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Endoscopic submucosal dissection for undifferentiated-type early gastric cancer: Do we have enough data to support this?

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Abstract

Although endoscopic submucosal dissection (ESD) is now accepted for treatment of early gastric cancers (EGC) with negligible risk of lymph node (LN) metastasis, ESD for intramucosal undifferentiated type EGC without ulceration and with diameter ≤ 2 cm is regarded as an investigational treatment according to the Japanese gastric cancer treatment guidelines. This consideration was largely based on the analysis of surgically resected EGCs that contained undifferentiated type EGCs; however, results from several institutes showed some discrepancies in sample size and incidence of LN metastasis. Recently, some reports about the safety and efficacy of ESD for undifferentiated type EGC meeting the expanded criteria have been published. Nonetheless, only limited data are available regarding long-term outcomes of ESD for EGC with undifferentiated histology so far. At the same time, endoscopists cannot ignore the patients' desire to guarantee quality of life after the relatively non-invasive endoscopic treatment when compared to conventional surgery. To satisfy the needs

of patients and provide solid evidence to support ESD for undifferentiated EGC, we need more delicate tools to predict undetected LN metastasis and more data that can reveal predictive factors for LN metastasis.

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Key words: Early gastric cancer; Endoscopic submucosal dissection; Undifferentiated histology; Indications

Core tip: Endoscopic submucosal dissection (ESD) for intramucosal undifferentiated (UD) type early gastric cancer (EGC) without ulceration and with diameter ≤ 2 cm is regarded as an investigational treatment according to the Japanese gastric cancer treatment guidelines. In contrast, the controversial results about the safety of ESD for UD-EGC fulfilling the criteria have been reported and a little is known about the long-term outcomes. Therefore, in this review, we focused on the safety and therapeutic efficacy of ESD for UD-EGC with reference to risks for lymph node metastasis within the proposed criteria as well as the short-term and long-term outcomes of ESD for UD-EGC.

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INTRODUCTION

Early gastric cancer (EGC) is defined as gastric cancer that is confined to the mucosa or submucosa, irrespective

Depth \ Histology	Mucosal cancer				Submucosal cancer	
	No ulceration		Ulceration		SM1	≤ SM2
	≤ 20 mm	> 20 mm	≤ 30 mm	> 30 mm	≤ 30 mm	Any size
Differentiated						
Undifferentiated						

■ Absolute indications for EMR or ESD ■ Expanded indications for ESD
■ Consider surgery ■ Surgery (Gastrectomy and lymph node dissection)

Figure 1 Absolute and expanded indication for endoscopic mucosal resection and endoscopic submucosal dissection for early gastric cancer. SM1: Tumor invasion into the upper third of the submucosa ($\leq 500 \mu\text{m}$); SM2: Tumor invasion into the mid-third of the submucosa ($> 500 \mu\text{m}$). EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

of the presence of regional lymph node (LN) metastases^[1]. In the Eastern hemisphere, up to 70% of all gastric cancers are diagnosed as EGCs (due to mass population screening)^[2-4], whereas in the Western hemisphere, the rate of gastric cancers identified as EGCs accounts for only about 15%^[5,6]. EGC reveals a favorable prognosis compared with advanced gastric cancer, with 5-year survival rates being in excess of 90% to 95%, based on Korea, Japan, and European data^[7-13].

In Eastern countries, endoscopic resection (ER), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), has been widely accepted as a minimally invasive treatment for EGC with a negligible risk of LN metastasis^[14-18]. Recently, considerable data have also been reported from the Western world as ER is gaining wide acceptance^[19-21]. Tumors indicated for ER as a standard treatment are differentiated-type adenocarcinomas without ulceration, of which the depth of invasion is clinically diagnosed as mucosal layer and the diameter is $\leq 20 \text{ mm}$ ^[22]. Gotoda *et al.*^[23] studied surgically resected specimens of EGC and suggested the following four expanded indication criteria for endoscopic treatment of EGC without LN metastasis: (1) differentiated intramucosal cancer without ulceration, regardless of size; (2) differentiated intramucosal cancer with ulceration and diameter $\leq 30 \text{ mm}$; (3) differentiated minute submucosal penetrative cancer in diameter $\leq 30 \text{ mm}$; and (4) undifferentiated (UD) type intramucosal cancer without ulceration and diameter $\leq 20 \text{ mm}$. In particular, surgery was still considered in the UD-EGC meeting the expanded criteria because endoscopic *en-bloc* removal was sometimes difficult in this type of tumors (Figure 1)^[24,25]. However, Hirasawa *et al.*^[26] added to the body of evidence that there is no LN metastasis in patients with UD-EGC within the expanded criteria. This study revealed the 95%CI of the calculated risk of metastasis to nodes was 0%-0.96%, while the earlier study by Gotoda *et al.*^[23] showed that of risk was 0%-2.6% due to small sample size ($n = 141$), which may potentially be inferior to the outcomes of surgical resection.

Along these lines, the Japanese gastric cancer treatment guidelines (2010, ver. 3) state that ER for these UD-EGCs is regarded as an investigational treatment, and that ESD, not EMR, should be employed. In contrast, clinical practice guidelines, according to both National

Comprehensive Cancer Network^[27] and European Society for Medical Oncology^[28], do not yet recognize ER for EGCs meeting the expanded criteria as safe. Moreover, the controversial results about the safety of ESD for UD-EGC fulfilling the criteria have been reported and a little is known about the long-term outcomes. Therefore, in this review, we focused on the safety and therapeutic efficacy of ESD for UD-EGC with reference to risks for LN metastasis within the proposed criteria as well as the short-term and long-term outcomes of it.

PREOPERATIVE ASSESSMENT OF LN METASTASIS

The most important factor concerning endoscopic treatment with curative intent is the prediction of regional LN metastasis before treatment^[22,27,28]. Reported rates of LN metastasis in EGC range from 5.7% to 20% based on the analysis of surgically resected specimen of EGC^[29-34]. UD-EGC demonstrates 4.2% to 4.9% and 19.0% to 23.8% of LN metastasis in the mucosal and submucosal invasive tumors, respectively^[23,26]. To date, no imaging modality has been proven to be consistently accurate in assessing LN metastasis in EGC^[35,36]. Endoscopic ultrasound (EUS) is one of most studied procedures for the locoregional staging of gastric cancer. Reported sensitivities and specificities of EUS to detect LN metastases in gastric cancers varied widely, between 16.7% and 95.3%, and between 48.4% and 100%, respectively^[35]. EUS demonstrated a moderate accuracy that seems to describe advanced T stage (T3 and T4) better than N or less advanced T stage^[37,38]. Although a clinically relevant benefit of EUS to distinguish intramucosal lesions from submucosal lesions should be further improved^[39], EUS is an important imaging modality for preoperative assessment to exclude LN metastasis as well as to confirm deeper wall invasion including the proper muscle layer. Nevertheless, we should consider that UD histology would cause under-diagnosis and affect the accuracy of EUS compared to the differentiated histology^[40].

In addition to the diagnostic role of magnifying endoscopy with narrow-band imaging (ME-NBI) for determining tumor margin in EGC^[41,42], ME-NBI has been suggested as a supporting tool for the assessment of

Table 1 Curability for endoscopic resection of early gastric cancer

Curability criteria	
Curative resection	<i>En bloc</i> resection, no lateral and vertical margin positivity, no lymphovascular invasion Intramucosal cancer, differentiated histology, size \leq 20 mm, No ulcerative finding
Curative resection for expanded indications	<i>En bloc</i> resection, no lateral and vertical margin positivity, no lymphovascular invasion Intramucosal cancer, differentiated histology, size $>$ 20 mm, no ulcerative finding Intramucosal cancer, differentiated histology, size \leq 30 mm, presence of ulcerative finding SM 1 depth of invasion, differentiated histology, size \leq 30 mm, no ulcerative finding Intramucosal cancer, undifferentiated histology, size \leq 20 mm, no ulcerative finding
Non-curative resection	Any resection that does not satisfy one of the above criteria

SM: Submucosa.

invasion depth in EGC^[43-46]. In contrast to the usefulness of ME-NBI for evaluating invasive depth in esophageal or colon cancer^[47,48], the utility of ME-NBI for determining invasion depth in EGC is not conclusive, because the invasive tumor is often not exposed at the surface and the mucosal structure remains, even when cancer invades the submucosa. Therefore, it is difficult to estimate reliably the depth of invasion by surface appearance^[49]. ME-NBI should also distinguish findings suggestive of submucosal invasion from those indicative of the UD histologic type^[44,45]. The findings of a nonstructural pattern in the neoplastic lesion of the stomach on ME^[45] or no surface pattern and sparse microvessels (markedly distorted, isolated, heterogeneous) or with avascular areas on ME-NBI^[44] are indicative of undifferentiated type adenocarcinoma or differentiated cancer with deep submucosal invasion. In contrast, ME-NBI images of UD-EGC were very closely related to the histopathological findings in other study^[50], and therefore, this imaging tool can be useful in the pretreatment assessment of the histopathological patterns of cancer development and the lateral extent of UD-EGC. Thus, the role of ME-NBI in differentiation of histologic types in addition to invasive depth should be validated through further prospective studies.

Other imaging modalities including abdominal ultrasound (AUS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) achieved limited success to stage preoperative LN status^[35,36]. A meta-analysis by Seevaratnam *et al*^[36] showed that imaging modalities range in overall accuracy from 53.4% (MRI) to 68.1% (AUS), in sensitivity from 40.3% (PET) to 85.3% (MRI), and in specificity from 75.0% (MRI) to 97.7% (PET), with no significant differences between modalities. To date, there are no clinically relevant imaging tools to detect the submucosal invasion and the LN metastasis in EGC that are critical conditions for determining proper candidates for ER.

RISK FACTORS FOR LN METASTASIS AND PROPOSED CRITERIA FOR ESD

Because currently available imaging modalities fail to accurately evaluate nodal status, endoscopic resectability according to nodal status in EGC and subsequent curability are still determined by means of the presence or absence of certain tumor characteristics which were obtained from the analysis of surgically resected EGC. According to the Japanese gastric cancer treatment guidelines^[22], the main risk factors predictive of LN metastasis in EGC are histologic type, depth of invasion, ulceration, size, and lymphovascular invasion largely based on two large-scale datasets^[23,26]. These factors consist of absolute and expanded indications as well as curability of ER with *en bloc* resection and negative lateral/vertical margin (Table 1)^[22,51]. A meta-analysis by Kwee *et al*^[52] identified the characteristics related to LN metastasis in EGC, including age, gender, location, size, macroscopic type, ulceration, histologic type in accordance with Japanese and Lauren classification, lymphovascular invasion, submucosal vascularity, a proliferating cell nuclear antigen labeling index, a matrix metalloproteinase-9-positivity, a gastric mucin phenotype, and a vascular endothelial growth factor-C-positivity. These factors revealed partially different correlations with LN metastasis in intramucosal and submucosal EGCs, respectively.

With regard to LN metastasis particularly in UD-EGC, many recent studies investigated the risk factors and suggested their criteria for ER of UD-EGC (Table 2)^[23,26,53-65]. The overall rates of LN metastasis in UD-EGC varied from 7.9% to 24.5%; however, the heterogeneous composition in subtypes of UD histology in lesions from 15 studies should be taken into account.

Size of lesion

Although the intramucosal lesions without ulceration and diameter \leq 20 mm have been considered as rational criteria for ESD in UD-EGC by Japanese researchers^[23,26], different ER criteria have also been suggested with various standards in size, depth of invasion, and presence of ulcerative finding^[53-65]. Concerning lesion size, a majority of recent studies (11/15, 73.3%) suggested that a diameter of 20 mm to 30 mm would be the upper limit of the size criterion for UD-EGC to be amenable to treatment with ESD; however, the remaining four studies proposed a diameter of 10 or 15 mm as the upper limit of the criterion, based on their results suggesting the possibility of LN metastasis even in smaller UD-EGC^[54,60,64,65]. Debates over the size criterion were highlighted by several reports of LN metastasis of UD-EGCs within the expanded criteria, including a diameter \leq 20 mm^[31,66-70]. Moreover, the size discrepancy between pathologic size and endoscopic size should be resolved, because we can only determine the indications of ER based on the endoscopically estimated size. While a previous study revealed that endoscopic visual estimation method was found to show

Table 2 Proposed criteria for endoscopic resection of undifferentiated type early gastric cancer

Study	Year	Country	No. of patients with UD-EGC	No. of patients with PD/SRC/MC	LNM in UD-EGC, n (%)	LNM in proposed criteria	Risk factors related to LNM in UD-EGC	Proposed criteria of ER for UD-EGC			
								Size, mm	Depth of invasion	Ulcer	LVI
Tong <i>et al</i> ^[53]	2011	China	193	81/102/7/3 ¹	46 (23.8)	0/72	Size, depth of invasion, LVI, Histologic type	NS or ≤ 20	M or SM	NS	No
Kim <i>et al</i> ^[54]	2011	South Korea	707	288/419/0	65 (9.2)	0/101	Size, depth of invasion, LVI, Age ²	15 ³	M	NS	No
Li <i>et al</i> ^[55]	2010	China	108	85/16/7	16 (14.8)	0/25	Size, depth of invasion, LVI	20	M	NS	No
Park <i>et al</i> ^[56]	2009	South Korea	215	Only SRC	17 (7.9)	0/57	Depth of invasion, LVI	25	SM2	NS	No
Kunisaki <i>et al</i> ^[57]	2009	Japan	573	182/378/13	74 (12.9)	0/85	Size, depth of invasion, LVI	20	M	NS	No
Hirasawa <i>et al</i> ^[26]	2009	Japan	3843	NA	504 (13.1)	0/310	Size, depth of invasion, LVI	20	M	No	No
Hanaoka <i>et al</i> ^[58]	2009	Japan	143	NA	35 (24.5)	0/41	Size, depth of invasion, LVI, Histologic type	30	$\leq 500 \mu\text{m}^4$	NS	No ⁵
Ye <i>et al</i> ^[59]	2008	South Korea	591	266/316/9	79 (13.4)	0/119	Size, depth of invasion, LVI	25	M	NS	No
Park <i>et al</i> ^[60]	2008	South Korea	234	Only PD	25 (21.6)	0/56	Size, depth of invasion, LVI	15	M or $\leq 500 \mu\text{m}$	NS	No
Li <i>et al</i> ^[61]	2008	China	85	Only PD	12 (14.1)	0/25	Size, depth of invasion, LVI	20	M	NS	No
Li <i>et al</i> ^[62]	2008	South Korea	646	307/330/9	61 (9.4)	1/201	Size, depth of invasion, LVI	20	M	NS	No
Ha <i>et al</i> ^[63]	2008	South Korea	641	248/388/5	100 (15.6)	0/77	Size, depth of invasion, LVI, histologic type	20	M	NS	No
Hyung <i>et al</i> ^[64]	2004	South Korea	289	NA	43 (14.9)	NA	Size, depth of invasion, LVI, histologic type	15	M	NS	No
Abe <i>et al</i> ^[65]	2004	Japan	175	68/104/3	32 (18.3)	0/6	Size, LVI	10	M	NS	No
Gotoda <i>et al</i> ^[23]	2000	Japan	2341	NA	243 (10.4)	0/141	Size, depth of invasion, LVI, histologic type, ulcer, macroscopic type	20	M	No	No

¹Three patients had EGCs with histology of undifferentiated adenocarcinoma; ²Young age less than 45 years was related to the lymph node metastasis of only poorly-differentiated carcinoma; ³Size criteria were ≤ 25 mm in poorly-differentiated adenocarcinomas and ≤ 15 mm in signet-ring cell carcinomas, respectively; ⁴The depth of invasion in proposed criteria was $\leq 500 \mu\text{m}$ or no more from the lower margin of the muscularis mucosae; ⁵Hanaoka *et al* also suggested the proportion of undifferentiated components $< 50\%$ as one of criteria. UD-EGC: Undifferentiated type early gastric cancer; PD: Poorly-differentiated adenocarcinoma; SRC: Signet-ring cell carcinoma; MC: Mucinous carcinoma; LNM: Lymph node metastasis; ER: Endoscopic resection; LVI: Lympho-vascular invasion; M: Mucosa; SM: Submucosa; NS: Not significant; NA: Not available.

reliable agreement with pathologic measurements in EGC treated with ER^[71], other earlier ESD series showed the mean size discrepancies ranged from 5.8 mm to 6.8 mm, which are not negligible in ER for EGC^[72,73]. In UD-EGC, the margins of the lesion tend to be obscured compared to the differentiated histology, which was found to cause frequent margin failure of ESD in our previous report^[74]. Thus, a standard reliable measurement method is required through further prospective studies^[75].

Submucosal invasion

Some studies suggest that a shallow submucosal invasion is an acceptable depth of invasion in ESD for UD-EGC^[53,56,58,60]. However, this suggestion should be reserved until EUS is more reliable for determination of invasive depth, because there is a high chance of endo-sonographically underestimated depth of invasion and subsequently higher vertical margin positivity in poorly-differentiated EGC^[40,74], in addition to the difficult assessment of depth of invasion in UD-EGC^[76-79]. Additionally, the numbers of enrolled UD-EGCs in these studies, suggesting a minute submucosal invasion as a criterion

for ER, were relatively small compared with other studies. More importantly, the majority of recent studies reported the LN metastasis in a depth of submucosal invasion^[23,26,54,55,57,59,61-65].

Ulceration

Ulceration within the lesion is the representative finding with heterogeneity. More than moderate heterogeneity was identified at previous meta-analysis with possible explanation for this heterogeneity due to the interobserver variability between studies for the assessment of tumor ulcerations^[52]. Furthermore, this may be due to the different definitions in addition to the interobserver variability for the assessment of ulcerations^[52,67,75,80]. Though most of the recent studies (13/15, 86.7%) did not consider the ulcer finding in their proposed criteria, patients with tumor ulcerations had a significantly higher risk of LN metastasis in intramucosal EGC irrespective of histological type at meta-analysis^[52]. And ulcerous change decreases the accuracy of EUS diagnosis for the invasive depth of EGC^[81]. Therefore, we do not consider ER for UD-EGCs with ulceration as safe.

Table 3 Clinical characteristics of representative studies on endoscopic resection for undifferentiated type early gastric cancer

Study	Year	Country	No. of patients with UD-EGC	No. of patients with PD/SRC	Age (yr) ¹	Sex (male)	SM invasion	Ulcer	Size (mm) ¹	Size > 20 mm
Kim <i>et al.</i> ^[80]	2013	South Korea	74	55/19	61.8 ± 12.0	40 (54.1)	16 (21.6)	11 (14.9)	19.9 ± 12.5	36 (48.6)
Abe <i>et al.</i> ^[87]	2013	Japan	97	18/77/2 ²	62.0 (35.0-88.0) ³	55 (56.7)	19 (19.6)	9 (9.3)	12.0 ³	14 (14.4)
Park <i>et al.</i> ^[88]	2012	South Korea	77	47/15 ⁴	60.9 (33.0-82.0)	49 (63.6)	12 (15.6)	4 (5.2)	23.3 ± 14.0	35 (45.5)
Okada <i>et al.</i> ^[89]	2012	Japan	103 ⁵	12/91	59.0 (34.0-91.0)	48 (46.6)	10 (9.7)	1 (1.0)	8.0 (1.0-33.0) ³	NA
Kamada <i>et al.</i> ^[76]	2012	Japan	46	NA	65.5 (29.0-90.0)	24 (52.2)	7 (15.2)	1 (2.2)	NA	8 (17.4)
Yamamoto <i>et al.</i> ^[90]	2010	Japan	58	48/10	64.0 (33.0-81.0)	31 (53.4)	7 (12.1)	2 (3.4)	11.0 (2.0-28.0)	5 (8.6)
Kang <i>et al.</i> ^[73]	2010	South Korea	60	30/30	56.7 ± 10.4	31 (51.7)	17 (28.3)	17 (28.3)	26.3 ± 12.9	31 (51.7)
Kim <i>et al.</i> ^[74]	2009	South Korea	58	17/41	55.0 (26.0-81.0)	26 (44.8)	NA	0 (0)	13.3 ± 6.5	4 (6.9)

Data are expressed as absolute numbers (percentage) or mean ± SD. ¹Data are expressed as mean with standard deviation or range; ²Two patients had EGCs with histology of moderately to poorly differentiated adenocarcinoma; ³Data are expressed as median with or without range; ⁴Fifteen patients had EGCs with mixed type histology; ⁵A total of 103 EGCs in 101 patients were enrolled. UD-EGC: Undifferentiated type early gastric cancer; PD: Poorly-differentiated adenocarcinoma; SRC: Signet-ring cell carcinoma; SM: Submucosa; NA: Not available.

Lymphovascular invasion

Only the absence of lymphovascular invasion was the criterion included by all studies, which was consistent with the results of a meta-analysis revealing that lymphatic tumor invasion is the strongest predictor for LN metastasis in both mucosal and submucosal gastric cancer^[52]. For this reason, EGCs with lymphovascular invasion in endoscopically resected specimen should be treated by further surgery^[22]. However, the Japanese gastric cancer treatment guidelines are not based on the status of lymphovascular invasion. The lymphovascular invasion is involved in the decision of curability of ER, since its evaluation can only be available in specimens obtained by ER. Moreover, the determination of lymphovascular invasion sometimes lacks objectivity possibly because of the inability to distinguish lymphatics from blood vessels on conventional hematoxylin-eosin staining^[82]. Several studies suggested an endoscopic elevated macroscopic type^[83] and a stromal cell-derived factor-1 α as risk factors of lymphovascular invasion^[84] with reports of usefulness of immunohistochemical staining for detection^[82,85,86]. Considering the importance of lymphovascular invasion for prediction of LN metastasis, prospective studies of preoperative prediction for lymphovascular invasion are warranted.

CLINICAL CHARACTERISTICS

Clinical characteristics of recent representative studies on ER for UD-EGC are summarized in Table 3^[73,74,76,80,87-90]. All eight studies were analyzed retrospectively. The numbers of lesions ranged from 46 to 103 lesions and were not large enough to elicit conclusive results. Six studies performed solely ESD^[73,76,80,87,89,90] and the rest carried out both EMR and ESD^[74,88]. Inclusion criteria of these studies were based on the expanded criteria except those of two studies by Kim *et al.*^[80] and Kang *et al.*^[73]. The study by Kim *et al.*^[80] included patients who refused surgery and were treated by ESD as an experimental treatment. The study by Kang *et al.*^[73] included patients with UD-EGC with ulceration. Submucosal invasion and ulcers were noted in 9.7%-19.6% and 1.0%-9.3% of lesions satisfying

the expanded criteria, respectively. The two studies that included patients who refused surgery and lesions with ulcerations in endoscopic finding showed relatively high submucosal invasion and ulceration rates. The inaccurate endoscopic size estimation in UD-EGCs is well noted in the studies, because the lesions with size > 20 mm were noted in up to 45.5% of lesions^[88]. Particularly, the study including intramucosal UD-EGC with size \leq 20 mm regardless of ulcerations revealed notably higher SM invasion (28.3%), ulcer finding (28.3%), and size > 20 mm (51.7%) rates^[73]. The overall inaccuracies of assessment of depth of invasion, ulcerative findings, and size of UD-EGC tumors fulfilling the expanded criteria are not negligible, and thus ESD criteria based on endoscopic and histologic findings in UD-EGC should have more restrictions compared to differentiated EGC. To overcome this limitation, new methods beyond the current level of technology are strongly needed.

SHORT-TERM OUTCOMES

In addition to a very low possibility of LN metastasis, the safety of ESD for UD-EGC can be established based on the feasibility of curative resection with acceptable complication rates and consequently favorable long-term outcomes.

Short-term outcomes, including *en bloc* resection, complete resection, curative resection, and complication rates, of ER for UD-EGC are listed in Table 4^[73,74,76,80,87-90]. Whereas homogeneous definitions of *en bloc* resection applied for the studies, the definitions of complete resection category were heterogeneous depending on the involvement of *en bloc* resection or lymphovascular invasion or submucosal invasion^[73,74,80,87,90]. Additionally, the definitions of curative resection in some studies did not clarify the involvement of *en bloc* resection^[80,89,90]. The overall rates of *en bloc* resection, complete resection, and curative resection of ER for UD-EGCs varied from 83.1% to 100%, from 55.0% to 90.7%, and from 31.1% to 82.5%, respectively, while those of ESD for UD-EGCs meeting the expanded criteria ranged from 91.3% to 99.0%, from 89.7% to 90.7%, and from 63.9% to 82.5%, respec-

Table 4 Short-term outcomes of endoscopic resection for undifferentiated early gastric cancer *n* (%)

Study	LMP	VMP	LVI	<i>En bloc</i> resection	Complete resection	Curative resection	OP after ER ¹	Residual tumor ²	LNM ²	Bleeding	Perforation
Kim <i>et al</i> ^[80]	NA	NA	10 (12.5)	67 (90.5)	54 (73.0)	23 (31.1)	19/51 (37.3)	NA	NA	1 (1.4)	3 (4.1)
Abe <i>et al</i> ^[87]	5 (5.2)	4 (4.1)	3 (3.1)	96 (99.0)	88 (90.7)	62 (63.9)	21/35 (60.0)	1/21 (4.8)	2/21 (9.5)	4 (4.1)	4 (4.1)
Park <i>et al</i> ^[88]	12 (15.6) ³		5 (6.5)	64 (83.1)	NA	35 (45.5)	11/42 (26.2)	NA	0/11 (0.0)	NA	NA
Okada <i>et al</i> ^[89]	5 (4.9) ³		2 (2.0)	102 (99.0)	NA	85 (82.5)	10/18 (55.6)	2/10 (20.0)	0/10 (0.0)	9 (8.7)	1 (1.0)
Kamada <i>et al</i> ^[76]	5 (10.9)	4 (8.7)	4 (8.7)	42 (91.3)	NA	NA	5	1/5 (20.0)	NA	2/46 (4.3)	2 (4.3)
Yamamoto <i>et al</i> ^[90]	1 (1.7)	0 (0.0)	2 (3.4)	57 (98.3)	52 (89.7)	46 (79.3)	8/12 (66.7)	2/8 (25.0)	0/8 (0.0)	5 (8.6)	2 (3.4)
Kang <i>et al</i> ^[73]	14 (23.3)	11 (18.3)	15 (25.0)	60 (100)	33 (55.0)	NA	15/27 (55.6)	6/15 (40.0)	2/15 (13.3)	1 (1.7)	1 (1.7)
Kim <i>et al</i> ^[74]	10 (52.6)	9 (47.4)	NA	49 (84.5)	39 (67.2)	NA	9/19 (47.4)	4/9 (44.4)	1/9 (11.1)	8 (13.8)	1 (1.7)

¹Proportions are ratio of additional operation to incomplete or non-curative endoscopic resection; ²Data are the incidence of residual tumor or lymph node metastasis in specimens obtained by additional operation; ³Data are cases with lateral and/or vertical margin positivity. LMP: Lateral margin positivity; VMP: Vertical margin positivity; LVI: Lymphovascular invasion; OP: Operation; ER: Endoscopic resection; LNM: Lymph node metastasis; NA: Not available.

tively^[76,87,89,90]. The results of ESD for cases within the expanded criteria were comparable with the outcomes of ESD for differentiated EGCs fulfilling the criteria of 93.0% to 95.7% and 81.0% to 91.1% for *en bloc* and complete resection rates, respectively^[91-93]. In contrast, the curative resection rate seems to be lower than that of differentiated EGCs, which is 91.1%^[93]. This may arise from less accurate endoscopic size estimation in UD-EGC due to an ill-defined margin of tumor infiltration^[41,94,95] and several distinct features of UD-EGC, including a larger size and submucosal infiltration that can lead to higher rates of lymphovascular invasion^[73,82,90,96-98], compared with EGCs with differentiated histology. Therefore, the achievement of reasonable curative resection rate in ESD for UD-EGC is critical by means of more precisely defining of curable lesions.

Further surgical treatments were performed in 26.2% to 60.0% of patients with incomplete or non-curative ER. The presence of residual tumor and LN metastasis in surgical specimens after incomplete or non-curative ER were detected in 4.8% to 44.4% and 0% to 13.3% of cases. The overall rates of bleeding and perforation varied from 1.4% to 13.8% and from 1.0% to 4.3%, respectively, whereas those of ESD for UD-EGCs meeting the expanded criteria ranged from 4.1% to 8.7% and from 1.0% to 4.3%, respectively. The results from lesions within the criteria were comparable with the bleeding and perforation rates of ESD for differentiated EGCs fulfilling the criteria, which were 2.1% to 4.9% and 2.4% to 6.6%, respectively^[91-93]. In terms of procedure-related complications, ESD for UD-EGC appears not to be inferior to ESD for EGC with differentiated histology.

LONG-TERM OUTCOMES

Only limited data are available regarding long-term outcomes of ESD for UD-EGC^[51,80,87,89], although the recurrences after ER have been shown in 0% to 6.9% with follow-up durations ranging from 16 to 45.6 mo^[73,74,76,88,90]. Okada *et al*^[89] reported the first study regarding long-term outcomes of ESD for UD-EGC with limited median follow-up periods. The 5-year cause-specific survival rate among 78 patients with curative resection of UD-EGC

was 100%, which was as high as the reported data for gastrectomy^[99,100]; however, the median follow-up period was only 36 mo. The cumulative 3- and 5-year disease-free survival rates are 96.7% (95%CI: 92.0%-100%) and 96.7% (95%CI: 92.0%-100%), respectively. During the follow-up period, all patients survived, and no cases of local recurrence and/or distant metastasis were observed. There were only second ESDs for one synchronous lesion of one patient 6 mo after the primary ESD (1/78, 1.3%) and two metachronous lesions of another patient after 23 mo (1/78, 1.3%).

Abe *et al*^[87] analyzed the overall 5-year survival of 79 UD-EGC patients that underwent ESD, while they enrolled 97 patients for short-term outcomes analyses. Of the 46/79 patients in the long-term outcome group who had curative resection, none had local recurrence or LN or distant metastasis, and none died of gastric cancer during a median follow-up of 76.4 mo. The 5-year overall survival rate after curative resection was 93.0%, and no patient died of gastric cancer. These favorable results are comparable to long-term outcomes of those who underwent ESD for differentiated EGC and surgery for intramucosal gastric cancer, which have the overall survival rates of 92.4% to 97.1%^[101-103] and 93.5%^[104], respectively. The 5-year cumulative incidence of metachronous gastric cancer was 11.4% in the patients with curative resection and they were treated with ESD.

Kim *et al*^[80] reported consistent results showing a local recurrence rate of 5.5% and a 5-year overall survival rate of 93.7% among 74 enrolled patients with median follow-up period of 34 mo (range 7-81 mo). All 4 recurred lesions did not meet the expanded indications and all underwent noncurative resection. There was no mortality related to ESD for treatment of EGC during follow-up, whereas a total of five patients died after ESD due to underlying diseases (four patients) and lung metastasis (one patient).

The questionnaire study on long-term outcomes of curative ESD for EGC at six Japanese institutions with follow-up rates of at least 90% over a minimum 5-year period was reported by Oda *et al*^[51]. Of a total of 1289 patients with curative resections for the expanded indications, the long-term outcomes of 58 patients with

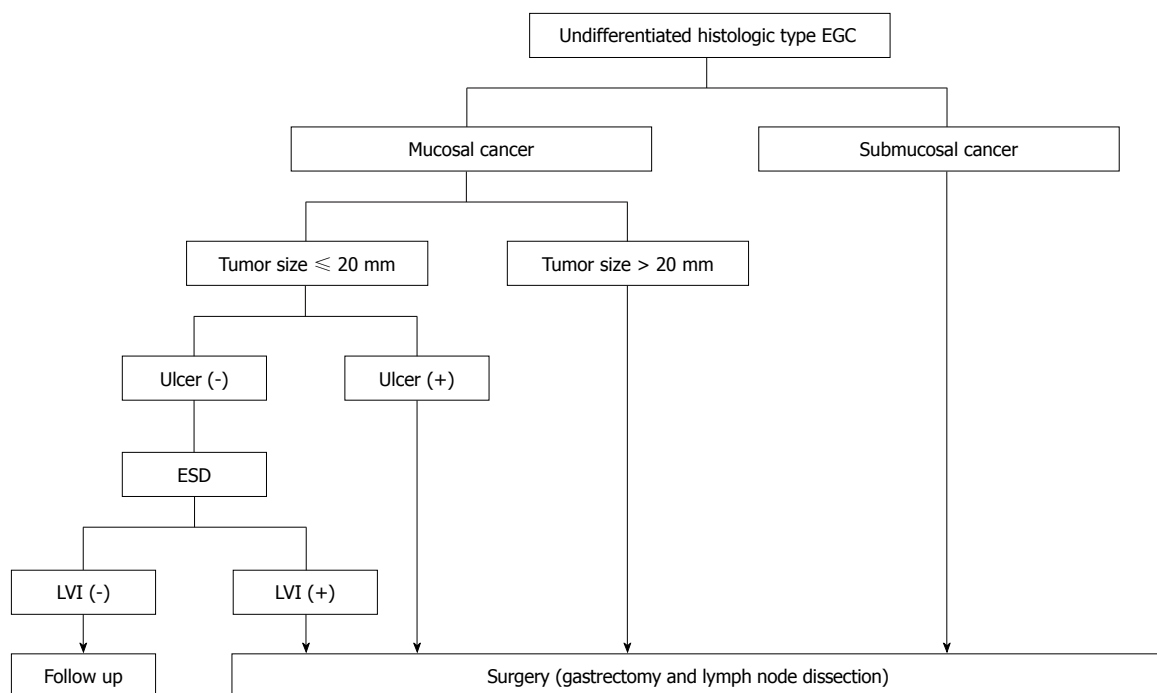


Figure 2 Treatment algorithm for undifferentiated type early gastric cancer according to depth of invasion, tumor size, ulceration, and lymphovascular invasion. EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; LVI: Lymphovascular invasion.

intramucosal UD-EGC ≤ 20 mm in size without ulcerations were analyzed, and 96.6% of them (56/58) were followed up for at least 5 years. The overall mortality rate was 10.7% (6/56), and there was no local recurrence, or distant metastasis, or gastric cancer-related death during their long-term follow-up periods.

In addition to the 5-year survival outcomes, the long-term data on metachronous EGCs after ESD for UD-EGC are also lacking. The cumulative incidences of metachronous lesions varied from 1.3% to 11.4% during median follow-up periods with a range of 36–76.4 mo^[87–89]. This finding is comparable to the annual incidences of metachronous lesions after ESD for differentiated EGC, which ranged from 1.9% to 3.9%^[105,106] as well as reports of remnant gastric cancers occurring in 1.8% to 5% of patients who have had surgical treatment for gastric cancer^[107,108]. Therefore, careful periodic endoscopic surveillance should be performed, because UD histology is a possible risk factor associated with the occurrence of metachronous lesions after ER^[109]. Although the clinical importance of scheduled endoscopic surveillance after curative resection are recently evaluated through large-volume multicenter study^[110], further studies on surveillance follow-up after curative ESD for UD-EGC, compared with curative cases in differentiated EGC, are warranted.

PROSPECTS FOR THE FUTURE

A combination of laparoscopic sentinel node biopsy and ESD for UE-EGC is an attractive option as a novel, whole stomach-preserved, minimally invasive approach with histological confirmation of LN metastasis. How-

ever, a number of technical controversies should be resolved to accept the laparoscopic sentinel node mapping and consequent intraoperative ESD as an acceptable treatment. These include the accuracy of intraoperative pathological diagnosis, the necessity of full-thickness resection, and the possibility of cancer cells being present in afferent lymphatic vessels leading to sentinel nodes^[111]. In particular, a well-designed, multicenter feasibility study of laparoscopic sentinel node mapping and biopsy for UD-EGC should be conducted, though the accuracy of determining LN status by laparoscopic sentinel node biopsy is generally acceptable in cases with EGC^[112–114].

Natural orifice transluminal endoscopic surgery (NOTES) is another promising area to supplement ESD by providing for the means for performing secure gastric closure at the time of the accidental perforation without recourse to surgical operation, or as a complement for endoscopic sentinel node biopsy^[115–117]. The potential indications of NOTES have been suggested with a wide spectrum of upper gastrointestinal diseases, including submucosal malignancy and morbid obesity in female patients^[118–120]. Furthermore, the first prospective study of 14 patients with EGC who had a risk for LN metastasis and who were treated by hybrid NOTES was reported and suggested that hybrid NOTES may be useful as a bridge between ER and laparoscopic surgery^[121]. Nevertheless, given the relatively technical complexity and limits, NOTES has not been proven to remarkably superior to laparoscopic means so far.

CONCLUSION

Based on the results of studies on short- and long-term

outcomes, the expanded criteria for ESD of UD-EGC are feasible with reference to therapeutic efficacy and safety in the long-term period if curative resection is accomplished, although more long-term outcomes are needed. We now suggest the treatment algorithm for UD-EGC according to depth of invasion, tumor size, ulceration, and lymphovascular invasion (Figure 2). This is consistent with the conditions of curative resection according to the Japanese gastric cancer treatment guidelines^[23,26]. However, we should recognize the limitation of current diagnostic and histological tools to predict LN metastasis. The innovative improvement of preoperative imaging modalities and well-defined criteria predictive of LN metastasis from multicenter, prospective studies would reduce the limitation.

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