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Review Article

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Endoscopic Resection of Undifferentiated-type Early Gastric Cancer

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ABSTRACT

Early detection of gastric cancer is crucial because the survival rate can be improved through curative treatment. Although surgery and gastrectomy with lymph node dissection remain as the gold standard for curative treatment, early gastric cancer (EGC) with negligible risk of lymph node metastasis can be treated with endoscopic resection (ER), such as endoscopic submucosal dissection. Among gastric cancers, undifferentiated-type cancer is distinguished from differentiated-type cancer in various aspects in terms of clinical features and pathophysiology. The undifferentiated-type cancer is also known to be associated with an aggressive behavior and a poor prognosis. Therefore, the indication of ER for undifferentiated EGC is limited compared with differentiated-type. Recent studies have reported that ER for undifferentiated EGC is safe and shows favorable short- and long-term outcomes. However, it is necessary to understand the details of the research results and to selectively accept them. In this review, we aimed to evaluate the current practice guidelines and the short-term and long-term outcomes of ER for undifferentiated type EGC.

Keywords: Stomach neoplasms; Endoscopic submucosal dissection

INTRODUCTION

Early gastric cancer (EGC) is defined as an invasive gastric cancer that invades no more deeply than the submucosa, irrespective of lymph node metastasis (LNM) [1,2]. In Korea and Japan, EGC accounts for up to 70% of newly diagnosed gastric cancers [3,4]. Although the mainstay treatment for gastric cancer, whether early or advanced, is surgical resection, for EGC with negligible risk of LMN, endoscopic resection (ER), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), has been widely accepted as a minimally invasive treatment option [5-9]. The undifferentiated types of gastric adenocarcinoma are known to be associated with more aggressive biological behaviors and infiltrative growths and, therefore, have worse prognoses than the differentiated types. Furthermore, the indications for ER for the undifferentiated types are limited compared to those for the differentiated types [10,11]. The Korean Practice Guideline for Gastric Cancer 2018 states that ER could be considered for the undifferentiated types (poorly differentiated tubular or poorly cohesive) of EGC (UD-EGC) without ulcers, given that the endoscopically

estimated tumor size was ≤2 cm and the depth of invasion corresponded to clinically mucosal cancer. The Japanese and European guidelines also present the same ESD criteria for UD-EGC [12-14]. However, ESD for UD-EGC has a weak grade of recommendation in Korea. Similarly, in Japan, it is included in the expanded indications that are not absolute. In Europe, it is recommended that gastrectomy should always be considered on an individual basis (taking into account patient age and preference, and co-morbidities) using a multidisciplinary approach. Therefore, care should be taken in its clinical applications. In this review, we focused on the safety, therapeutic efficacy, and short-term and long-term outcomes of ESD in UD-EGC.

HISTOLOGIC CLASSIFICATION OF UNDIFFERENTIATED-TYPE HISTOLOGY GASTRIC CANCER

According to the fifth edition of the World Health Organization (WHO) classification, which was revised in 2019, the predominant histological types of gastric adenocarcinoma are tubular adenocarcinoma, poorly cohesive carcinoma with signet-ring cell type (PCC-SRC), poorly cohesive carcinoma with non-signet-ring cell type (PCC-NOS), and mucinous adenocarcinoma (MAC). Furthermore, for the WHO, the term undifferentiated carcinoma refers to a malignant epithelial tumor with no glandular structures or other features to indicate definite differentiation.

This differs from the definition provided in the Japanese Gastric Cancer Association guideline, which is generally used in ESD. In the Japanese gastric cancer treatment guidelines 2014, undifferentiated-type carcinoma includes poorly differentiated adenocarcinoma (PDA; por1, por2) and signet-ring cell carcinoma (sig) [15]. Mucinous adenocarcinoma (muc), depending on the type of tumor cells present (such as signet ring cells, etc.), is sometimes also categorized in the undifferentiated-type. Among the gastric cancer classification by the WHO, poorly differentiated tubular adenocarcinoma, PCC-SRC, and PCC-NOS are considered as undifferentiated-type carcinomas by the Japanese classification due to the lack of tubular or glandular structures. In the Korean Gastric Cancer Association Nationwide Survey on Gastric Cancer in 2014, it was found that poorly differentiated tubular adenocarcinoma and PCC accounted for 28.5% and 18.1% of all gastric cancers, respectively [16].

CLINICAL CHARACTERISTICS OF UD-EGC

The clinical characteristics of the recent studies on ER for UD-EGC are listed in **Table 1** [17-33]. All 17 studies were retrospectively analyzed. The number of lesions in the analysis ranged from 46 to 201, which was not sufficient to form a conclusive result. One study conducted conventional EMR, EMR with precutting, and ESD [18]. Meanwhile, 5 studies performed EMR and ESD [21,23,25,27,29]. The remaining carried out only ESD [17,19,20,22,24,26,28,30-33].

The inclusion criteria for all the studies were based on the expanded criteria suggested by Gotoda et al. [34], except for those by Kim et al. [18] and Kang et al. [22]. The patients who refused the surgery of their own will and were experimentally treated with ESD were included in the study by Kim et al. [18]. On the other hand, the study by Kang et al. [22] included patients with UD-EGC with ulceration, which is beyond the ESD criteria. The histological types included in each study are presented in **Table 1**. The histological types studied include

Table 1. Clinical characteristics of studies on endoscopic resection for undifferentiated-type histology early gastric cancer in expanded indication

Study	Country	Type of histology	No. of patients with UD-EGC	No. of patients with PDA/SRC	Age (yr)	Sex (male)	SM invasion	Ulcer	Size (mm)	Size >20 mm
Kim et al. [23]	South Korea	PDA, SRC	58	17/41	55.0 (26.0–81.0)	26 (44.8)	NA	0 (0)	13.3±6.5	4 (6.9)
Yamamoto et al. [32]	Japan	PDA, SRC	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 et al. [22]	South Korea	PDA, SRC	60	30/30	56.7±10.4	31 (51.7)	17 (28.3)	17 (28.3)	26.3±12.9	31 (51.7)
Park et al. [21]	South Korea	PDA, SRC, mixed adenocarcinoma	77	47/15/15†	60.9 (33.0–82.0)	49 (63.6)	12 (15.6)	4 (5.2)	23.3±14.0	35 (45.5)
Okada et al. [19]	Japan	PDA, SRC	103	12/91	59.0 (34.0–91.0)	48 (46.6)	10 (9.7)	1 (1.0)	8.0 (1.0–33.0)	NA
Kamada et al. [20]	Japan	PDA, SRC	46	NA	65.5 (29.0–90.0)	24 (52.2)	7 (15.2)	1 (2.2)	NA	8 (17.4)
Choi et al. [24]	South Korea	PDA, SRC, PDA+SRC	82	24/28/30‡	53.5±12.7	43 (52.4)	10 (11.2)	NA	NA	0
Park et al. [33]	South Korea	Not mentioned	116	NA	NA	NA	NA	NA	NA	NA
Kim et al. [18]	South Korea	PDA, SRC	74	55/19	61.8±12.0	40 (54.1)	16 (21.6)	11 (14.9)	19.9±12.5	36 (48.6)
Abe et al. [17]	Japan	PDA, SRC, moderately to PDA	97	18/77/2§	62.0 (35.0–88.0)	55 (56.7)	19 (19.6)	9 (9.3)	12	14 (14.4)
Oka et al. [25]	Japan	PDA, SRC, MAC	125	58/65/2¶	62.0	70 (56.0)	28 (22.4)	11 (8.8)	NA	16 (12.8)
Kim et al. [26]	South Korea	PDA, SRC	209	82/127	NA	NA	NA	0	17.2±12.0	NA
Min et al. [27]	South Korea	PDA, SRC	59	42/17	56.8 (22.0–84.0)	41 (69.5)	16 (27.1)	NA	NA	26 (44.1)
Inokuchi et al. [28]	Japan	PDA, SRC, MAC	40*	NA	69.5 (40.0–88.0)	25 (65.8)	9 (22.5)	9/40 (22.5)	17 (2–36)	11 (27.5)
Ahn et al. [29]	South Korea	PDA, SRC, mixed undifferentiated carcinoma (poorly differentiated and signet ring cells)	101	54/26/21†	57 (46.0–64.0)	55 (54.5)	9 (8.9)	NA	15 (15–20)	17 (16.8)
Park et al. [30]	South Korea	PDA, SRC	81**	23/58	55.0±9.8	33 (40.7)	NA	NA	10.6±5.2	NA
Lim et al. [31]	South Korea	PDA, SRC, MAC	126	64/59/3¶	59.9±12.0	66 (52.4)	33 (26.1)	4 (3.2)	24.0±11.8	67 (53.2)

Data expressed as absolute numbers (percentage), mean±standard deviation or median with or without range.
UD-EGC = undifferentiated types (poorly differentiated tubular or poorly cohesive) of early gastric cancer; PDA = poorly differentiated adenocarcinoma; SRC = signature ring cell carcinoma; PDA+SRC = poorly differentiated adenocarcinoma with signet ring cell features; MAC = mucinous adenocarcinoma; SM = submucosa; NA = not available; EGC = early gastric cancer.
*A total of 40 EGCs in 38 patients were enrolled; †Mixed type histology; ‡PDA+SRC; §Two patients had EGCs with histology of moderately to poorly differentiated adenocarcinoma; ¶Mucinous adenocarcinoma; **Propensity score matching.

mixed-type adenocarcinoma [21,29], moderate to PDA [17], or PDA with signet ring cell components [24] in UD-EGC. Submucosal invasion was reported to be present in 8.9%–28.3% of patients, whereas ulceration was seen in 0% to 28.3% of the patients. These rates were relatively high in the 2 studies that included patients who refused surgery and those who had endoscopic ulceration. Three studies, especially those that included MAC, showed relatively high submucosal invasion rates [25,28,31]. Although ESD was performed based on the expanded criteria, the proportion of lesions exceeding 2 cm in ESD specimens was reported to be up to 53.2% [31], which represented the inaccuracy and difficulty in estimating the lesion endoscopically in UD-EGC. Although the ESD in UD-EGC was decided on and performed with endoscopic findings (including lesion size, depth of invasion, and ulceration in diagnostic endoscopy), because of the results and discrepancy of the ESD specimens, curability needs to be applied more strictly, unlike differentiated-type histology EGC.

SHORT-TERM OUTCOMES OF ER FOR UD-EGC

Short-term outcomes, including en bloc resection, complete resection, curative resection, and complication rates of ER for UD-EGC, were reviewed (**Table 2**) [17-33]. En bloc resection was homogenously defined in the studies as the resection of the tumor in one piece with no endoscopically residual tumor, i.e., tumor resected in one piece without fragmentation. However, the definitions of complete resection and curative resection were heterogeneous as different studies had different considerations. Some definitions of complete resection

Table 2. Short-term outcomes of endoscopic resection for undifferentiated early gastric cancer

Study	LMP*	VMP*	LVI*	En bloc resection*	Complete resection*	Curative resection*	Additional OP after incomplete or noncurative ER	Residual tumor in op specimen	LNM†	Bleeding*	Perforation*
Kim et al. [23]	10 (17.2)	9 (15.5)	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)
Yamamoto et al. [32]	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 et al. [22]	14 (23.3)	11 (18.3)	11 (18.3)‡/ 4 (6.7)§	60 (100)¶	33 (55.0)	17 (28.3)	15/27 (55.6)	6/15 (40.0)	2/15 (13.3)	1 (1.7)	1 (1.7)
Park et al. [21]	12 (16.7)**		5 (6.5)	64 (83.1)	NA	35 (45.5)	11/42 (26.2)	NA	0/11 (0.0)	NA	NA
Okada et al. [19]	5 (4.9)**		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 et al. [20]	5 (10.9)	4 (8.7)	4 (8.7)	42 (91.3)	NA	NA	5	1/5 (20.0)	NA	2 (4.3)	2 (4.3)
Choi et al. [24]	8 (9.8)	7 (8.5)	4 (4.9)	72 (87.8)	66 (80.5)	NA	9/16 (56.2)	NA	NA	NA	NA
Park et al. [33]	25 (21.6)	0 (0.0)	NA	106 (91.4)	91 (78.4)	NA	NA	NA	NA	7 (6.0)	6 (5.2)
Kim et al. [18]	NA	NA	10 (13.5)	67 (90.5)††	54 (73.0)	23 (31.1)	19/51 (37.3)	NA	NA	1 (1.4)	3 (4.1)
Abe et al. [17]	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)
Oka et al. [25]	NA	NA	NA	NA	101 (80.8)	81 (64.8)	4/11 (36.4)	0/4 (0.0)	0/4 (0.0)	NA	NA
Kim et al. [26]	46 (22.0)	34 (16.3)	8 (3.8)	191 (91.4)	NA	115 (55.0)	65/94 (69.1)	NA	NA	NA	NA
Min et al. [27]	11 (18.6)	2 (3.4)	9 (15.3)	56 (95.0)	43 (72.9)	20 (33.9)	0/3 (0.0)‡‡	0 (0.0)	0 (0.0)	6 (10.2)	5 (8.5)
Inokuchi et al. [28]	5 (12.5)	5 (12.5)	4 (10.0)	39 (97.5)	30 (75.0)	16 (40.0)	10/24 (41.7)	1/10 (10.0)	0/10 (0.0)	3 (7.7)	1 (2.6)
Ahn et al. [29]	9 (8.9)	3 (3.0)	4 (4.0)	100 (99.0)	87 (86.1)	71 (70.3)	15/30 (50.0)	NA	NA	11 (10.9)	1 (1.0)
Park et al. [30]	NA	NA	NA	78 (96.3)	73 (90.1)	71 (87.7)	NA	NA	NA	0 (0.0)	3 (3.7)
Lim et al. [31]	15 (11.9)	NA	17 (13.5)	NA	NA	NA	NA	NA	NA	NA	NA

Data expressed as number (percentage).
LMP = lateral margin positivity; VMP = vertical margin positivity; LVI = lymph vascular invasion; OP = operation; ER = endoscopic resection; LMN = lymph node metastasis; NA = not available; UD-EGC = undifferentiated types (poorly differentiated tubular or poorly cohesive) of early gastric cancer.
*The numbers in parentheses indicate the percentage of the total number of UD-EGC; †Data include the incidence of residual tumor or lymph node metastasis in specimens obtained by additional operation after incomplete or non-curative endoscopic resection; ‡Data include the cases with lymphatic invasion; §Data include the cases with vascular invasion; ¶Data include patients with UD-EGC with ulceration; **Data include the cases with lateral and/or vertical margin positivity; ††Data include the patients who refused surgery and were treated with endoscopic submucosal dissection as an experimental treatment; ‡‡Three incomplete or noncurative ER patients did not undergo additional surgery at the patient's will.

depended on the involvement of en bloc resection [22,23], on lymphovascular invasion [18,24,30,31], or on perineural invasion [31]. Meanwhile, the definition of curative resection in some studies did not clarify whether en bloc resection along was involved [18,19,32] or if both en bloc and piecemeal resection were included [21]. The overall rates of *en bloc* resection, complete resection, and curative resection of ER were 83.1%–100%, 67.2%– 90.7%, and 28.3% –87.7%, respectively.

The rates of en bloc resection, complete resection, and curative resection of ESD for differentiated-type EGC within the absolute and expanded criteria were noted to range from 84.1% to 97.3%, 84.1% to 93.7% [22,27,33,35-37], and 86.9% to 93.4% [33,36,37]. The results of the differentiated-type EGC with the absolute criteria were reported to be 86.7%–98.6%, 94.8%–97.3%, and 89.1%–97.1% [33,35-37]. Compared with EGCs with differentiated-type histology, these results may be due to the less accurate endoscopic size estimation in UD-EGC, which was based on the ill-defined infiltrative margin of the lesion, larger size, and higher rate of lymphovascular invasion. Additional surgical treatment after incomplete or noncurative resection with ER was performed in 0%–69.1% of patients. The study by Min et al. [27] showed no additional operation rate because of the patient's refusal to undergo surgery of their own will. The presence of residual tumor and LNM in surgical specimens ranged from 0% to 44.4% and 0.5% to 13.3% of patients, respectively. The rates of bleeding and perforation in UD-EGC were 0%–13.8% and 1.0%–8.5%, respectively. The highest rate of bleeding was noted in the study by Kim et al. (13.8%) [23], with most of bleeding occurring during the procedure (6 cases) or within 24 hours (2 cases). These were controlled endoscopically. The results of bleeding and perforation in the differentiated-type EGC with the absolute and expanded criteria were reported to be at 2.5%–6.6% and 1.3%–4.4%, respectively [22,27,33,35-37]. The results for the differentiated-type EGC with the absolute

Table 3. Short-term outcomes of endoscopic resection for undifferentiated early gastric cancer with histology

Study	No. of patients with UD-EGC, PDA	No. of patients with UD-EGC, SRC	LMP		VMP		LVI		En bloc resection		Complete resection		Curative resection	
			PDA	SRC	PDA	SRC	PDA	SRC	PDA	SRC	PDA	SRC	PDA	SRC
Kim et al. [23]	17	41	NA	NA	NA	NA	NA	NA	14 (82.4)	35 (85.4)	10 (58.8)	29 (70.7)	NA	NA
Kang et al. [22]	30	30	5 (16.7)	9 (30.0)	7 (23.3)	4 (13.3)	L: 6 (20.0) V: 3 (10.0)	L: 5 (16.7) V: 1 (3.3)	NA	NA	16 (53.3)	17 (56.7)	NA	NA
Park et al. [21]	47	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	17 (48.6)	9 (25.7)
Choi et al. [24]*	24	28	3 (12.5)	1 (3.6)	3 (12.5)	1 (3.6)	1 (4.2)	1 (3.6)	21 (87.5)	26 (92.9)	18 (75.0)	25 (89.3)	NA	NA
Kim et al. [26]	82	127	15 (33.3)	31 (63.3)	34 (36.3)	23 (51.1)	NA	NA	74 (90.2)	117 (92.1)	NA	NA	37 (45.1)	78 (61.4)
Min et al. [27]	42	17	6 (14.3)	5 (29.4)	2 (4.8)	0 (0.0)	7 (16.7)	2 (11.8)	40 (95.2)	16 (94.1)	32 (76.2)	11 (64.7)	NA	NA
Ahn et al. [29]*	54	26	NA	NA	NA	NA	NA	NA	70 (98.6)	30 (100.0)	NA	NA	37 (52.1)	21 (29.6)

Data expressed as number (percentage).
UD-EGC = undifferentiated types (poorly differentiated tubular or poorly cohesive) of early gastric cancer; PDA = poorly differentiated adenocarcinoma; SRC = signature ring cell carcinoma; LMP = lateral margin positivity; VMP = vertical margin positivity; LVI = lymphovascular invasion; NA = not available; L = lymphatic invasion; V = vascular invasion.
*Two studies including PDA, SRC, and PDA+SRC.

criteria were reported to range from 0.9% to 6.0% and 0.8% to 2.9% [33,35-37]. The procedure-related complications in ESD appeared to be slightly less in UD-EGC than in the EGCs with differentiated-type histology.

When analyzing each outcome according to pathology, the lateral margin positivity was high in signet ring cell carcinoma (SRC), whereas vertical margin positivity (VMP) was high in PDA. Furthermore, PDA showed good vertical invasion, whereas SRC was characterized to have good horizontal invasion [38,39], except for the studies by Choi et al. [24] and Ahn et al. [29] (Table 3). These studies divided and analyzed the histologic types of UD-EGC into PDA, SRC, and PDA+SRC. The percentage of patients with PDA+SRC was 36.6% (n=30) and 20.8% (n=21) of all UD-EGC patients. Other studies did not mention PDA+SRC, and we could not confirm whether they were excluded from the analysis or grouped together as PDA or SRC. The high rate of lymphovascular invasion in PDA is thought to be an extension of the higher VMP. The rate of en bloc resection and complete resection tended to be higher in SRC than in PDA, 92.1%–100% vs. 82.4%–98.6%, 56.7%–89.3% vs. 53.3%–75.0%, respectively. The curative resection rate was up to 61.4% in SRC, in contrast to 45.1% in PDA.

LONG-TERM OUTCOMES

We also reviewed the long-term outcomes, including recurrence rate, local recurrence, distant metastasis, synchronous lesion, metachronous lesion after curative resection, and noncurative resection with the expanded criteria, and local recurrence after ER with the beyond expanded criteria in UD-EGC (Table 4).

The recurrence rate after curative ER was 0.0%–13.8%, with follow-up durations ranging from 16.0 to 63.1 months [17-24,27,30-32]. In contrast, Kim et al. [23] and Kang et al. [22] reported that the recurrence rate after complete resection met the expanded indication.

Long-term data for metachronous EGCs after ESD for UD-EGC are limited. The cumulative incidence of metachronous lesions after curative resection varied from 2.4% to 11.4% during the median follow-up period, which ranged from 32.7 to 40.9 months [17,19,21,26,29]. After noncurative resection, the cumulative incidence of metachronous lesions varied from 0.0%

Table 4. Long-term outcomes of endoscopic resection for undifferentiated early gastric cancer

Study	Follow-up duration	Overall Recurrence	Recurrence after curative resection	Metachronous lesion after curative resection	Recurrence after noncurative resection	Recurrence after noncurative resection with additional surgery	Recurrence after noncurative resection without additional surgery	Metachronous lesion after noncurative resection	Recurrence after complete resection of beyond expanded criteria	Recurrence after incomplete resection of beyond expanded criteria	5-year OS in curative resection (%)	5-year OS in noncurative resection (%)	5-year DSS (%)
Kim et al. [23]	19.0±12.0	2/39 (5.1)*	2/39 (5.1)*	NA	NA	NA	NA	NA	NA	2/19 (10.5)	NA	NA	NA
Yamamoto et al. [32]	24	0/59 (0.0)	0/47 (0.0)	NA	0/12 (0.0)	NA	NA	NA	NA	NA	NA	NA	NA
Kang et al. [22]	16	0/18 (0.0)*	0/18 (0.0)*	NA	NA	NA	NA	NA	NA	0/42 (0.0)	NA	NA	NA
Park et al. [21]	40.9 (9.3–152.3)	4/77 (5.1)	0/35 (0.0)	1/35 (2.9)	4/42 (9.5)	NA	NA	2/42 (4.8)	NA	NA	NA	NA	NA
Okada et al. [19]	40.0 (19–92)	0/96 (0.0)	0/78 (0.0)	2/78 (2.6)	0/18 (0.0)	0/10 (0.0)	0/8 (0.0)	0/18 (0)	NA	NA	96.1	NA	100
Kamada et al. [20]	45.6	1/46 (2.2)	0/34 (0.0)	NA	1/12 (8.3)	0/5 (0.0)	1/7 (14.3)	NA	NA	NA	NA	NA	NA
Choi et al. [24]	37.4	3/82 (3.7)	NA	NA	NA	NA	NA	NA	2/66 (3.0)	1/16 (6.3)	NA	NA	NA
Park et al. [33]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kim et al. [18]	34.0 (7.0–81.0)	4/29 (13.8)	0/23 (0.0)	NA	0/6 (0.0)	NA	NA	NA	2/31 (6.5)	2/14 (14.3)	NA	NA	NA
Abe et al. [17]	76.4	2/91	0/46 (0.0)	11.4%	2/33 (6.0)	1/19 (5.3)	1/14 (7.1)	NA	NA	NA	93.0	82.5	NA
Kim et al. [26]	32.7±22.2	NA	0 (0.0)	5 (2.4)	2/94 (2.1)	NA	NA	1 (0.5)	NA	NA	98.6	NA	NA
Min et al. [27]	27.5 (8–109)	0	0	0	0/3 (0.0)	NA	NA	0	NA	NA	NA	NA	NA
Inokuchi et al. [28]	45.3 (18.2–89.8)	NA	0	0	1/22 (4.5)	0/10 (0.0)	1/12 (8.3)	0	NA	NA	93.3	91.7	100
Ahn et al. [29]	60 (48–80)	NA	1/71 (1.4)	2/71 (2.8)	4/30 (13.3)	0/15 (0.0)	4/15 (26.7)	3/30 (10)	NA	NA	94.7	96.3	100
Park et al. [30]	47.1 (30.7–70.0)	11/111 (9.9)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lim et al. [31]	63.1 (43.5–93.7)	10/104 (9.6)	NA	NA	NA	NA	NA	NA	NA	NA	96.8	NA	100

Data expressed as number (percentage), mean±standard deviation or median (range).
OS = overall survival; DSS = disease-specific survival; NA = not available.
*Recurrence rate after complete resection.

to10.0%, regardless of whether or not they received additional surgery after non-curative ESD [19,21,26]. In addition to the study by Ahn et al. [29], among the 30 patients who underwent noncurative resection, 13 patients did not undergo additional surgery, and among them, 3 metachronous lesions were observed (10%). This finding was comparable to the annual incidence of metachronous lesions after ESD for differentiated EGC, which ranged from 1.9% to 4.0% [40-43].

For patients who corresponded to the beyond expanded criteria, local recurrence was reported at 3.0% for complete resection [24] and 0.0%–10.5% for incomplete resection [22-24]. The definition of incomplete resection was different in the 3 studies. Kim et al. [23] defined an end-positive lateral or vertical cut (including submucosal invasion) and reported a local recurrence of 10.5%. Choi et al. [24] histologically defined the presence of residual remnant lesions or lymphatic and vascular infiltrations and reported 6.3%. Kang et al. [22] who recorded a 0% local recurrence, reported that incomplete resection occurred when the tumor was resected in multiple fragments, with resected margins positive for cancer invasion or lymphovascular infiltration. The 5-year overall survival (5YOS) was reported to range from 93.0% to 98.6% in curative resection with the expanded criteria [17,19,26,28,29,31]. Inokuchi et al. [28] reported a 5YOS of 93.3% after curative resection, with one patient mortality due to another disease at 49.3 months after ESD (data without cause of death). When noncurative resection was performed with the expanded criteria, the 5YOS was reported to be 82.5%–96.3% [17,28,29]. Abe et al. [17] reported a 5-year mortality rate of 6.7% among patients who received additional surgery and 17.5% for patients who underwent non-curative resection without additional surgery. Inokuchi et al. [28] reported that the 5-year mortality rate after noncurative resection followed by additional surgery was 0%; in contrast, it was 8.3% among those who did not undergo surgery. One patient who did not undergo surgery after a noncurative resection died of esophageal cancer at 16.4 months after ESD. The 5-year mortality rate in curatively resected patients ranged from 1.4% to 7.0%, with no patient dying of gastric cancer. On the other hand, the 5-year disease-specific survival rate for gastric cancer was 0% [19,28,29,31]. The 3- and 5-year survival rates were 99.0% and 98.6%, respectively, with no significant difference between curative resection patients with PDA and SRC [26].

CONCLUSION

In conclusion, even in undifferentiated cancer, the short- and long-term oncological results of curative resection do not show significant differences from differentiated cancer. There is also no significant difference in surgical resection in terms of treatment modality. Therefore, it is considered reasonable to maintain the current indications. However, in many cases of undifferentiated adenocarcinoma, the boundary is unclear; therefore, caution is required when evaluating the boundary before ESD in order to achieve sufficient resection of the margins. In the future, it would be necessary to introduce personalized indications that consider age, comorbidities, and life expectancy.

REFERENCES

1. Ahn YO, Park BJ, Yoo KY, Kim NK, Heo DS, Lee JK, et al. Incidence estimation of stomach cancer among Koreans. J Korean Med Sci 1991;6:7-14.
   PUBMED | **CROSSREF**

2. Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, et al. Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. Cancer 1992;70:1030-1037.
   PUBMED | CROSSREF

3. Eom BW, Jung KW, Won YJ, Yang H, Kim YW. Trends in gastric cancer incidence according to the clinicopathological characteristics in Korea, 1999-2014. Cancer Res Treat 2018;50:1343-1350.
   PUBMED | CROSSREF

4. Yamashita K, Sakuramoto S, Nemoto M, Shibata T, Mieno H, Katada N, et al. Trend in gastric cancer: 35 years of surgical experience in Japan. World J Gastroenterol 2011;17:3390-3397.
   PUBMED | CROSSREF

5. Lee JH, Kim JJ. Endoscopic mucosal resection of early gastric cancer: experiences in Korea. World J Gastroenterol 2007;13:3657-3661.
   PUBMED | CROSSREF

6. Ohkuwa M, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 2001;33:221-226.
   PUBMED | CROSSREF

7. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D, et al. A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. Gastrointest Endosc 1999;50:560-563.
   PUBMED | CROSSREF

8. Hirao M, Masuda K, Asanuma T, Naka H, Noda K, Matsuura K, et al. Endoscopic resection of early gastric cancer and other tumors with local injection of hypertonic saline-epinephrine. Gastrointest Endosc 1988;34:264-269.
   PUBMED | CROSSREF

9. Tada M, Murakami A, Karita M, Yanai H, Okita K. Endoscopic resection of early gastric cancer. Endoscopy 1993;25:445-450.
   PUBMED | CROSSREF

10. Adachi Y, Yasuda K, Inomata M, Sato K, Shiraishi N, Kitano S. Pathology and prognosis of gastric carcinoma: well versus poorly differentiated type. Cancer 2000;89:1418-1424.
    PUBMED | CROSSREF

11. Moriguchi S, Kamakura T, Odaka T, Nose Y, Maehara Y, Korenaga D, et al. Clinical features of the differentiated and undifferentiated types of advanced gastric carcinoma: univariate and multivariate analyses. J Surg Oncol 1991;48:202-206.
    PUBMED | CROSSREF

12. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean practice guideline for gastric cancer 2018: an evidence-based, multi-disciplinary approach. J Gastric Cancer 2019;19:1-48.
    PUBMED | CROSSREF

13. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer. Forthcoming 2020.
    PUBMED | CROSSREF

14. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015;47:829-854.
    PUBMED | CROSSREF

15. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1-19.
    PUBMED | CROSSREF

16. Information Committee of Korean Gastric Cancer Association. Korean Gastric Cancer Association nationwide survey on gastric cancer in 2014. J Gastric Cancer 2016;16:131-140.
    PUBMED | CROSSREF

17. Abe S, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Odagaki T, et al. Short- and long-term outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. Endoscopy 2013;45:703-707.
    PUBMED | CROSSREF

18. Kim YY, Jeon SW, Kim J, Park JC, Cho KB, Park KS, et al. Endoscopic submucosal dissection for early gastric cancer with undifferentiated histology: could we extend the criteria beyond? Surg Endosc 2013;27:4656-4662.
    PUBMED | CROSSREF

19. Okada K, Fujisaki J, Yoshida T, Ishikawa H, Suganuma T, Kasuga A, et al. Long-term outcomes of endoscopic submucosal dissection for undifferentiated-type early gastric cancer. Endoscopy 2012;44:122-127.
    PUBMED | CROSSREF

20. Kamada K, Tomatsuri N, Yoshida N. Endoscopic submucosal dissection for undifferentiated early gastric cancer as the expanded indication lesion. Digestion 2012;85:111-115.
    PUBMED | CROSSREF

21. Park J, Choi KD, Kim MY, Lee JH, Song HJ, Lee GH, et al. Is endoscopic resection an acceptable treatment for undifferentiated EGC? Hepatogastroenterology 2012;59:607-611.
    PUBMED | CROSSREF

22. Kang HY, Kim SG, Kim JS, Jung HC, Song IS. Clinical outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. Surg Endosc 2010;24:509-516.
    PUBMED | CROSSREF

23. Kim JH, Lee YC, Kim H, Song KH, Lee SK, Cheon JH, et al. Endoscopic resection for undifferentiated early gastric cancer. Gastrointest Endosc 2009;69:e1-e9.
    PUBMED | CROSSREF

24. Choi MH, Hong SJ, Han JP, Song JY, Kim DY, Seo SW, et al. Therapeutic outcomes of endoscopic submucosal dissection in undifferentiated-type early gastric cancer. Korean J Gastroenterol 2013;61:196-202.
    PUBMED | CROSSREF

25. Oka S, Tanaka S, Higashiyama M, Numata N, Sanomura Y, Yoshida S, et al. Clinical validity of the expanded criteria for endoscopic resection of undifferentiated-type early gastric cancer based on long-term outcomes. Surg Endosc 2014;28:639-647.
    PUBMED | CROSSREF

26. Kim JH, Kim YH, Jung DH, Jeon HH, Lee YC, Lee H, et al. Follow-up outcomes of endoscopic resection for early gastric cancer with undifferentiated histology. Surg Endosc 2014;28:2627-2633.
    PUBMED | CROSSREF

27. Min BH, Kang KJ, Lee JH, Kim ER, Min YW, Rhee PL, et al. Endoscopic resection for undifferentiated early gastric cancer: focusing on histologic discrepancies between forceps biopsy-based and endoscopic resection specimen-based diagnosis. Dig Dis Sci 2014;59:2536-2543.
    PUBMED | CROSSREF

28. Inokuchi Y, Kobayashi M, Kudo K, Yamada H, Inoue S, Nishimura K, et al. Outcomes and precautions of endoscopic submucosal dissection for undifferentiated-type early gastric cancer. Therap Adv Gastroenterol 2015;8:255-262.
    PUBMED | CROSSREF

29. Ahn JY, Park HJ, Park YS, Lee JH, Choi KS, Jeong KW, et al. Endoscopic resection for undifferentiated-type early gastric cancer: immediate endoscopic outcomes and long-term survivals. Dig Dis Sci 2016;61:1158-1164.
    PUBMED | CROSSREF

30. Park JC, Lee YK, Kim SY, Roh Y, Hahn KY, Shin SK, et al. Long-term outcomes of endoscopic submucosal dissection in comparison to surgery in undifferentiated-type intramucosal gastric cancer using propensity score analysis. Surg Endosc 2018;32:2046-2057.
    PUBMED | CROSSREF

31. Lim JH, Kim J, Kim SG, Chung H. Long-term clinical outcomes of endoscopic vs. surgical resection for early gastric cancer with undifferentiated histology. Surg Endosc 2019;33:3589-3599.
    PUBMED | CROSSREF

32. Yamamoto Y, Fujisaki J, Hirasawa T, Ishiyama A, Yoshimoto K, Ueki N, et al. Therapeutic outcomes of endoscopic submucosal dissection of undifferentiated-type intramucosal gastric cancer without ulceration and preoperatively diagnosed as 20 millimetres or less in diameter. Dig Endosc 2010;22:112-118.
    PUBMED | CROSSREF

33. Park CH, Shin S, Park JC, Shin SK, Lee SK, Lee YC, et al. Long-term outcome of early gastric cancer after endoscopic submucosal dissection: expanded indication is comparable to absolute indication. Dig Liver Dis 2013;45:651-656.
    PUBMED | CROSSREF

34. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000;3:219-225.
    PUBMED | CROSSREF

35. Ahn JY, Jung HY, Choi KD, Choi JY, Kim MY, Lee JH, et al. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications. Gastrointest Endosc 2011;74:485-493.
    PUBMED | CROSSREF

36. Lee H, Yun WK, Min BH, Lee JH, Rhee PL, Kim KM, et al. A feasibility study on the expanded indication for endoscopic submucosal dissection of early gastric cancer. Surg Endosc 2011;25:1985-1993.
    PUBMED | CROSSREF

37. Yamaguchi N, Isomoto H, Fukuda E, Ikeda K, Nishiyama H, Akiyama M, et al. Clinical outcomes of endoscopic submucosal dissection for early gastric cancer by indication criteria. Digestion 2009;80:173-181.
    PUBMED | CROSSREF

38. Kim H, Kim JH, Lee YC, Kim H, Youn YH, Park H, et al. Growth patterns of signet ring cell carcinoma of the stomach for endoscopic resection. Gut Liver 2015;9:720-726.
    PUBMED | CROSSREF

39. Kim GH. Understanding growth patterns of signet ring cell carcinoma of the stomach is necessary for successful endoscopic resection. Gut Liver 2015;9:695-696.
    PUBMED | CROSSREF

40. Kato M, Nishida T, Yamamoto K, Hayashi S, Kitamura S, Yabuta T, et al. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. Gut 2013;62:1425-1432.
    PUBMED | CROSSREF

41. Hahn KY, Park JC, Kim EH, Shin S, Park CH, Chung H, et al. Incidence and impact of scheduled endoscopic surveillance on recurrence after curative endoscopic resection for early gastric cancer. Gastrointest Endosc 2016;84:628-638.e1.
    PUBMED | CROSSREF

42. Nasu J, Doi T, Endo H, Nishina T, Hirasaki S, Hyodo I. Characteristics of metachronous multiple early gastric cancers after endoscopic mucosal resection. Endoscopy 2005;37:990-993.
    PUBMED | CROSSREF

43. Nakajima T, Oda I, Gotoda T, Hamanaka H, Eguchi T, Yokoi C, et al. Metachronous gastric cancers after endoscopic resection: How effective is annual endoscopic surveillance? Gastric Cancer 2006;9:93-98.
    PUBMED | CROSSREF