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ORIGINAL ARTICLE

Feasibility of further expansion of the indications for endoscopic submucosal dissection in undifferentiated-type early gastric cancer

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Abstract

Background Based on Japanese guidelines for endoscopic submucosal dissection (ESD) in undifferentiated-type early gastric cancer (UD-EGC), UD-predominant mixed-type (M-UD) EGC is considered high risk for lymph node metastasis (LNM). However, differences in LNM risk between pure UD (P-UD) and M-UD remain unclear. This study assessed risk factors for LNM considering differences between P-UD and M-UD and identified pathological features related to the lowest LNM risk.

Methods This single-center, retrospective study included 1425 patients with UD-EGC treated with surgical resection between April 2005 and May 2017. We divided patients into those with and without LNM and compared background characteristics and post-operative pathological results between groups. Patients were further stratified based on depth, tumor diameter, ulcerative findings, lymphatic invasion, vascular invasion, and histological type to clarify post-operative pathological features associated with the lowest LNM risk.

Results When comparing background characteristics and post-operative pathological results, multivariate analysis showed that, in patients with LNM, tumor diameters were significantly larger, and there were higher rates of submucosal invasion, lymphatic invasion, and M-UD histological type. In patients with absence of ulcerative findings, absence of lymphatic invasion, and absence of vascular invasion, no LNM occurred among those with intramucosal P-UD tumor diameters of 1–40 mm (1–20 mm: 95% confidence interval [CI], 0–5.5%; 21–40 mm: 95% CI, 0–6.1%).

Conclusions Intramucosal P-UD EGC patients with absence of ulcerative findings, absence of lymphatic invasion, absence of vascular invasion, and tumor diameters of ≤ 40 mm did not show LNM. We suggest expanding indications for ESD to include these patients.

Keywords Gastric cancer · Endoscopic submucosal resection · Gastric carcinoma · Lymph node metastasis

Introduction

Since the development of endoscopic submucosal resection (ESD), endoscopic resection has been possible for early gastric cancers (EGC) with a large tumor diameter. Therefore, the treatment of EGC has become less invasive [1–6]. However, because all undifferentiated-type EGCs (UD-EGC) carry a high risk of lymph node metastasis (LNM), traditional surgical treatment remains the current standard treatment according to Japanese gastric cancer treatment guidelines [7].

However, Hirasawa et al. stratified intramucosal UD-EGC patients who underwent surgical resection based on tumor diameter, presence or absence of lymphatic invasion and vascular invasion, and presence or absence of ulcerative

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findings [8]. Among patients with absence of ulcerative findings, absence of lymphatic invasion, and absence of vascular invasion, none showed LNM in tumors with a diameter of ≤ 20 mm [8]. Therefore, tumors with a diameter of ≤ 20 mm and no LNM are listed in the Japanese gastric cancer treatment guidelines 2014 (ver. 4) as indicated for ESD as an investigational treatment (expanded indication) [7]. Two reports on the long-term prognosis after ESD in patients with these lesions have reported a 5-year survival rate of approximately 100% [9, 10]. However, there have also been reports of no significant differences in 5-year survival rates between patients who undergo surgery and those who undergo ESD [11].

A multicenter collaborative prospective study on the long-term prognosis of tumors of ≤ 20 mm in diameter, with the absence of ulcerative findings and absence of lymphatic invasion and vascular invasion and intramucosal UD-EGC (JCOG1009/1010), is in progress [12]. If the long-term prognosis in this study is good, it may support the use of ESD as the standard treatment for these lesions. Furthermore, further expansions of the indications for ESD in UD-EGC may be feasible.

Notably, Takizawa et al. and Hanaoka et al. examined surgical specimens of UD-EGCs and found that the risk of LNM was higher in undifferentiated-type predominant mixed-type (M-UD) cancers than in pure undifferentiated-type cancers (P-UD) [13, 14]. However, according to the Japanese guidelines [7], P-UD and M-UD are collectively treated as UD-EGC. Consequently, differences in LNM risk between P-UD and M-UD have not been given much consideration. Therefore, the aim of this study was to compare the background characteristics and post-operative pathological results in patients with and without LNM. We also aimed to clarify the post-operative pathological features of patients with the lowest risk of LNM by stratification based on possible influential variables, including P-UD and M-UD. These data could be used to assess the feasibility of further expansion of the indications for ESD in UD-EGC.

Methods

This was a single-center, retrospective, observational study. We extracted patient data from electronic medical records of patients who met the following inclusion criteria: (1) patients with UD-EGC (intramucosal or submucosal cancer) who underwent surgery as the initial treatment at the Cancer Institute Hospital between April 2005 and May 2017, (2) patients with positive post-operative UD-EGC results on pathological tests, (3) patients with a single lesion, and (4) patients in whom pathological results could be collected retrospectively.

The exclusion criteria were as follows: (1) patients with remnant cancer or gastric tube cancer, (2) patients with multiple lesions, (3) patients who had undergone chemotherapy and/or radiation, and (4) patients in whom ESD had already been performed.

We first clarified the backgrounds of the patients (age and sex) and determined their post-operative pathological results (location of tumor, depth, tumor diameter, presence or absence of ulcerative findings, presence or absence of lymphatic invasion and vascular invasion, LNM, and histological type). We then divided patients into two groups based on the presence or absence of LNM. Background characteristics and post-operative pathological results were compared between groups to identify significant risk factors for LNM. The cutoff value for age was set to the median of the overall study population. Moreover, to the best of our knowledge, there have been no reports regarding detailed examination of lesions > 20 mm; therefore, the cutoff value for tumor diameter was set to the median for cases with presence of LNM because many lesions were presumed to be > 20 mm in cases with LNM. Following the clarification of the post-operative pathological features of patients with the lowest risk of LNM, we performed stratification based on possible influential variables according to the results of univariate analysis.

All patients with UD-EGC who were treated with surgery underwent pretreatment conventional endoscopy, dye-spraying endoscopy, and magnifying endoscopy with narrow-band imaging to determine the extent and depth of the tumor. Before the treatment, the advantages and disadvantages of the surgery were fully explained to each patient, and each patient provided informed consent to undergo surgery. This study was approved by the institutional review board (IRB) of the Cancer Institute Hospital (IRB number: 2017–1068), and it conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

Pathological validation

For each surgically resected specimen, the sections were prepared at 5-mm intervals for pathological evaluation. Pathologists who specialized in gastrointestinal pathology performed all pathological examinations. The measurements and assessments undertaken were maximum tumor diameter, invasion depth, histological type, presence or absence of ulcerative findings (ulcers and scars that extend deep into the submucosa), lymphatic invasion, vascular invasion, oral margin, anal margin, and presence or absence of LNM. Immunostaining on histological assessment was performed to explore lymphatic invasion (by D2-40 staining) and vascular invasion (by Victoria blue hematoxylin–eosin staining) when the depth was indicative of submucosal cancer or when lymphovascular invasion was suspected based on

hematoxylin–eosin staining. R0 (no cancer in any resection margins) surgical patients were considered curative resection patients based on the Japanese guidelines [7]. All patients were classified into P-UD or M-UD cancer groups based on the post-operative pathological results. A case of P-UD was defined as a case that only had the UD component. A case of M-UD was defined as a case in which the UD component exceeded 50% of the lesion with a differentiated-type component.

Based on the Japanese guidelines, the UD components comprised poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma, while the differentiated-type components comprised moderately or well-differentiated adenocarcinoma and papillary adenocarcinoma.

Statistical analysis

The chi-squared test was used to compare the two groups, based on the presence or absence of LNM. The *F* test was performed to determine whether distributions exhibited equal variance between the two groups for age and tumor diameter. If the *F* test showed significance, the median, interquartile range, and overall range by age and tumor diameter were calculated and analyzed by Mann–Whitney *U* test. If the *F* test showed no significance, the mean, standard deviation by age, and tumor diameter were calculated and analyzed by *t* test. When comparing patients with and without LNM, a multivariate analysis (logistic regression analysis) was performed on variables that showed significant differences in the univariate analysis described above. The odds ratio and 95% confidence interval (CI) were calculated. In addition, we calculated the rate and 95% CI of LNM in patients based on possible influential variables identified in univariate analysis. Statistical significance was set at $p < 0.05$ for both univariate and multivariate analyses. JMP software, version 13.2 (SAS® Institute Inc., Cary, NC, USA), was used for statistical analyses.

Results

A total of 1844 UD-EGC patients who received initial treatment (ESD: 361 patients, surgery: 1483 patients) at the Cancer Institute Hospital between April 2005 and May 2017 were initially enrolled in this study. After exclusion criteria were applied, 1425 patients and 1425 UD-EGC lesions were included in the analysis (Fig. 1). Background characteristics and post-operative pathological results are shown in Table 1. The median age of the patients was 60 years. The median tumor diameter was 30 mm (interquartile range: 20–43.5 mm). LNM was present in 170 (11.9%) patients and absent in 1255 (88.1%) patients.

The prevalence of submucosal invasion, the presence of lymphatic invasion, the presence of vascular invasion, the presence of ulcerative findings, and the prevalence of M-UD type were significantly higher in the LNM group (Table 2). The median tumor diameter of cases with LNM was 40 mm. Tumor diameters were significantly larger (>40 mm) in the LNM group.

Tumor diameter of > 40 mm was significantly associated with LNM (Table 3). Submucosal invasion, presence of lymphatic invasion, and prevalence of M-UD were also significantly higher in patients with LNM (Table 3).

Based on the above results, intramucosal UD EGC patients were stratified based on tumor diameter, histological

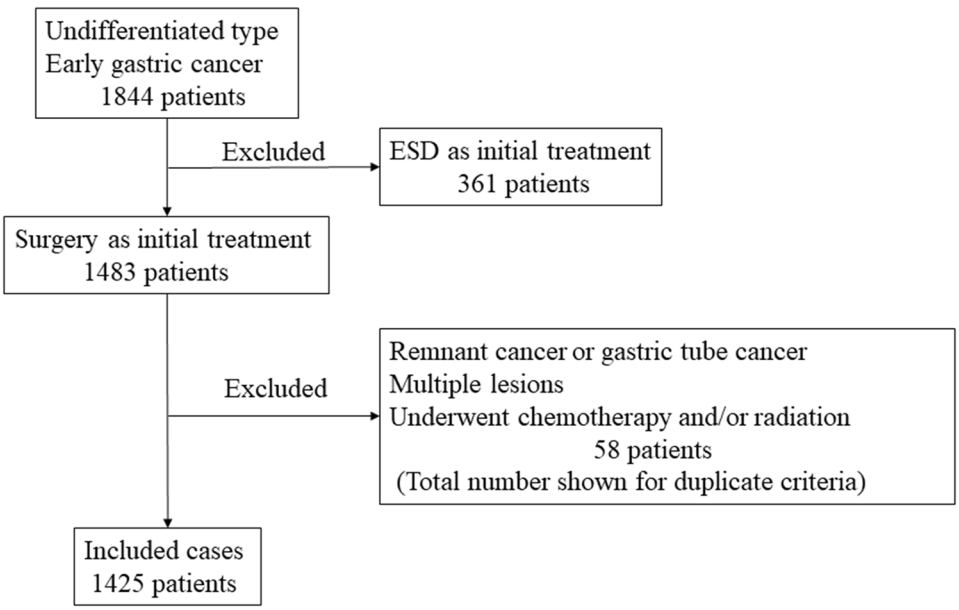

Fig. 1 Flowchart of patient inclusion and exclusion. *ESD* endoscopic submucosal resection

Table 1 Background characteristics and post-operative pathological results of patients

	1425 cases, 1425 lesions
Age (years)	
Median	60 (50–68) [19–91][a]
Sex	
Male	711 (49.9)
Female	714 (50.1)
Location	
Upper third	208(14.6)
Middle third	939 (65.9)
Lower third	278 (19.5)
Depth of invasion	
Intramucosal cancer	707 (49.6)
Submucosal cancer	718 (50.4)
Tumor diameter (mm)	
Median	30 (20–43.5) [2–140][a]
Ulcerative findings	
Presence	353 (24.7)
Absence	1072 (75.2)
Lymphatic invasion	
Presence	294 (20.6)
Absence	1131 (79.4)
Vascular invasion	
Presence	159 (11.2)
Absence	1266 (88.8)
Histological type	
Pure undifferentiated-type[b]	900 (63.2)
Undifferentiated-type predominant mixed-type[c]	525 (36.8)
LNM	
Presence	170 (11.9)
Absence	1255 (88.1)

LNM lymph node metastasis

[a]Data are presented as number (%), except age and tumor diameter, which are expressed as median (interquartile range) [range]

[b]Pure undifferentiated-type: poorly differentiated adenocarcinoma and/or signet ring cell carcinoma, and/or mucinous adenocarcinoma

[c]Undifferentiated-type predominant mixed-type: poorly differentiated adenocarcinoma and/or signet ring cell carcinoma, and/or mucinous adenocarcinoma with differentiated-type components comprising moderately differentiated or well-differentiated adenocarcinoma and papillary adenocarcinoma

type, presence or absence of lymphatic invasion, the presence or absence of vascular invasion, and the presence or absence of ulcerative findings in which significant differences were found in univariate analysis (Table 4). In patients with absence of ulcerative findings, absence of lymphatic invasion, and absence of vascular invasion, LNM did not occur for P-UD tumors with a diameter of 1–40 mm or for M-UD tumors with a diameter of 1–30 mm. However, there were fewer M-UD tumors than P-UD tumors. In the other groups, although the tumor diameter was 1–20 mm, LNM was positive; alternatively, because the number of cases was one or two, it was difficult to interpret the results.

We calculated the rate of LNM and the 95% CI in patients with absence of ulcerative findings, absence of lymphatic invasion, and absence of vascular invasion (Table 5). The 95% CI was 0–6.1% for P-UD patients without LNM, a tumor diameter of 21–40 mm, absence of ulcerative findings, absence of lymphatic invasion, and absence of vascular invasion.

Discussion

In this study, we stratified cases of intramucosal UD-EGC based on tumor diameter, histological type, presence or absence of lymphatic invasion, presence or absence of vascular invasion, and presence or absence of ulcerative findings to clarify the post-operative pathological features of patients with the lowest risk of LNM. To the best of our knowledge, our study is the first detailed investigation of the proportion of LNM that included stratification of tumors by diameter, with consideration of the histological type (P-UD and M-UD).

In this study, the independent risk factors for LNM in UD-EGC were submucosal invasion, lymphatic invasion, M-UD, and a tumor diameter of > 40 mm. With the exception of one lesion, vascular invasion was also present in lesions with submucosal invasion, and/or lymphatic invasion. Therefore, although there was a significant difference regarding vascular invasion in univariate analysis, there was no significant difference in multivariate analysis. Submucosal invasion and lymphatic invasion have been previously reported as factors that are significantly correlated with LNM [8, 15–18], and the results of this study were similar to those of other reports in the literature. Takizawa et al. reported that M-UD was a significant risk factor for LNM in intramucosal UD-EGC [13] and Hanaoka et al. reported similar results for submucosal invasive UD-EGC [14]; our results are compatible with these previously reported results. However, the factors underlying the high rates of LNM in intramucosal M-UD patients with absence of ulcerative findings, absence of lymphatic invasion, and absence of vascular invasion were not clarified in the previous reports. Since pathological sections were prepared at 5-mm intervals for pathological evaluation, evidence of lymphatic invasion and vascular invasion may have been concealed within these sections. Therefore, if pathological sections are prepared at < 5-mm intervals, the numbers of intramucosal cases with presence of lymphatic and/or vascular invasion may increase. In the future, differences in pathology analysis should be considered.

A tumor diameter of > 20 mm has been reported as a significant risk factor for LNM [8, 15, 19], and the results

Table 2 Results of chi-squared test and *t* test comparisons of the background of patients and post-operative pathological results based on the presence or absence of LNM

	Presence of LNM[a] ($n=170$)	Absence of LNM ($n=1255$)	p value[b]
Age (years)			
Mean ± SD	58.7 ± 12.4[c]	58.5 ± 12.9	0.8327
> 60 years	78 (45.9)	586 (47.0)	0.8423
≤ 60 years	92 (54.1)	669 (53.3)	
Sex			
Male	82 (48.2)	629 (49.9)	0.6447
Female	88 (51.8)	626 (50.1)	
Location			
Upper third	22 (12.9)	186 (14.8)	0.2567
Middle third	107 (62.9)	832 (66.3)	
Lower third	41 (24.1)	237 (18.9)	
Depth			
Intramucosal cancer	27 (15.9)	680 (54.2)	< 0.0001*
Submucosal cancer	143 (84.1)	575 (45.8)	
Tumor diameter (mm)			
Median	40 (26–52) [5–140][c]	28 (20–41) [2–135]	< 0.0001*
≤ 40 mm	82 (48.2)	318 (25.3)	< 0.0001*
> 40 mm	88 (51.8)	937 (74.7)	
Ulcerative findings			
Absence	32 (18.8)	321 (25.6)	0.0494*
Presence	138 (81.2)	934 (74.4)	
Lymphatic invasion			
Absence	69 (40.6)	1062 (84.6)	< 0.0001*
Presence	101 (59.4)	193 (15.4)	
Vascular invasion			
Absence	127 (74.7)	1139 (90.8)	< 0.0001*
Presence	43 (25.3)	116 (9.2)	
Histological type			
Pure undifferentiated-type[d]	66 (38.8)	834 (66.5)	< 0.0001*
Undifferentiated predominant mixed-type[e]	104 (61.2)	421 (33.6)	

[a]*LNM* lymph node metastasis

[b]The *t* test was used to compare mean ± standard deviation (SD) values for age after confirming non-significance by *F* test. The Mann–Whitney *U* test was used to compare median values for tumor diameter after confirming significance by *F* test. The chi-squared test was used to compare the presence and absence of LNM groups in terms of age (>60 years or ≤ 60 years), sex, location, depth, tumor diameter (<40 mm or ≥ 40 mm), ulcerative findings, lymphatic invasion, vascular invasion, and histological type

[c]Data are presented as number (%), except age, which is expressed as mean ± SD, and tumor diameter, which is expressed as median (interquartile range) [range]

[d]Pure undifferentiated-type: poorly differentiated adenocarcinoma and/or signet ring cell carcinoma, and/or mucinous adenocarcinoma,

[e]Undifferentiated-type predominant mixed-type: poorly differentiated adenocarcinoma and/or signet ring cell carcinoma, and/or mucinous adenocarcinoma with differentiated-type components comprising moderately differentiated or well-differentiated adenocarcinoma and papillary adenocarcinoma

*Statistically significant

of this study are consistent with those of previous reports. We stratified intramucosal UD-EGC patients based on tumor diameter, presence or absence of lymphatic invasion and vascular invasion, histological type (P-UD or M-UD), and presence or absence of ulcerative findings. Hirasawa et al. stratified intramucosal UD carcinoma patients who underwent surgical resection [8]. However, the results of their report did not include data regarding histological type (P-UD or M-UD). Because we included histological type (P-UD or M-UD) stratification in our analysis, our data are more detailed than the data described by Hirasawa et al. in terms of histological type.

Table 3 Logistic regression analysis for comparison of patient background and post-operative pathological results based on the presence or absence of LNM

	Odds ratio	95% CI[a]	*p* value
Depth			
Intramucosal cancer	1		
Submucosal cancer	2.5	1.5–4.2	0.0003*
Tumor diameter			
≤ 40 mm	1		
> 40 mm	2.5	1.8–3.6	< 0.0001*
Ulcerative findings			
Absence	1		
Presence	1.4	0.9–2.1	0.1587
Lymphatic invasion			
Absence	1		
Presence	4.8	3.1–7.3	< 0.0001*
Vascular invasion			
Absence	1		
Presence	1.0	0.7–1.7	0.8632
Histological type			
Pure undifferentiated-type[b]	1		
Undifferentiated-type predominant mixed-type[c]	2.0	1.4–2.9	0.0002*

[a]*CI* confidence interval

[b]Pure undifferentiated-type: poorly differentiated adenocarcinoma and/or signet ring cell carcinoma, and/or mucinous adenocarcinoma

[c]Undifferentiated-type predominant mixed-type: poorly differentiated adenocarcinoma and/or signet ring cell carcinoma, and/or mucinous adenocarcinoma with differentiated-type components comprising moderately differentiated or well-differentiated adenocarcinoma and papillary adenocarcinoma

*Statistically significant

Table 4 Stratification based on tumor diameter, histological type, presence or absence of LVI, and presence or absence of ulcerative findings in intramucosal undifferentiated-type carcinoma

Post-operative pathological result	P-UD	LNM	M-UD	LNM
1–20 mm UL−, LVI−	66	0	14	0
21–30 mm UL−, LVI−	36	0	9	0
31–40 mm UL−, LVI−	23	0	10	1 (10.0)[a]
41–50 mm UL−, LVI−	13	1 (7.7)	8	1 (11.1)
> 50 mm UL−, LVI−	10	1 (10.0)	9	0
1–20 mm UL+, LVI−	110	3 (2.7)	30	1 (3.3)
21–30 mm UL+, LVI−	97	2 (2.1)	38	0
31–40 mm UL+, LVI−	61	2 (3.3)	24	1 (4.2)
41–50 mm UL+, LVI−	48	2 (4.2)	17	2 (11.8)
> 50 mm UL+, LVI−	41	0	34	9 (26.5)
1–20 mm UL−, LVI+	0	0	0	0
21–30 mm UL−, LVI+	0	0	0	0
31–40 mm UL−, LVI+	1	1 (100)	0	0
41–50 mm UL−, LVI+	0	0	0	0
> 50 mm UL−, LVI+	1	0	0	0
1–20 mm UL+, LVI+	2	0	0	0
21–30 mm UL+, LVI+	2	0	0	0
31–40 mm UL+, LVI+	2	0	0	0
41–50 mm UL+, LVI+	1	1 (100)	0	0
> 50 mm UL+, LVI+	0	0	0	0

UL ulcerative findings, *LVI* lymphatic invasion and/or vascular invasion, *P-UD* pure undifferentiated-type, *M-UD* undifferentiated-type predominant mixed-type, *LNM* lymph node metastasis

[a]Data are presented as number (%)

Sekiguchi et al. [19] validated a risk scoring model for predicting LNM based on tumor size, invasion depth, histological type, presence or absence of ulcerative findings, and presence or absence of lymphatic invasion and vascular invasion in all cases of EGC. They reported higher rates of lymphatic invasion, vascular invasion, and submucosal invasion; large tumor diameters; and higher prevalence of ulcerative findings and M-UD in patients with LNM [19]. However, because the cutoff value of the tumor diameter was set to 20 mm in that study, detailed examination of lesions larger than 20 mm was not performed [19]. Therefore, because we have adopted a 40-mm cutoff value with regard to the histological type, our data are more detailed than the data described by Sekiguchi et al. in terms of tumor diameter assessment.

The results of our study suggest for the first time that LNM does not occur in intramucosal P-UD carcinoma patients with absence of ulcerative findings, absence of lymphatic invasion, absence of vascular invasion, and a tumor diameter of ≤ 40 mm. The 95% CI for P-UD patients without LNM, a tumor diameter of 21–40 mm, absence of ulcerative findings, absence of lymphatic invasion, and absence of vascular invasion was 0–6.1%. Based on the current Japanese gastric cancer treatment guidelines [7], less than 1% of 95% CI is regarded as within expanded indications for ESD. Therefore, the upper limit of the 95% CI of the LNM rate was high. However, based on the results of this study, we suggest expansion of the indications for ESD to include patients with an endoscopic tumor diameter of ≤ 40 mm, absence of endoscopic ulcerative findings, absence of endoscopic submucosal invasion, and P-UD on biopsy (Fig. 2). In curative evaluation, in P-UD carcinomas in which R0 resection was performed by ESD, we suggest expansion of the indications for curative resection to include patients with a pathological tumor diameter of ≤ 40 mm, absence of pathological ulcerative findings, absence of pathological submucosal invasion, absence of lymphatic invasion, and absence of vascular invasion. Moreover, the frequency of serious surgery-related deaths and early post-operative deaths is reportedly higher in elderly patients [20–22]. Therefore,

Table 5 LNM rates and 95% CIs in the group of patients without ulcerative findings and LVI

Post-operative pathological result	P-UD	LNM	LNM 95% CI (%)	M-UD	LNM	LNM 95% CI (%)
1–20 mm, UL-, LVI-	66	0	0–5.5	14	0	0–21.5
21–40 mm, UL-, LVI-	59	0	0–6.1	19	1 (5.3)[a]	0.9–24.6
> 41 mm, UL-, LVI-	23	2 (8.7)	2.4–26.8	17	1 (5.9)	1.0–27.0

UL ulcerative findings, *LVI* lymphatic invasion and/or vascular invasion, *P-UD* pure undifferentiated-type, *M-UD* undifferentiated-type predominant mixed-type, *LNM* lymph node metastasis, *CI* confidence interval

[a]Data are presented as number (%)

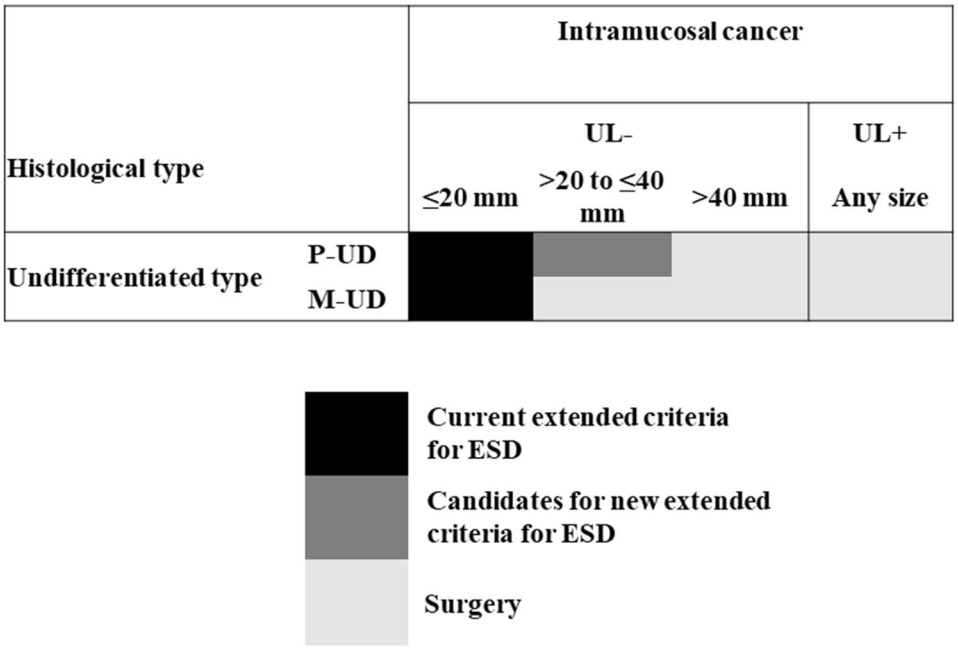

Fig. 2 Extended criteria for endoscopic submucosal resection in undifferentiated-type early gastric cancer. Cases of endoscopic tumor with a diameter of < 40 mm, absence of endoscopic ulcerative findings, absence of pathological invasion depth, and pure undifferentiated-type carcinoma classification on biopsy are suggested as additions for indications for ESD. *ESD* endoscopic submucosal resection, *UL* ulcerative findings, *P-UD* pure undifferentiated-type, *M-UD* undifferentiated-type predominant mixed-type

although the upper limit of the 95% CI of the LNM rate was high in terms of the above criteria, we propose expansion of the indications for ESD to include patients who meet the above criteria for elderly patients or patients with severe comorbidities.

The major limitation of this study was its single-center, retrospective design. Therefore, the upper limit of the 95% CI of the LNM rate was high because the number of patients was small. Moreover, it is unclear whether the indication should be extended to tumor size ≤ 30 mm or ≤ 40 mm, because of the small number of cases in each category in this study. In the future, multicenter collaborative studies with larger populations are necessary. Hatta et al. [18] proposed an eCura system that involved a low risk of lymph node metastasis, thus allowing follow-up without additional gastrectomy. However, their study lacked data regarding UD-type EGC. In subsequent multicenter collaborative studies, we will perform risk stratification of UD-type EGC and propose a risk scoring model for these cases. Another limitation of this study was that, for each surgically resected specimen, the sections were prepared at 5-mm intervals for pathological evaluation, while ESD specimens were prepared at 2-mm intervals. Therefore, it is also necessary to prospectively examine long-term prognosis to establish ESD as standard treatment for post-ESD patients who meet the above criteria. However, given that this study included large number of UD-EGC surgery cases over a period of 12 years at a cancer specialty hospital, our results are sufficiently meaningful in that they can serve as the basis for the feasibility of expanded indications for ESD when evaluating subjects for multicenter prospective studies.

In conclusion, our findings suggest that intramucosal P-UD EGC patients with absence of ulcerative findings, absence of lymphatic invasion, absence of vascular invasion, and tumor diameters of ≤ 40 mm have the lowest risk of LNM. We suggest including these patients in the expanded indications for curative resection of ESD in UD-EGC. In the future, our results can be the basis for subject selection in multicenter, prospective studies.

Author contributions Conceptualization: YH, SI, SN, NY, JF; methodology: YH, SI, NI; formal analysis and investigation: YH, NI; writing—original draft preparation: YH; writing—review and editing: YH, TY, KK, NI, SN; funding acquisition: YH; resources: YH, SI, SN, SY, AI, TY, TH, TT, KK, MO, TS, JF; supervision: YH, JF.

Compliance with ethical standards

Conflict of interest There is no conflict of interest associated with this study.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent to be included in the study, or the equivalent, was obtained from all patients.

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