

## Outcomes of Endoscopic Submucosal Dissection for Early Gastric Cancer with Undifferentiated-Type Histology: A Clinical Simulation Using a Non-Selected Surgical Cohort

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**Background/Aims:** Outcomes of endoscopic submucosal dissection (ESD) for undifferentiated-type early gastric cancer (EGC) need to be further evaluated. We aimed to simulate the outcomes of ESD for undifferentiated-type EGC from a surgical database. **Methods:** Among 802 patients who underwent gastrectomy with endoscopic biopsy for poorly differentiated adenocarcinoma (PD-type) or signet ring cell carcinoma (SRC-type), ESD candidates meeting the expanded indication (n=280) were selected by reviewing the endoscopic images. According to the surgical pathologic results, the outcomes of the ESD simulation were evaluated. **Results:** Among the candidates, 104 (37.1%) were PD-type and 176 (62.9%) were SRC-type. The curative resection (CR) rate was 42.1%. Among the patients with CR, three patients (2.5%) showed lymph node metastasis (LNM). Three EGCs with CR and LNM were mucosal cancers  $\geq 1.0$  cm in size. The CR rate was higher in the SRC-type than in the PD-type (48.3% vs 31.7%, respectively,  $p=0.007$ ). In the SRC-type, the CR rate was increased, with a smaller size criterion for the ESD indication, but was similar between the 1.0 cm and 0.6 cm criteria (63.3% and 63.6%, respectively), whereas the CR rate was below 50% in all of the different tumor size criteria (2.0 to 0.6 cm) in the PD-type. **Conclusions:** In undifferentiated-type EGC, ESD should be considered in selected patients with tumor sizes  $<1$  cm and SRC histology. (*Gut Liver* 2018;12:263-270)

**Key Words:** Early gastric cancer; Endoscopic mucosal resection; Undifferentiated

### INTRODUCTION

Endoscopic submucosal dissection (ESD) has been established as a standard treatment of early gastric cancers (EGCs) meeting the absolute indication. In addition, expanded indications were proposed by Gotoda *et al.*<sup>1</sup> based on detailed pathologic analysis of surgical database about the risk factors of lymph node (LN) metastasis. Recent guidelines include expanded indications for possible candidate of endoscopic treatment of EGC, although Japanese guidelines consider them experimental.<sup>2,3</sup> Expanded indications can be divided into two subgroups, differentiated-type and undifferentiated-type EGC.<sup>4</sup> Although clinical outcomes of endoscopic treatment for differentiated-type EGC meeting expanded indications were excellent,<sup>5-10</sup> it remains unclear for undifferentiated-type EGC.

Although there have been a number of studies about ESD for undifferentiated-type EGC,<sup>11-16</sup> they have an important limitation of selection bias. Most of them are small retrospective studies with unclearly defined inclusion criteria. Patients were usually enrolled when the final histology after ESD was undifferentiated-type histology, either poorly differentiated adenocarcinoma (PD-type) or signet ring cell carcinoma (SRC-type). The initial endoscopic biopsy-proven histology prior to ESD, however, was heterogeneous. Many studies thus included patients who showed differentiated-type EGC on the forceps biopsy and undifferentiated-type EGC on the final ESD pathology.<sup>12,16</sup> Indeed, most cases with undifferentiated-type histology were not prospectively selected by expanded indications but were retrospectively collected by the final ESD pathology.

In our institution, patients with endoscopic biopsy-proven undifferentiated-type gastric cancer underwent surgery. In order

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Received on June 7, 2017. Revised on July 19, 2017. Accepted on August 18, 2017. Published online December 26, 2017

pISSN 1976-2283 eISSN 2005-1212 <https://doi.org/10.5009/gnl17247>

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to avoid selection bias, we selected ESD candidates (feasible for ESD) meeting expanded indications from the surgical cohort of endoscopically suspected undifferentiated-type EGC on the forceps biopsy. Using these ESD candidates, we simulated ESD outcomes with reference to surgical pathologic results. In addition, we assessed the outcomes of simulated ESD with various size criteria of expanded indication and with a different curative resection (CR) size definition to suggest the optimal size criteria for ESD in undifferentiated-type EGC.

## MATERIALS AND METHODS

### 1. Subjects

Between January 2014 and December 2014, subtotal gastrectomy or total gastrectomy for gastric cancer was performed in a total of 1,336 consecutive patients at Samsung Medical Center, Seoul, Korea. Among them, we identified 802 patients who had undifferentiated-type (PD-type or SRC-type) gastric cancer on the result of endoscopic forceps biopsy. From them, we included 537 patients whose endoscopic diagnosis was EGC. Endoscopic images of the 537 patients were reviewed by an ESD expert (J.H.L.) to select ESD candidates meeting expanded indications (tumor with a diameter of 20 mm or smaller, confined to mucosa, and without ulceration). Findings of abdomen computed tomography were used as a reference to exclude cases with distant metastasis or regional LN metastasis. Finally, 280 EGCs seemed to be feasible for ESD and underwent ESD simulation (Fig. 1). This study protocol was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) at Samsung Medical Center, Seoul, Korea (IRB number: 2015-06-056-001). The IRB waived the requirement for informed consent, because we used de-identified data.

### 2. Data collection

The following information were collected from each patient: age, sex, endoscopic tumor size, tumor location, endoscopic tumor gross type, pathologic tumor size, final tumor pathology, depth of tumor invasion, and presence of LN metastasis on pathology. Endoscopic tumor size was defined as the maximal tumor size at endoscopy and pathologic tumor size was measured upon the microscopic examination from the resected specimen. Tumor locations were categorized by longitudinal axis of the stomach. The axis was divided into three sections (the upper third containing the fundus, cardia, and upper body, the middle third containing the mid-body, lower body, and angle, and the lower third containing the antrum and pylorus).<sup>17</sup> Tumor gross types were classified by their predominant type. The protruded type and superficial elevated type were classified as elevated type. The superficial flat type was classified as flat type, and the superficial depressed type and excavated type were classified as depressed type.<sup>18</sup>

The fixed ESD specimen was sectioned serially at 2-mm

intervals, parallel to a line that included the closest resection margin of the specimen so that both lateral and vertical margins could be assessed. The depth of tumor invasion was then evaluated along with lymphovascular invasion and differentiation. However, the surgical specimen was sectioned serially at 4-mm intervals.

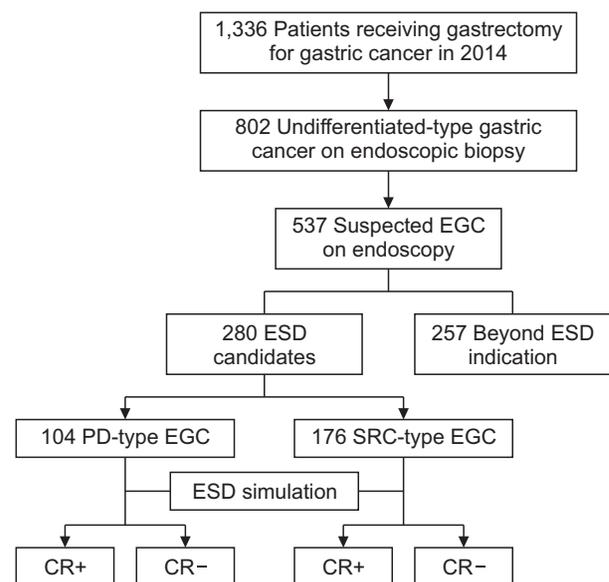
### 3. Outcomes of simulated ESD

According to the final pathologic result of surgical specimen, outcomes of simulated ESD were evaluated. CR rate was assessed on the assumption that ESD was done by *en bloc* resection without technical failure. CR of undifferentiated-type EGC was defined when tumor was smaller than 2 cm, confined to mucosa lesion, without ulceration, and without lymphovascular invasion in the surgical specimens.<sup>19</sup>

In addition, CR rate was assessed when different size criteria (1.5, 1.0, and 0.6 cm) of expanded ESD indication for undifferentiated-type EGC were applied. Modified CR of undifferentiated-type EGC defined when tumor was smaller than 3 cm, confined to mucosa lesion, and without ulceration in the surgical specimens was also assessed.

### 4. Statistical analysis

Statistical results are presented as the mean±standard deviation or number of patients (%). Continuous variables were com-



**Fig. 1.** Subject flow. Among the 1,336 gastric cancer patients undergoing gastrectomy in 2014, 802 undifferentiated-type gastric cancer patients were identified based on endoscopic biopsy. Among them, 537 patients whose endoscopic diagnosis was early gastric cancer (EGC) were included. By reviewing endoscopic images of the 537 patients, we selected endoscopic submucosal dissection (ESD) candidates meeting the expanded indications. The curative resection (CR) rate was assessed on the assumption that the ESD was performed by *en bloc* resection without technical failure. PD, poorly differentiated; SRC, signet ring cell.

pared parametrically using Student t-test. Categorical variables were compared using the chi-square test or Fisher exact test as appropriate. Two-sided p-values <0.05 were taken as statistically significant. Statistical analyses were conducted using the SPSS Statistics version 21.0 software (IBM Corp., Armonk, NY, USA).

## RESULTS

### 1. Characteristics of endoscopically suspected undifferentiated-type EGCs

Table 1 shows the characteristics of endoscopically suspected EGC with undifferentiated-type histology on the forceps biopsy. Among the 537 EGCs, 206 (38.3%) were PD-type and 331 (61.7%) were SRC-type. The mean endoscopic tumor size was  $2.17 \pm 1.41$  cm. Ulceration was observed in 95 (17.7%) tumors at endoscopy. Tumor location was upper in 60 (11.1%), middle in 316 (58.9%), and lower stomach in 161 (30.0%). The tumor gross type was flat/depressed in 486 (90.5%) and elevated in 51

**Table 1.** Baseline Characteristics of Endoscopically Suspected Undifferentiated-Type Early Gastric Cancer

	Total (n=537)	PD-type (n=206)	SRC-type (n=331)	p-value*
Age, yr	52.9±11.2	54.0±11.8	52.2±10.8	0.079
Male sex	258 (48.0)	105 (51.0)	153 (46.2)	0.284
Endoscopic tumor size, cm	2.17±1.41	2.21±1.41	2.14±1.41	0.613
Ulceration at endoscopy	95 (17.7)	39 (18.9)	56 (16.9)	0.563
Pathologic tumor size, cm	3.03±2.05	3.15±1.99	2.95±2.09	0.275
Size discrepancy, cm	-0.85±1.69	-0.94±1.60	-0.80±1.75	0.366
Final pathology				<0.001
MD	38 (7.0)	28 (13.6)	10 (3.0)	
PD	269 (50.0)	153 (74.3)	116 (35.0)	
SRC	230 (43.0)	25 (12.1)	205 (62.0)	
Location				0.956
Upper	60 (11.1)	24 (11.7)	36 (10.9)	
Middle	316 (58.9)	120 (58.3)	196 (59.2)	
Lower	161 (30.0)	62 (30.0)	99 (29.9)	
Gross type				0.022
Flat/depressed	486 (90.5)	194 (94.2)	292 (88.2)	
Elevated	51 (9.5)	12 (5.8)	39 (11.8)	
Depth of invasion				0.539
Mucosa	332 (61.8)	124 (60.2)	208 (62.8)	
Submucosa and beyond	205 (38.2)	82 (39.8)	123 (37.2)	
Lymphovascular invasion	83 (15.5)	39 (18.9)	44 (13.3)	0.079
LN metastasis	73 (13.6)	28 (13.6)	45 (13.9)	0.988

Data are presented as mean±SD or the number (%).

PD, poorly differentiated; SRC, signet ring cell; MD, moderately differentiated; LN, lymph node.

\*Comparison between the PD-type and the SRC-type.

(9.5%). The mean pathologic tumor size was  $3.03 \pm 2.05$  cm and size discrepancy between endoscopic estimation and surgical specimen was  $-0.85 \pm 1.69$  cm. According to the final pathologic results, 38 EGCs (7.0%) were differentiated-type EGCs (all moderately differentiated), 269 (50.0%) were PD-type EGCs, and 230 (43.0%) were SRC-type EGCs; 332 (61.8%) were confined to the mucosal layer, 168 (31.3%) were invading into the submucosal layer, and 37 (6.9%) were beyond the submucosal layer; 83 (15.5%) had lymphovascular invasion; LN metastasis was found in 73 EGCs (13.6%). These characteristics of undifferentiated-type EGC did not differ by endoscopic forceps biopsy-proven histology (PD-type vs SRC-type) except for the tumor gross type and final histologic type. PD-type EGD had more frequent flat/depressed type (94.2% vs 88.2%,  $p=0.022$ ) and showed more frequent histologic discrepancy ( $p<0.001$ ) than SRC-type EGC.

### 2. Characteristics of ESD candidate EGCs

Table 2 shows the characteristics of ESD candidate EGCs (n=280) meeting expanded indications among the endoscopically suspected undifferentiated-type EGCs. The mean age was  $52.5 \pm 10.9$  years and 131 patients (46.0%) were male. The mean

**Table 2.** Comparison of the Characteristics between ESD Candidates and Beyond ESD Indication

	Expanded indication (n=280)	Beyond ESD indication (n=257)	p-value
Age, yr	52.5±10.9	53.35±11.5	0.385
Male sex	131 (46.8)	127 (49.4)	0.542
Endoscopic tumor size, cm	1.21±0.46	3.21±1.36	<0.001
Ulceration at endoscopy	0	95 (37.0)	<0.001
Pathologic tumor size, cm	2.13±1.29	4.01±2.27	<0.001
Size discrepancy, cm	-0.92±1.24	-0.79±2.07	0.395
Pathology			0.544
PD	104 (37.1)	102 (39.7)	
SRC	176 (62.9)	155 (60.3)	
Location			<0.001
Upper	16 (5.8)	44 (17.1)	
Middle	166 (59.2)	150 (58.3)	
Lower	98 (35.0)	63 (24.5)	
Gross type			0.678
Flat/depressed	252 (90.0)	234 (91.0)	
Elevated	28 (10.0)	23 (9.0)	
Depth of invasion			<0.001
Mucosa	208 (74.2)	124 (48.2)	
Submucosa and beyond	72 (25.8)	133 (51.8)	
Lymphovascular invasion	22 (7.8)	61 (23.7)	<0.001
LN metastasis	22 (7.8)	51 (19.8)	<0.001

Data are presented as mean±SD or the number (%).

ESD, endoscopic submucosal dissection; PD, poorly differentiated; SRC, signet ring cell; LN, lymph node.

endoscopic tumor size was  $1.21 \pm 0.46$  cm. On the forceps biopsy, 104 (37.1%) were PD-type and 176 (62.9%) were SRC-type. Tumor location was upper in 16 (5.8%), middle in 166 (59.2%), and lower stomach in 98 (35.0%). The endoscopic tumor gross type was flat/depressed in 252 (90.0%) and elevated in 28 (10.0%). The mean pathologic tumor size was  $2.13 \pm 1.29$  cm. Size discrepancy between endoscopic estimation and surgical specimen was  $-0.92 \pm 1.24$  cm. According to the final pathologic results, 208 EGCs (74.2%) were confined to the mucosal layer and 72 (25.8%) were invading into the submucosal layer; LN metastasis was found in 22 (7.8%).

There were no differences between ESD candidate EGCs ( $n=280$ ) and EGCs beyond ESD indication ( $n=257$ ) in terms of age, sex, size discrepancy, endoscopic gross type, and forceps biopsy histology. However, ulceration was observed at endoscopy in 95 (37.0%) of beyond ESD indication group. In addition, ESD candidate group had smaller endoscopic and pathologic tumor sizes ( $1.21 \pm 0.46$  cm and  $2.13 \pm 1.29$  cm vs  $3.21 \pm 1.36$  cm and  $4.01 \pm 2.27$  cm, all  $p < 0.001$ ), less frequent upper stomach and more frequent lower stomach location (5.8% and 35.0% vs 17.1% and 24.5%,  $p < 0.001$ ), less frequent submucosal tumor invasion (25.8% vs 51.8%,  $p < 0.001$ ), less frequent lymphovascular invasion (7.8% vs 23.7%,  $p < 0.001$ ), and less frequent LN metastasis (7.8% vs 19.8%,  $p < 0.001$ ) than beyond ESD indication group.

### 3. Outcomes of simulated ESD

CR rate was 42.1% (118) in the ESD candidate EGCs ( $n=280$ ). CR rate was lower in PD-type EGC than in SRC-type EGC (31.7% vs 48.3%,  $p=0.007$ ). Causes of non-CR ( $n=162$ ) were as follows: tumor size  $>2$  cm in diameter in 121 (74.7%), submucosa or beyond tumor invasion in 72 (44.5%), and lymphovascular

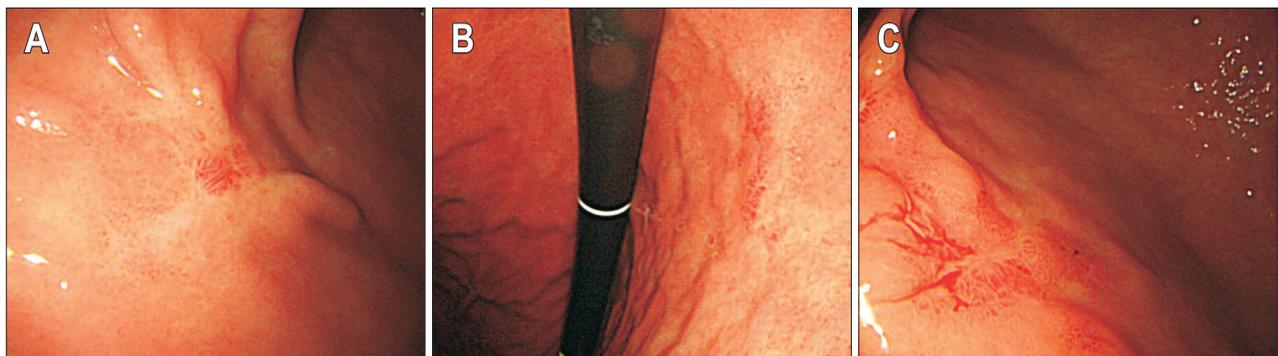
invasion in 22 (13.6%). According to the endoscopic forceps biopsy-proven histology, causes of non-CR were as follows: tu-

**Table 3.** Comparison of the Characteristics between the CR and Non-CR Groups among the Endoscopic Submucosal Dissection Candidates Meeting the Expanded Criteria

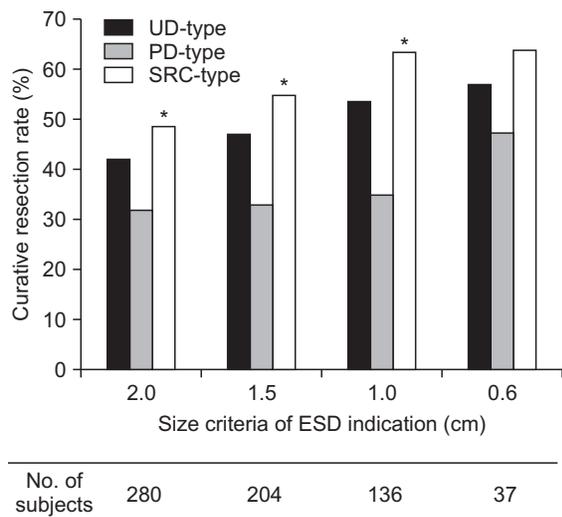
	CR (n=118)	Non-CR (n=162)	p-value
Age, yr	$51.9 \pm 10.3$	$53.0 \pm 11.3$	0.847
Male sex	56 (47.4)	75 (46.2)	0.421
Endoscopic tumor size, cm	$1.08 \pm 0.43$	$1.30 \pm 0.46$	$<0.001$
Pathologic tumor size, cm	$1.22 \pm 0.45$	$2.78 \pm 1.30$	$<0.001$
Size discrepancy, cm	$-0.14 \pm 0.43$	$-1.48 \pm 1.33$	$<0.001$
Pathology			0.007
PD	33 (28.0)	71 (45.6)	
SRC	85 (72.0)	91 (54.4)	
Location			0.080
Upper	3 (2.5)	13 (8.0)	
Middle	68 (57.6)	98 (60.5)	
Lower	47 (39.9)	51 (31.5)	
Gross type			0.747
Flat/depressed	107 (90.6)	145 (89.5)	
Elevated	11 (9.4)	17 (10.5)	
Depth of invasion			$<0.001$
Mucosa	118 (100)	90 (55.5)	
Submucosa and beyond	0	72 (44.5)	
Lymphovascular invasion	0	22 (13.6)	$<0.001$
LN metastasis	3 (2.5)	19 (11.7)	0.004

Data are presented as mean  $\pm$  SD or the number (%).

CR, curative resection; PD, poorly differentiated; SRC, signet ring cell; LN, lymph node.



**Fig. 2.** Esophagogastroduodenoscopy appearances of three undifferentiated-type early gastric cancers meeting the curative resection criteria and exhibiting lymph node (LN) metastasis. All were mucosal cancers with mixed histology of poorly differentiated adenocarcinoma (PD-type) with a signet ring cell carcinoma (SRC-type) component. (A) A 57-year-old female with a 1.3 cm, ill-defined, pale, depressed lesion with abnormal converging folds, such as cutting and tapering on the anterior side of the angle. Endoscopic biopsy revealed the SRC-type, and the final result was a 1.5 cm mucosal cancer with metastasis to two out of 67 regional LNs. (B) A 64-year-old female with a 1.7 cm, pale, depressed lesion with an erythematous tumor island on the posterior wall of the lower body. Endoscopic biopsy indicated the PD-type, and the final result was a 1.1 cm mucosal cancer with metastasis to one out of 42 regional LNs. (C) A 46-year-old female with a 1.0 cm, pale, geographic, depressed lesion with an erythematous tumor island on the antero-greater curvature side of the proximal antrum. Endoscopic biopsy revealed the PD-type, and the final result was a 1.4 cm mucosal cancer with metastasis to two out of 37 regional LNs.



**Fig. 3.** Number of endoscopic submucosal dissection (ESD) candidates and their curative resection rate according to the different size criteria of the ESD indication.

UD, undifferentiated; PD, poorly differentiated; SRC, signet ring cell. \* $p < 0.05$  on comparison between PD-type and SRC-type.

mor size  $> 2$  cm in diameter in 51 (71.8%) of PD-type and in 70 (76.9%) of SRC-type, submucosal or beyond tumor invasion in 35 (49.3%) of PD-type and in 37 (40.7%) of SRC-type, and lymphovascular tumor invasion in 12 (16.9%) of PD-type and in 10 (11.0%) of SRC-type.

In Table 3, characteristics were compared between CR and non-CR groups. There were no differences in terms of age, sex, tumor location, and endoscopic tumor gross type between the two groups. However, CR group had smaller endoscopic and pathologic tumor sizes and size discrepancy ( $1.08 \pm 0.43$  cm,  $1.22 \pm 0.45$  cm, and  $-0.14 \pm 0.43$  cm vs  $1.30 \pm 0.46$  cm,  $2.78 \pm 1.30$  cm, and  $-1.48 \pm 1.33$  cm, respectively; all  $p < 0.001$ ), lower frequent PD-type EGC (28.0% vs 45.6%,  $p = 0.007$ ), and less frequent LN metastasis (2.5% vs 11.7%,  $p = 0.004$ ) than non-CR group. Among the three EGCs with CR and LN metastasis, two were PD-type and one was SRC-type and all were mucosal cancers larger than 1.0 cm in size (Fig. 2).

When CR size criterion was modified from 2 cm to 3 cm, CR rate was 60.7% (170/280). However, LN metastasis was found in five (2.9%) patients with CR. According to the endoscopic forceps biopsy-proven histology, CR rate was higher in SRC-type EGC than in PD-type EGC (68.7% vs 47.1%,  $p < 0.001$ ) while rate of LN metastasis did not differ significantly (1.7% vs 6.1%,  $p = 0.145$ ) between SRC-type and PD-type EGC groups.

#### 4. Outcomes of simulated ESD for smaller EGCs

In Fig. 3, number of ESD candidates and their CR rate according to different size criteria (2.0, 1.5, 1.0, and 0.6 cm) of ESD indication for undifferentiated-type EGC are shown. When a size criterion of 1.5 cm was applied, number of ESD candidates was decreased by 27.1% (from 280 to 204) with CR rate of 47.1%

(32.4% in PD-type and 54.9% in SRC-type,  $p = 0.002$ ). Among the patients with CR, LN metastasis was found in two patients (2.1%, 2/96; one PD-type and one SRC-type) (Fig. 2). When 1.0 cm, number of ESD candidates was decreased by 51.4% (to 136) with CR rate of 53.6% (34.8% in PD-type and 63.3% in SRC-type,  $p = 0.002$ ). Among the patients with CR, LN metastasis was found in one patients (1.4%, 1/73; PD-type) (Fig. 2). When 0.6 cm, number of ESD candidate was decreased by 86.8% (to 37) with CR rate of 56.8% (46.7% in PD-type and 63.6% in SRC-type,  $p = 0.306$ ). Among the patients with CR, LN metastasis was not found. In PD-type EGC, CR rate was below 50% in all of different tumor size criteria (2.0, 1.5, 1.0, and 0.6 cm). In SRC-type EGC, CR rate was increased with smaller size criterion of ESD indication and was similar between 1.0 cm and 0.6 cm criteria.

## DISCUSSION

ESD has not been considered as a treatment option for undifferentiated-type EGC. As several studies showed LN metastasis is negligible in small undifferentiated-type mucosal lesion,<sup>20-23</sup> undifferentiated-type EGC was included in the expanded ESD indication in recent guidelines as an investigational treatment. Although there have been several studies suggesting ESD as an alternative treatment option in undifferentiated-type EGC,<sup>13,14,24</sup> large scaled long-term data of ESD is still insufficient. Furthermore, previous studies have a limitation of having selection bias as we discussed in the premise. To minimize the selection bias, we did ESD simulation using a non-selected surgical cohort and analyzed the outcomes according to the histopathological results on the assumption that ESD was done by *en bloc* resection without technical failure. CR rate of ESD simulation was calculated as 42.1%. However, CR rate was higher in SRC-type EGC than in PD-type EGC (48.3% vs 31.7%,  $p = 0.007$ ). In SRC-type EGC, CR rate was increased with smaller size criterion of ESD indication and was similar between 1.0 cm and 0.6 cm criteria while CR rate was below 50% in all of different tumor size criteria (2.0, 1.5, 1.0, and 0.6 cm) in PD-type EGC. In addition, no LN metastasis was found when CR was achieved in tumor smaller than 1 cm in size. Thus we could suggest that ESD for undifferentiated-type EGC should be considered in more selected patients, such as tumor size smaller than 1 cm with histology of SRC to achieve better outcomes.

In the previous studies, long-term outcomes of ESD for undifferentiated-type EGC are good when CR is achieved.<sup>14,15,25</sup> CR rates of ESD simulation in the present study are consistent with that of the previous real ESD studies.<sup>15,25</sup> In the recent retrospective study,<sup>25</sup> CR was also achieved more frequently in SRC-type EGC (61.4%) than in PD-type EGC (45.1%) after ESD for undifferentiated-type EGC. In our results, common causes of non-CR are tumor size  $> 2$  cm in diameter (74.7%) and submucosa or beyond tumor invasion (44.4%). To improve CR rate, accurate

determination of depth and extent of tumor is thus necessary. Unfortunately, however, this can be difficult in undifferentiated-type EGC. The accuracy of depth diagnosis by endoscopic ultrasound (EUS) in undifferentiated-type EGC has been known to be worse than in differentiated-type EGC.<sup>26</sup> Undifferentiated-type EGC can extend along the proliferative zone in the middle layer of the mucosa, leaving normal ducts covering the superficial epithelium.<sup>27</sup> In this case, even magnifying endoscopy with narrow band imaging was less useful.<sup>28</sup> In our results, larger tumor showed a tendency to be more underestimated in size on endoscopy while tumor <1 cm in size was not underestimated (Supplementary Table 1). In addition, among ESD candidates prediction of tumor depth was accurate only in 67.8% when tumor is >1 cm and ≤2 cm in size while 81.0% when ≤1 cm. Taken together, application of ESD for small lesion less than 1 cm and pretreatment circumferential mapping biopsy could be optimal strategy for improving CR rate. Furthermore, wide marking beyond estimated lesion during ESD would be necessary to secure enough resection margins.

In the previous report, PD-type EGC has pathological features such as submucosal invasion, ulcer, and lymphatic invasion that are less favorable to endoscopic treatment than that of SRC-type EGC.<sup>19</sup> We thus should take into account separate approach to these two types of EGC, not as a united type of undifferentiated-type histology. Indeed, CR rate was constantly below 50% in various size criteria of ESD indication while CR rate was increased beyond 60 % with smaller size criterion of ESD indication (1.0 and 0.6 cm).

The most important factor concerning ESD with curative intent is the prediction of LN metastasis. However, the reported rate of LN metastasis in undifferentiated-type EGC ranges from 5.7% to 20% which is higher than that of differentiated-type EGC.<sup>29-33</sup> Although Gotoda *et al.*<sup>1</sup> reported that LN metastasis was not found in the undifferentiated-type EGC smaller than 2 cm, confined to mucosa without ulceration, other studies proposed that expanded ESD indication for undifferentiated-type EGC should be narrowed to the smaller lesion.<sup>19,21,34,35</sup> These are consistent with our data which show no EGC smaller than 1.0 cm with CR had LN metastases (Supplementary Table 2). Thus, pathologic expanded indications with 2.0 cm size criterion may not be a good endpoint to define the optimal selection criteria for ESD. Indeed, the rate of LN metastasis was 2.5% in CR group. However, the risk of LN metastasis is 2.9% and 1.6% even in the low risk group by the prediction model for SRC-type and PD-type, respectively.<sup>36,37</sup> Therefore, expanded indication could be used to determine the feasible selection criteria for ESD in undifferentiated-type EGC. However, although the risk for LNM is very low, it should not be considered negligible in endoscopic resection.

Three EGCs (two PD-type and one SRC-type on endoscopic biopsy) with CR and LN metastasis had mixed histology with SRC component on the final pathologic results and were devel-

oped in women in their 40s to 60s. Previous case reports with LN metastasis from undifferentiated-type mucosal gastric cancer satisfying the expanded criteria showed similar characteristics of middle age women with mixed histology.<sup>38,39</sup> From these observations we could suggest that middle age woman with mixed histology needs more intense surveillance of recurrence although CR has been achieved.

The current study has some limitations. Firstly, ESD simulation was done on the assumption that ESD was done by *en bloc* resection without technical failure. Thus CR rate could be lower in real practice considering nonlifting, piecemeal resection, and complications during procedure. However, recent two studies reported the *en bloc* resection rate of 99% in ESD for undifferentiated-type EGC.<sup>14,15</sup> In addition, as wide marking of 10 mm beyond estimated lesion is usually applied in ESD for undifferentiated-type EGC difference in CR rate between ESD simulation and real ESD may not be significant. Second, preoperative evaluation using EUS was not done and could not be taken into account in our simulation. Although the role of EUS in predicting depth and extent of tumor is limited in undifferentiated-type EGC, preoperative EUS might enhance CR rate. Third, pathologic result of surgical specimen could underestimate depth of invasion and presence of lymphovascular invasion. Lastly, ESD candidates meeting expanded indications were selected from an ESD expert by reviewing endoscopic images. This may limit the generalizability of our results. Nevertheless, our study has strengths of minimized selection bias and large sample size. Because patients with endoscopic biopsy-proven undifferentiated-type gastric cancer underwent surgery in our institution, we could avoid selection bias from the non-selected surgical cohort. Using ESD simulation methods, we could analyze relatively large samples of undifferentiated-type EGC. In conclusion, our ESD simulation with a non-selected surgical cohort results suggest that ESD should be considered in more selected patients, such as tumor size smaller than 1 cm with histology of SRC to achieve better outcomes in undifferentiated-type EGC.

## CONFLICTS OF INTEREST

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

## ACKNOWLEDGEMENTS

Author contributions: D.S.K. and Y.W.M. analyzed the data and wrote the manuscript; S.H.K. and S.H.J. collected data; H.L., B.H.M., J.J.K., K.M.K., T.S.S., and S.K. were involved in the study design and undertook critical revision of the manuscript; J.H.L. designed the study and revised the manuscript.

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