lymphovascular infiltration as a (presumably) statistically significant predictor of lymph node metastasis continue to be viewed as evidence to support a recommendation of further surgery in cases in which the first ESD revealed lymphovascular invasion [5–8]; however, few pathologists participated in the analysis (blind diagnosis, quantitative estimation, and standardization) that were undertaken to establish this recommendation, and a consensus process, involving several pathologists, was not performed. Thus, the scientific merit of lymphovascular infiltration as a reliable predictor of persistent EGC has not been established. There have been very few studies of appropriate and feasible procedures to estimate cancer aggressiveness, such as extensive morphological investigation. Changing the width and numbers of the sections used in the pathology examination, adopting immuno-histological methods to identify lymphovascular invasion, and exploring molecular, not morphological, estimation could be useful in the assessment of the pathology of EGC. To the best of our knowledge, our study is the first in which the altered interpretation of cancer aggressiveness is estimated, retrospectively, when the number of gastric mucosa specimen blocks examined were reduced to (i) one-half or (ii) one-third of the original number. The aim of this study was to evaluate how different or similar the evaluation by methods i and ii is against the original procedure, as well as whether the decision based on hypothetical extracted data had a significant effect on actual patient outcome, based on a comparison of the actual outcome and the clinical decision based on the original observation.

Methods

This work was approved by the Institutional Review Board of Hamamatsu University School of Medicine (20-011) and was in accordance with 1964 Helsinki Declaration. The work is based on pathology archives and waivered on obtaining informed consent.

Case extraction

This retrospective study was conducted at Seirei Hamamatsu General Hospital, Japan. From January 2010 to October 2014, 442 patients diagnosed with gastric neoplasms (501 lesions, in total) underwent ESD. According to the recommendation of the Japanese Classification System, 15th edition [9], resected specimens were serially cut into bands 2–5 mm in width, perpendicular to the long axis (the "routine" method) of the whole area and were macroscopically identified as cancer or precancerous on the gastric mucosa. Each section was microscopically evaluated to identify the vertical extent of deep tumors on the cut surface of the section. At the same time, any lymphovascular permeation was identified using hematoxylin and eosin (HE) and Elastica van Gieson staining (EVG). In some ambiguous cases, immunohistochemistry using D2-40 as a lymph vessel marker was used. In all cases, two additional sections of the outside adjacent area, one next to the first section and the other next to the last ones of the specimen, were cut so that margins of the short axis were free of tumor (Fig. 1a).

The depth measured using microscope with micrometer from each slide and the presence/absence of lymphovascular invasion are shown in Supplementary Table 1. Data extractions were performed in the manner described below, and the interpretations based on these extractions were compared to the original data, as shown in Supplementary Table 1.

Data extracting procedure

(i) Every other section was selected; that is, the hypothetical observation coverage of the surface of the sections was every 6–10 mm, perpendicular to the long axis (the column "1/2 method" in Supplementary Table 2).
(ii) Every third section was selected; that is, the hypothetical observation coverage of the surface of the sections was every 9–15 mm, perpendicular to the long axis (the column "1/3 method" in Supplementary Table 3).

Furthermore, in practical settings, the cut width varies from case to case, from approximately 2–6 mm, depending on the decision of the pathologist in charge of the case. Thus, we

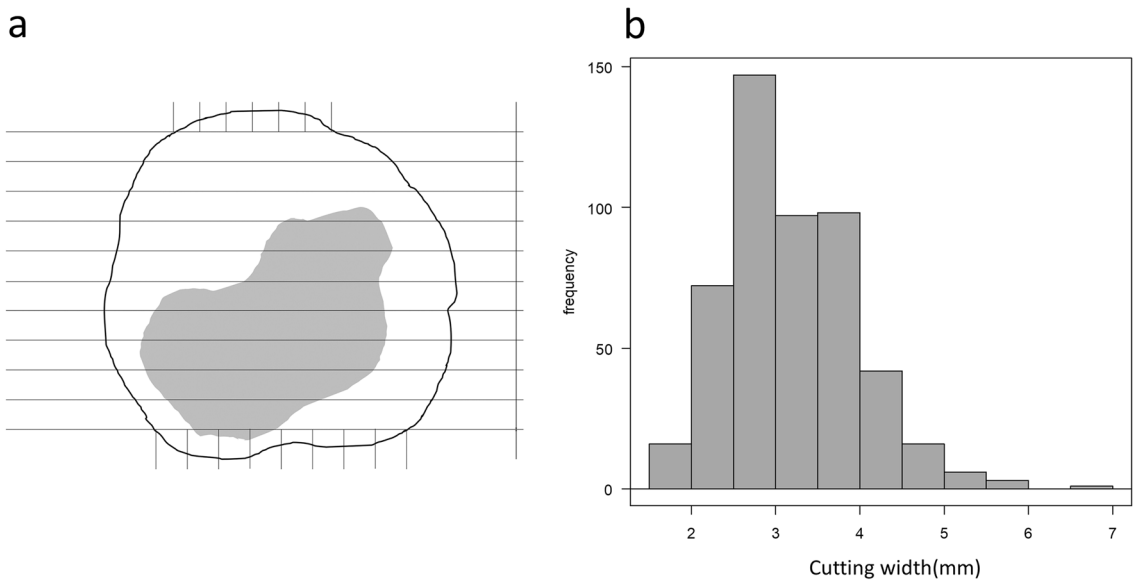

Fig. 1 **a** Typical process to detect and assess tumors in early-stage gastric cancer (ESG) in specimens obtained from endoscopic submucosal dissection (ESD). Shaded area is macroscopically identified tumor area. **b** Histogram of cutting widths. In most of the cases, the cut width is approximately 3 mm, which is the recommended width in the Japanese gastric cancer classification system [9]

reviewed all the photographs of the cutouts, recorded the exact width of the cut-out specimen in these cohorts, and calculated the width (in mm) of each cut-out specimen.

We then regrouped 498 lesions based on their actual cut-out widths; the groups being: < 3 mm, 3–4 mm, and > 4 mm.

Statistical analyses were conducted using EZR for R [10]. *P*-values less than 0.05 were considered statistically significant. In some cases, hypothesis testing for differences in the population proportions was performed.

Immunohistological analysis

The following immunostaining was performed on ESD specimens from 36 patients who underwent surgery due to lymphovascular invasion or depth of tumor, to determine whether antigen expression can predict outcomes; in particular, antigens involved in lymph node function—MUC2, MUC5AC, MUC6, CDX2, E-cadherin, p53, pepsinogen 1—as well as sodium/potassium ATPase and RhoA. Immunostaining was performed according to the previous report [11] Experienced pathologists (SK, YO, KS, and HS) blindly evaluated staining area and strength ranging from negative (−) to strongly positive (3 +).

Results

Baseline clinical characteristics

We evaluated specimens from 442 patients (representing 501 lesions) who underwent endoscopic examination and were diagnosed with EGC at our hospital between January, 2010, and October, 2014. Three cases were excluded because the specimens could not be resected *en bloc*. In total, 498 lesions were analyzed from 439 cases (Fig. 2). The median age was 72 years (range, 38–95), and 344 (78.3%) of the patients were male. The median tumor size was 16 mm (range: 4–112 mm), measured endoscopically. In some cases, measurements were not performed, and these cases were excluded from the analysis. The depth of the tumor in the 402 lesions was categorized as T1a(M). The macroscopic appearance types were I or IIa (elevated) in 153, IIb or IIc (flat or depressed) in 218, and mixed (combined elevated and depressed) in 93 lesions. The histological type of tumor was differentiated in 443, mixed in 41, and undifferentiated in 14 lesions (Table 1).

The distribution of the maximum tumor diameter by age group in 10-year increments is shown in Supplementary Table 4.

Of the 439 cases, there were 79 cases of recurrence during and after the follow-up period (January, 1996 to October, 2021), and in 50 cases, simultaneous resection of multiple lesions was conducted. Surgery (total or subtotal gastrectomy) was performed in 36 cases. Surgery was not performed in 23 cases in which surgery would have been recommended based on the pathological findings, in accordance with the guidelines, but, in each case, the patient remained under observation because of problems with surgical tolerance due to old age.

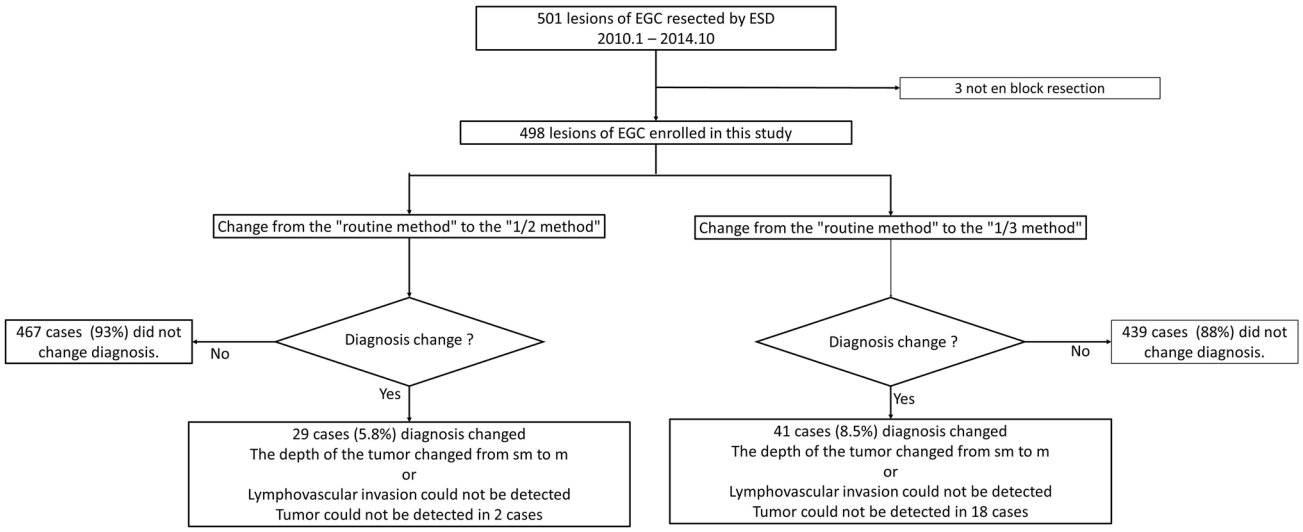

Fig. 2 Flow chart of this study. EGC, early gastric cancer; ESD, endoscopic submucosal dissection

Table 1 Clinicopathological characteristics

Age (median (range)), years	72(38 ~ 95)
Sex(Male: Female), *n*	344: 95
Tumor size (median (range)), mm	16 (4 ~ 112)
Depth(T1a(M): T1b1: T1b2(SM)), *n*	402: 66: 30
Macroscopic type(Elevated[*1]: Flat or depressed[*2]: Mixed[*3]: N/A[*4]), *n*	153: 218: 93: 34
Histological type(differentiated: mixed: undifferentiated[*5]), *n*	443:41:14

*[1]0-I, 0-IIa

*[2]0-IIb, 0-IIc

*[3]0-IIa + IIc, etc

*[4]*N/A* Not available

*[5]Differentiated (tub1, tub2, pap), undifferentiated (por1, por2, sig)

1/2 method vs. routine method

There were 29 cases (5.8%) of 498 lesions in which the assessment of tumor depth and vascular invasion changed when the examination was changed from the routine method to the 1/2 method (diagnostic change group). In addition, there were two cases in which the tumor could not be detected using the 1/2 method.

There are several characteristics of cases in which the 1/2 method generated underdiagnosis. The tumor size in these groups was significantly larger (22 mm vs. 16 mm; $P = 0.0378$) than in the cases in which the diagnosis was not altered using the 1/2 method. Univariate analysis of these cases (Supplementary Table 5) showed that tumor size was a significant predictor of diagnosis when the 1/2 method was used. There were no significant factors (e.g., sex or lesion recurrence), between the two groups (changed diagnosis and unchanged diagnosis).

Of the 29 patients in the changed diagnosis group, six underwent gastrectomy as an additional treatment, and one patient had lymph node metastasis (Fig. 3a–c). Of the six cases, two involved lymphovascular invasion and deep invasion, two deep invasions, and two gastrectomies due to vascular invasion (Table 2).

1/3 method vs. routine method

When the pathological examination was changed from the routine method to the 1/3 method, relative underdiagnosis of tumor depth and vascular invasion occurred in 43 (8.6%) of 498 lesions. In addition, in 18 cases, the tumors themselves could not be detected using the 1/3 method. The actual width of specimens for examination in these cases ranged from 5.4 to 20.4 mm. Tumor size in these 43 cases was significantly larger than that in the group, in which diagnosis was not altered by the use of the 1/3 method (20 vs. 16 mm, respectively; $P = 0.0398$). Tumor size was a significant predictor of diagnostic changes in the univariate analysis (Supplementary Table 6). There were no significant factors (neither sex nor tumor recurrence) in the change of diagnosis group and the no change group.

In 43 patients, the assessment of the pathology would have changed in terms of depth and lymphovascular permeability. In actuality, 10 out of these patients underwent gastrectomy, and only one patient had lymph node metastasis. This was the same case in which lymph node metastasis was found in a surgery recommended by both the routine and 1/2 methods. In addition, only one of the 18 cases in which tumors were missed by the 1/3 method actually proceeded

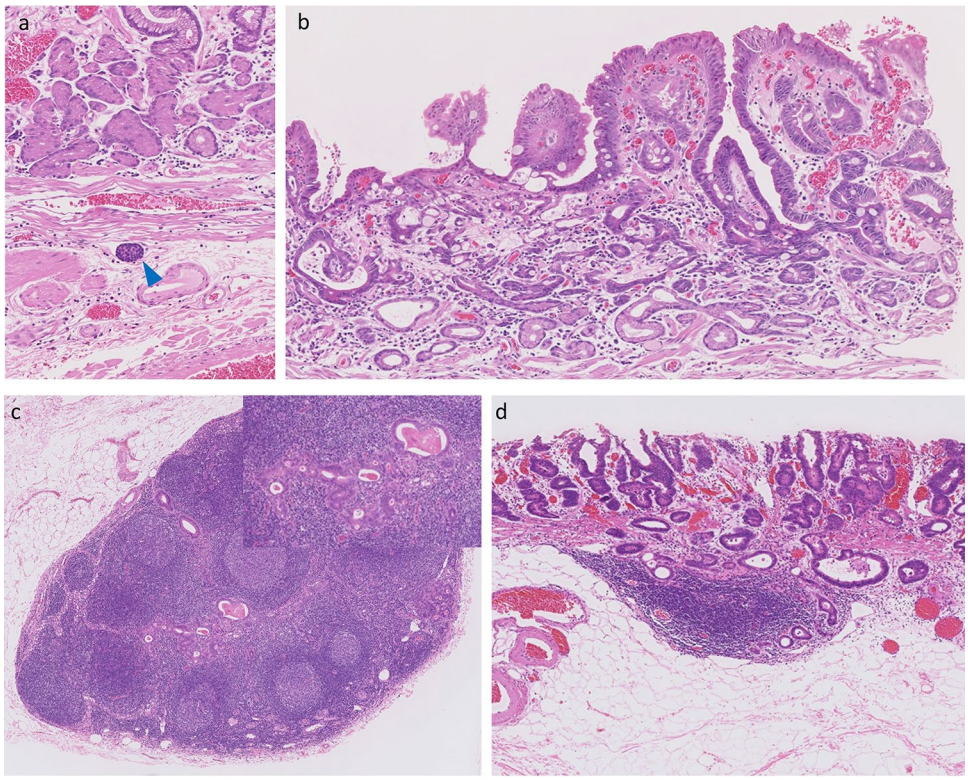

Fig. 3 **a** Lymphovascular invasion (S0222). Lymphatic invasion was missed by both 1/2 and 1/3 methods (arrowhead). Depth was SM1. Additional surgery revealed lymph node metastasis. **b** Histology of the main tumor. **c** Lymph node metastasis of S0222. High magnification of metastatic carcinoma (inset) **d** Cases with lymphatic invasion and surgery but no lymph node metastasis

Table 2 Clinicopathological characteristics of 6 cases re-categorized in 1/2 method

R-ID	Age	Sex	Tumor Size(mm)	Macroscopic Type	Original diagnosis	Histology	Findings by 1/2 method	Post operative pathological finding
S0033	61	Male	25	IIa	sm, ly(+)	mixed	m, ly(-)	No remnant of carcinoma, negative for lymph nodes metastasis
S0080	56	Male	15	IIa+IIc	sm, ly(+)	mixed	m, ly(-)	No remnant of carcinoma, negative for lymph nodes metastasis
S0109	63	Male	28	IIc	sm,v(+)	mixed	sm, v(-)	No remnant of carcinoma, negative for lymph nodes metastasis
S0170	56	Male	18	IIc	sm	differentiated	m	No remnant of carcinoma, negative for lymph nodes metastasis
S0218	65	Male	23	IIa+IIc	sm	differentiated	m	No remnant of carcinoma, negative for lymph nodes metastasis
S0222	59	Female	35	IIc	sm, ly(+)	mixed	sm, ly(-)	No remnant of carcinoma, positive for lymph node metastasis

to gastrectomy as an additional treatment because of submucosal invasion and undifferentiated components. No lymph node metastasis was found on postsurgical examination in this case. Of the 10 patients, based on the original pathological description, two had lymphovascular invasion and deeper invasion, four had deeper invasion, and four had only lymphovascular invasion (Table 3). In one case, a virtual reduction in the number of sections caused cryptic lymph node metastasis to be missed. In the remaining 33 cases, surgery failed to detect residual disease or pathological evidence of lymph node metastasis (Fig. 3d).

We examined whether these diagnostic changes were statistically significant in the 1/2 and 1/3 methods, and, in both cases, the test of difference in proportions showed that significant underdiagnosis occurred in the virtual 1/2 and 1/3 examinations (Supplementary Table 7).

We also examined whether there was a significant difference in tumor diameter in pT1b1 and pT1b2, but no significant difference was found ($P=0.148$). Similarly, we also examined lymphatic vascular invasion and found no significant difference ($P=1$).

Table 3 Clinicopathological characteristics of 10 cases re-categorized in 1/3 method

R-ID	Age	Sex	Tumor Size(mm)	Macroscopic Type	Original diagnosis	Histology	Findings by 1/3 method	Post operative pathological finding
S0033	61	Male	25	IIa	sm, ly(+)	mixed	m, ly(-)	No remnant of carcinoma, negative for lymph nodes metastasis
S0058	69	Female	12	IIa+IIc	sm	differentiated	m	No remnant of carcinoma, negative for lymph nodes metastasis
S0126	70	Female	26	IIc	sm	mixed	m	No remnant of carcinoma, negative for lymph nodes metastasis
S0170	56	Male	18	IIc	sm	differentiated	m	No remnant of carcinoma, negative for lymph nodes metastasis
S0181	65	Male	12	IIa+IIc	sm, ly(+)	differentiated	m, ly(-)	No remnant of carcinoma, negative for lymph nodes metastasis
S0218	65	Male	23	IIa+IIc	sm	differentiated	m	No remnant of carcinoma, negative for lymph nodes metastasis
S0220	71	Female	15	IIc	sm,v(+)	differentiated	sm, v(-)	No remnant of carcinoma, negative for lymph nodes metastasis
S0222	59	Female	35	IIc	sm, ly(+)	mixed	sm, ly(-)	No remnant of carcinoma, positive for lymph node metastasis
S0233	73	Male	42	IIa	sm, ly(+)	differentiated	sm, ly(-)	No remnant of carcinoma, negative for lymph nodes metastasis
S0468	77	Male	8	IIc	sm, v(+)	undifferentiated	sm, v(-)	No remnant of carcinoma, negative for lymph nodes metastasis

As mentioned in the Methods section, the recommended cut-off width of each sample is not always rigorously controlled in actual daily practice, and the widths are not constant. In reviewing all of the cases, we found that the cut-out width of specimens ranged from 1.8 to 6.8 mm (Fig. 1b). The specimens were divided into three groups: up to 3 mm, as per the guidelines (reference group), from 3 to 4 mm or less, and 4 mm or more. The test of difference in proportions was used to examine whether there was a statistically significant incidence of diagnostic change associated with either the 1/2 or 1/3 method, compared to the reference group. (Supplementary Table 8).

When grouped into the above three groups, the cut-out widths of the 1/2 method (4–6 mm) and reference group (up to 3 mm), and the cut-out widths of the raw data for the 4 mm or more group were almost the same (4–6.8 mm). That is, when the two groups—the virtual width by the 1/2 method and the real cut-width of 4 mm and greater—were compared using the difference in proportions test, there were no differences. The percentage of underdiagnosis caused by virtual reduction of the cut width did not differ at the 5% significance level.

When the patients were divided into three groups based on specimen width (≤ 3 mm, 3–4 mm, and ≥ 4 mm), the last group had significantly more submucosal invasion than the other two groups ($P = 0.0015$). There was no significant difference in vascular invasion between the groups.

Any of the immunohistological markers tested here did not predict the outcome (residual cancer and/or lymph node metastasis in gastrectomy cases) (Supplementary Table 9).

Discussion

We first describe the first analysis of the 1/2 and 1/3 methods. In both cases, tumor size was significantly larger in the modified diagnosis group. This result is similar to that of the previous study by Kumei et al. [12]. This suggests that vascular invasion and invasion of the submucosa may be overlooked if the specimen cutting width is too broad, in cases with larger tumor diameters. The lymphovascular permeation detected using routine methods may suggest mandatory gastrectomy, following the guidelines, but the rate of lymph node metastasis detected after surgery and postsurgical pathological examination of lymph nodes was small. Furthermore, the prognosis of these cases compared with dismissed surgery cases is not known.

In the second half of the analysis, specimens were grouped by cut-out width, and raw data from the reference group 1/2 method and the 4 mm or more group were examined with respect to difference in proportions; however, no difference was found at the 5% significance level. This result indicated the possibility of expanding the cut-out width to 4–5 mm. The results were considered significant enough to

warrant a change in the recommendation; that is, the width could be 4-to 5 mm rather than approximately 3 mm, as in the current version of the guidelines (JCS 15th edition).

However, the results also showed that submucosal invasion was significantly greater in the 3–4 mm group than in the 3 mm or less group when the cut-out width was divided into less than 3 mm, 3–4 mm, and > 4 mm. Because the current approach to the pathology considers depth but not spreading surface size to stage T factor, large but surfaced lesions would be expected to sometimes escape detection in the early diagnosis, which is a concern that has been voiced by several surgeons [13]. In contrast, the eCura system does consider tumor diameter as a risk factor [14]. In conclusion, the best cut-out width of the gastric mucosa specimens should be determined by the attending pathologists, endoscopists, and surgeons, bringing multiple perspectives to the assessment.

In the first international meeting of gastric cancer, nearly 30 years ago, in Kyoto, a multi-institutional study on metastasis of early cancer revealed that 4% of cases of early-stage cancer, preferentially IIc, and large tumors had lymph node metastasis [15]. Subsequently, predicting lymph node involvement in the early stage of gastric cancer has been a research goal in EGC pathology.

The limitations of our study include the fact that it was a retrospective study conducted at a single institution, and several biases may have influenced our interpretation.

More importantly, the option of surgery after pathological ESD evaluation depends on many factors, ranging from the subjective stance of the attending physician to the physical and social condition of the patient. In clinical settings, a straightforward application of the guidelines in forming the recommendation of surgery does not always occur. Therefore, it is not possible at this time to suggest or recommend an optimal specimen width for improved prognostication and treatment recommendations in EGC.

The cut-out widths in the current guidelines were established during the period when EMR was the mainstream method, and the rate of lymph node metastasis was calculated based on a comprehensive and painstaking analysis of numerous gastrectomy samples, with a p-value of 0.001 achieved from analysis of 15,785 cases [8]. Therefore, many gastrectomies have been performed for cases in which minute pathological findings suggest and majority of the cases are node-negative. The guideline is a product of compromise, weighing various factors: the fear that lesions might reoccur in the lymph node, the subjectiveness of pathologists, and possible damage as a result of surgery. No prospective study using different groups adopting different examined density are available and will be available. There is a lack of scientific evidence to support the use of large specimens comprehensively, and through microscopic analysis of ESD specimens, dismissing the assessment of the task of pathology division and the potential of these tissues as research resources.

A finer examination of 1-mm sections was evaluated by Kumei [12], but the clinical merit of this approach remains unclear. What is required to properly determine the significance of cut-out width is a study with a greater number of cases, especially those with lymph node metastasis and additional surgery indicated by any pathological, clinical, or radiological findings. We would be able to conduct multi-institutional collections of the cases who had actually positive lymphnodes after surgery, though these are relatively small among operated cases. These specimens (having some depth, LY/V, maybe wider area, and histological or immunohistological peculiarity) would generate considerably significant characteristics as high risk marker. Some mucin markers [16] and NGS studies of these would be possible measure though same numbers of the cases of negative lynmphnode metastases must be compared. The procedure would be tedious, but feasible. 3D transcriptomics of these cases would be interesting, too [17], though expensive. Prospective procedure would be "take the middle strip out for molecular analysis and morphological evaluation is done for opposite surface (supplementary Fig. 1).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10120-023-01396-z.

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Data availability Data is available on a reasonable request to Dr. Haruhiko Sugimura (hsugimur@po.kyoundo.jp).

Declarations

Conflict of interest All the authors do not have any conflict of interests in terms of the content of this manuscript.

Ethical approval This work was approved by the Institutional Review Board of Hamamatsu University School of Medicine (20-011) and was in accordance with 1964 Helsinki declaration. The work is based on archives and waivered on obtaining informed consent.

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