

Review Article



Endoscopic Resection of Undifferentiated Early Gastric Cancer

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ABSTRACT

Endoscopic resection (ER) is widely performed for early gastric cancer (EGC) with a negligible risk of lymph node metastasis (LNM) in Eastern Asian countries. In particular, endoscopic submucosal dissection (ESD) leads to a high en bloc resection rate, enabling accurate pathological evaluation. As undifferentiated EGC (UD-EGC) is known to result in a higher incidence of LNM and infiltrative growth than differentiated EGC (D-EGC), the indications for ER are limited compared with those for D-EGC. Previously, clinical staging as intramucosal UD-EGC ≤ 2 cm, without ulceration, was presented as ‘weakly recommended’ or ‘expanded indications’ for ER in the guidelines of the United States, Europe, Korea, and Japan. Based on promising long-term outcomes from a prospective multicenter study by the Japan Clinical Oncology Group (JCOG) 1009/1010, the status of this indication has expanded and is now considered ‘absolute indications’ in the latest Japanese guidelines published in 2021. In this study, which comprised 275 patients with UD-EGC (cT1a, ≤ 2 cm, without ulceration) treated with ESD, the 5-year overall survival (OS) was 99.3% (95% confidence interval, 97.1%–99.8%), which was higher than the threshold 5-year OS (89.9%). Currently, the levels of evidence grades and recommendations for ER of UD-EGC differ among Japan, Korea, and Western countries. Therefore, a further discussion is warranted to generalize the indications for ER of UD-EGC in countries besides Japan.

Keywords: Gastric cancer; Stomach; Neoplasms; Endoscopy; Endoscopic submucosal dissection

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and fourth leading cause of cancer-related deaths worldwide [1]. The prevalence of GC is higher in East Asian countries than in Western countries [2,3]. Screening programs have been developed in Korea and Japan to address GC mortality and increase the detection rate of early gastric cancer (EGC) [4]. Indeed, EGC accounts for up to 50%–70% of newly diagnosed GC in these countries [5–7]. With improvements in the detection of EGC, endoscopic resection (ER), especially endoscopic submucosal dissection (ESD), is currently widely performed in EGC patients with a negligible risk of lymph node metastasis (LNM) [8–11].

Conflict of Interest

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

Author Contributions

Conceptualization: H.Y., A.S.; Data curation: H.Y.; Supervision: A.S.; Visualization: H.Y., A.S.; Writing - original draft: H.Y., A.S.; Writing - review & editing: H.Y., A.S., M.M., S.M., N.S., S.H., Y.S., S.Y.

Undifferentiated EGC (UD-EGC) accounts for 35%–40% of EGC [12,13] and is reported to lead to a higher incidence of LNM and infiltrative growth than differentiated EGC (D-EGC) [14-17]. Although the indications for ER of UD-EGC are limited compared to those for D-EGC, there is accumulating evidence on the ER of UD-EGC based on clinical outcomes in East Asian countries [18-26]. In this review, we aimed to focus on current information and future perspectives on the ER of UD-EGC.

INDICATIONS FOR ER OF EGC

The indications for ER of EGC are stated in the guidelines of the United States, Europe, Korea, and Japan based on the risk of LNM [27-34]. Previously, only ‘clinically intramucosal (cT1a), D-EGC sized ≤2 cm with no finding of ulceration (ULO)’ was ‘strongly recommended’ for ER in the guidelines of the United States, Europe, and Korea [27-30] while ‘absolute indication’ (LNM risk <1% and expected to have therapeutic effect equivalent to surgical resection) was accepted for ER in the Japanese guidelines [31,32]. The lesions for 1) cT1a, D-EGC sized >2 cm with ULO; 2) cT1a, D-EGC sized ≤3 cm with ulceration (UL1); and 3) cT1a, UD-EGC sized ≤2 cm with ULO were ‘weakly recommended’ or ‘expanded indications’ for ER. In recent years, multicenter prospective studies by the Japan Clinical Oncology Group (JCOG) 0607 (a single-arm confirmatory trial of an expanded indication for ESD for intestinal-type gastric cancer) and JCOG 1009/1010 (a single-arm confirmatory trial of an expanded indication for ESD for UD-EGC) revealed that the 5 year-overall survival (OS) of ESD was comparable to that of surgical gastrectomy [18,35]. Consequently, these lesions have been integrated into ‘absolute indications’ in the latest Japanese guidelines published in 2021 (Fig. 1) [33,34]. ‘Expanded indications’ are now categorized as locally recurrent lesions in D-EGC, in which the depth of invasion is cT1a, following ER with endoscopic curability (eCura) C1 (described later in ‘CURABILITY AND MANAGEMET FOLLOWING ER OF EGC’). ‘Relative indications,’ a newly adopted criteria in the latest Japanese guidelines, are lesions that do not fulfil the ‘absolute or expanded indications,’ for which surgical gastrectomy is indicated as the standard treatment. However, for elderly patients or patients with severe comorbidities, ER could be an option as the invasiveness of surgical gastrectomy can now be indicated as ‘relative indications.’

Depth	Ulceration	Differentiated-type		Undifferentiated-type	
		≤2 cm	>2 cm	≤2 cm	>2 cm
cT1a (M)	ULO	Absolute indication		Absolute indication	Relative indication
	UL1	≤3 cm	>3 cm	Relative indication	
cT1b (SM)		Relative indication			

■ Absolute indication ■ Relative indication

Fig. 1. Criteria of the indication for ER of EGC in the JGCA guidelines (6th edition) and JGES guidelines (2nd edition). ER = endoscopic resection; EGC = early gastric cancer; JGCA = Japanese Gastric Cancer Association; JGES = Japanese Gastroenterological Endoscopy Society; M = cancer confined to the mucosa; ULO = without ulceration; UL1 = ulceration; SM = cancer invading the submucosa.

CURABILITY AND MANAGEMET FOLLOWING ER OF EGC

In the latest Japanese guidelines [33,34], endoscopic curability was assessed based on the risk of local recurrence and LNM and classified into ‘eCuraA, B, C1, and C2,’ as shown in **Fig. 2**. ‘eCuraA’ is a condition that can be considered as curative resection with equal or superior long-term outcomes compared to additional surgical resection, for which sufficient evidence is available. ‘eCuraB’ is also a condition that curability can be expected although sufficient long-term outcomes have not been obtained. ‘eCuraC’ was originally known as non-curative resection, which may require additional treatment. ‘eCuraC’ is subdivided into ‘eCuraC1’ and ‘eCuraC2’: ‘eCuraC1’ is a condition for D-EGC with merely positive lateral margin or piecemeal resection and a negligible risk of LNM, while ‘eCuraC2’ is a condition for lesions that have risks of LNM. For UD-EGC, all lesions that do not fulfil the conditions of ‘eCuraA’ are classified as ‘eCuraC2.’ Further, in D-EGC with UD component >2 cm in length or with submucosal invasion [36,37], the endoscopic curability is classified as ‘eCuraC2.’

It is unclear whether these criteria for curability can be extrapolated to Western populations. Based on the data of the national cancer Registry in the United States, the rate of LNM in surgically resected T1a EGC was 7.8% [38], which is higher than the LNM rates in large Asian series (2%–5%) [39–41]. Although this discrepancy may be related to differences in specimen handling, variations in biological aggressiveness among races or ethnicities in GC might also exist. This variation is because the rates of LNM in White Americans (9.6%) and African Americans (10.9%) almost doubled that of Asian/Pacific islanders (5.2%) in this study. Therefore, the ER for heterogeneous western populations requires further investigation.

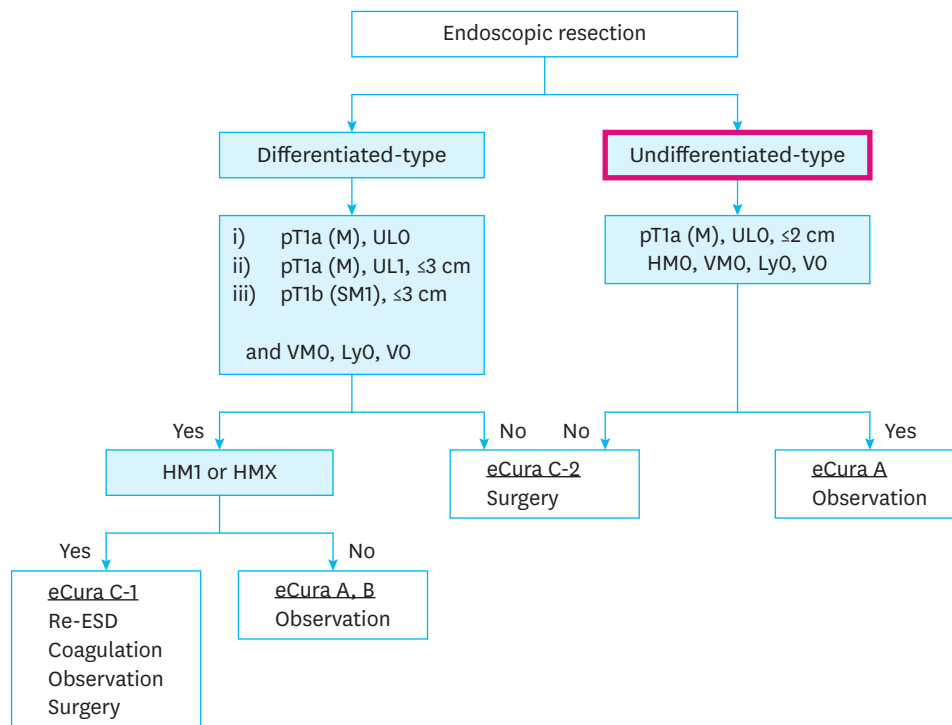


Fig. 2. Flowchart for the curability evaluation and therapeutic approach after ER of EGC in the JGCA guidelines (6th edition) and JGES guidelines (2nd edition). ER = endoscopic resection; EGC = early gastric cancer; JGCA = Japanese Gastric Cancer Association; JGES = Japanese Gastroenterological Endoscopy Society; M = cancer confined to mucosa; ULO = without ulceration; UL1 = ulceration; SM1 = cancer with submucosal invasion depth <500 μm; HMO = negative horizontal margin; HMI = positive horizontal margin; HMX = unevaluable horizontal margin; VMO = negative vertical margin; Ly0 = no lymphatic invasion; V0 = no vascular invasion; eCura = endoscopic curability; ESD = endoscopic submucosal dissection.

CLINICAL OUTCOMES OF ER FOR UD-EGC

Summary of JCOG1009/1010

Although the clinical outcomes of ER for UD-EGC have been reported to be favorable, previous studies were largely retrospective in nature [19-23,42-54]. Thus, JCOG1009/1010 was performed to assess the efficacy and safety of ESD for UD-EGC in a multicenter trial [18]. The inclusion criteria were cT1a/NO/MO, size ≤ 2 cm, no ulceration, and histologically proven UD components on biopsy. The primary endpoint was the 5-year OS rate of patients with UD-EGC as the dominant component. A total of 346 patients from 49 hospitals were enrolled in this study between February 2011 and May 2013. Of the 275 patients with UD-EGC as the dominant component, curative resection was achieved in 195 patients (70.9%). The 5-year OS and 5-year recurrence free survival (RFS) were 99.3% (95% confidence interval [CI], 97.1%–99.8%) and 98.9% (95% CI, 96.6%–96.6%), respectively. The threshold 5-year OS determined according to the expected 5-year OS adjusted for the age and sex was 89.9%; thus, the null hypothesis was rejected because the lower limit of the 95% CI of the 5-year OS was higher than the threshold 5-year OS. Based on this excellent result, the status of indications for ER has expanded in the latest Japanese guidelines, as mentioned earlier. The results of this study are presented in **Tables 1** and **2**.

Table 1. Short-term outcomes of patients undergoing ER for UD-EGCs that meet the ER indication

Author, year	Design	No. of cases	En bloc resection	Curative resection	Factors for non-curative resection						Adverse events	
					Size >20 mm	SM invasion	UL	HM+	VM+	LVI	Delayed bleeding	Perforation
Takizawa et al., 2021 [18]	Multi-center, prospective	275	98.50%	71.00%	13.10%	12.00%	7.60%	2.90%	4.70%	3.60%	3.3%*	0.40%
Ahn et al., 2016 [19]	Single-center, retrospective	101	99.00%	70.30%	16.80%	8.90%	NA	8.90%	3.00%	4.00%	10.90%	1.00%
Kim et al., 2014 [20]	Single-center, retrospective	209	91.40%	55.00%	NA	NA	0%	22.00%	16.30%	3.80%	NA	NA
Oka et al., 2014 [21]	Single-center, retrospective	125	NA	64.80%	12.80%	22.40%	8.80%	NA	NA	4.80%	4.10%	3.10%
Abe et al., 2013 [22]	Single-center, retrospective	97	99.00%	63.90%	14.40%	19.60%	9.30%	5.20%	4.10%	3.10%	4.10%	4.10%
Okada et al., 2012 [23]	Single-center, retrospective	103	99.00%	82.50%	NA	9.70%	1.00%	4.90%		2.00%	8.70%	1.00%

ER = endoscopic resection; UD-EGC = undifferentiated early gastric cancer; SM = submucosal; UL = ulceration; HM+ = positive horizontal margin; VM+ = positive vertical margin; LVI = lymphovascular invasion; NA = not available.

*Among 375 patients with cT1a/NO/MO, size ≤ 2 cm, no ulceration, and histologically proven UD components on biopsy.

Table 2. Long-term outcomes of patients undergoing ER for UD-EGC

Author, year	Design	No. of cases	5-year OS	Recurrence		
				LN or distant metastasis	Local	Metachronous
Suzuki et al., 2022 [24]	Multi-center, prospective	226 curative	94.20%	0.00%	0.40%	2.70%
Takizawa et al., 2021 [18]	Multi-center, prospective	195 curative	99.30%	0.00%	0.00%	2.0%*
		79 non-curative		1.30%	0.00%	NA
Ahn et al., 2021 [25]	Multi-center, retrospective	328 curative	96.10%	0.60%	1.20%	3.70%
Ahn et al., 2016 [19]	Single-center, retrospective	71 curative	94.70%	0.00%	1.40%	2.80%
		30 non-curative	96.30%	0.00%	3.30%	10.00%
Kim et al., 2014 [20]	Single-center, retrospective	115 curative	98.60%	0.00%	0.00%	2.40%
		94 non-curative	NA	1.40%	0.90%	0.50%
Abe et al., 2013 [22]	Single-center, Retrospective	46 curative	93.00%	0.00%	0.00%	11.40%
		33 non-curative	92.3% [†] , 82.5% [‡]	3.00%	3.00%	NA
Okada et al., 2012 [23]	Single-center, Retrospective	83 curative	96.10%	0.00%	0.00%	1.30%

ER = endoscopic resection; UD-EGC = undifferentiated early gastric cancer; OS = overall survival; LN = lymph node; NA = not available.

*Post-hoc analysis (Abe et al. [26]) among 198 (including 3 ineligible for the main study) patients undergoing curative ER for UD-EGCs.

[†]Among 19 patients who underwent additional surgery after non-curative resection.

[‡]Among 14 patients who did not undergo additional surgery after non-curative resection.

Short-term outcomes

The short-term outcomes of patients who underwent ER for UD-EGC that met the ER indications are outlined in **Table 1**. In these studies, ER for UD-EGC led to a high en bloc resection rate (91.4%–99.0%) with acceptable rates of adverse events (delayed bleeding: 3.3%–10.9%, perforation: 0.4%–3.1%) [18-23]. However, the curative resection rate of ER may not be satisfactory, ranging from 55.0%–82.5% [18-23], and is reported to be lower than that for D-EGC [55]. In a large Japanese multicenter prospective study (the J-Web/EGC study) involving 10,031 EGC lesions, the curative resection rate was 83.4% (7,960/9,544) for D-EGC lesions, while that for UD-EGC lesions was only 48.3% (235/487) [56]. Regarding the factors for non-curative resection, a positive horizontal margin was reported to be more frequently observed in UD-EGC than in D-EGC [57-61]. However, only 3% of patients had positive horizontal margins in JCOG1009/1010 [18]. This finding may be because biopsies from the peripheral site of the lesion before ESD were mandatory in this trial. Notably, the Japanese guideline recommends taking biopsies from the surroundings of the lesion [34]. Further, ER with larger margins can be considered to reduce the non-curative resection of UD-EGC. Instead of a positive horizontal margin, a size >2 cm was the most common cause (13.1%) of non-curative resection in this trial. In a post-hoc analysis, preoperative tumor size >1 cm was an independent risk factor for non-curative resection (histological tumor size >2 cm) for ESD with UD components [62]. This result may be related to the difficulty in predicting the tumor extent and horizontal margins. However, the horizontal margin can be confirmed histologically with peripheral biopsies, while estimating the size can still be difficult and underestimated during preoperative diagnosis with endoscopy. Although non-curative resections are not rare for ESD of UD-EGC, improving the accuracy of preoperative diagnosis is needed to evaluate the indication for ESD and enhance the probability of curative resection.

Long-term outcomes

Table 2 shows the long-term outcomes of patients who underwent ER for UD-EGC. The 5-year OS for patients undergoing curative resection was 94.2%–98.6% and that for patients undergoing non-curative resection was 82.5%–96.3% [18-20,22-25]. The number of patients with recurrence after curative resection was small. LNM or distant metastasis and local recurrence were observed in 0.0%–0.6% and 0.0%–1.4% of patients undergoing curative resection [18-20,22-25]. The incidence of metachronous recurrence was similar among the studies and relatively low (1.3% to 3.7%) for patients after curative resection [18-20,22-25]. In fact, UD-EGC is reported to be associated with a lower risk of metachronous recurrence than D-EGC. Ishioka et al. [63] reported that the 5-year cumulative incidence of metachronous recurrence after curative resection in the UD-EGC group was significantly lower than that in the D-EGC group (3.5% vs. 20.8%, $P=0.01$). Abe et al. [26] also revealed that the 5-year cumulative incidence of metachronous recurrence after curative resection in the UD-EGC was 1.0%, with a median follow-up period of 5.8 years in a post-hoc analysis of JCOG1009/1010 trial. The lower incidence of metachronous recurrence in UD-EGC may be explained by the difference in pathogenesis between UD-EGC and D-EGC. UD-EGC tends to develop during the progression of atrophic gastritis, whereas the development of D-EGC is associated with severe atrophic gastritis and intestinal metaplasia caused by *Helicobacter pylori* infection. In three randomized controlled trials, *H. pylori* eradication was reported to reduce metachronous recurrence after ER for D-EGC [64-66]. However, whether *H. pylori* eradication is associated with the development of metachronous recurrence of UD-EGC remains unknown, and further investigations are warranted.

HISTOLOGICAL DIFFERENCES WITHIN UD-EGC

According to the Japanese Classification of Gastric Carcinoma [67], which is generally used for the histological classification of ER for EGC, UD-EGC includes poorly differentiated adenocarcinoma (PDA) and signet ring cell carcinoma (SRC). Mucinous adenocarcinoma can also be categorized as UD-EGC when derived from the UD type or is found in the submucosal layer. A mixed histological type of tumor consisting of components of both D-EGC and UD-EGC also exists. This mixed type is classified as D-EGC or UD-EGC, depending on its quantitative predominance.

Mixed-type EGC is commonly identified during a review of ER specimens rather than in biopsies before ER [68]. There is some debate regarding the handling of mixed-type EGC, as mixed-type is known to be associated with more aggressive biological behavior than the non-mixed type [69-72]. In a recent systematic review and meta-analysis, patients with UD-predominant mixed EGC were found to have a significantly higher risk of submucosal invasion and LNM than those with pure UD-EGC [70]. **Table 3** summarizes the frequency of LNM in the surgical specimens of EGC for UD-predominant mixed EGC and pure UD-EGC. The incidence of LNM for UD-predominant mixed EGC was 7.4%–7.8% in intramucosal EGC and 29.8%–36.8% in submucosal EGC, whereas that for pure UD-EGC was 2.5%–4.1% and 7.9%–16.5%, respectively [73-77]. Although it remains unclear whether new ER indication criteria are necessary for UD-predominant mixed EGC, the risk stratification of LNM according to the histological subgroups may enable more individualized care for patients with UD-EGC. In a single-center retrospective study that evaluated 1,425 patients with surgically resected UD-EGC, no LNM was observed among 115 intramucosal pure UD-EGC sized ≤ 40 mm with absence of ulceration and lymph vascular invasion (1–20 mm: 95% CI, 0%–5.5%; 21–40 mm: 95% CI, 0%–6.1%) [73]. Thus, there may be room for further expansion of the indications for ER. According to Horiuchi et al., UD-predominant mixed EGC tends to undergo non-curative resection as such lesions are more likely to have a tumor diameter > 20 mm, submucosal invasion, and the presence of ulcerative findings than pure UD-type lesions of patients who underwent ESD for UD-EGC [78]. However, it remains challenging to accurately diagnose mixed-type EGC before resection using biopsies [79]. Although Inuyama et al. [80] reported that the combination of magnifying endoscopy with narrow band imaging and biopsy had significantly higher sensitivity and accuracy for diagnosing UD-predominant mixed EGC compared with biopsy alone (sensitivity: 86.2% vs. 41.4%, $P < 0.0001$; accuracy: 82.6% vs. 69.3%, $P < 0.0001$), this was a retrospective study

Table 3. Frequency of LNM in surgical specimens of EGC for UD-predominant mixed type and pure UD type

Author, year	Design	Depth	UD-predominant mixed type		Pure UD type	
			No. of cases	LNM	No. of cases	LNM
Horiuchi, 2022 [73]	Single-center, retrospective	M+SM	525	19.80%	900	7.30%
		M	193	7.80%	514	2.50%
		SM	332	29.80%	386	13.70%
Sekiguchi, 2016 [74]	Single-center, retrospective	M+SM	469	20.50%	1,202	8.60%
		M	217	7.40%	765	4.10%
		SM	252	31.70%	437	16.50%
Takizawa, 2013 [75]	Single-center, retrospective	M	217	7.40%	765	4.10%
Miyamae, 2016 [76]	Single-center, retrospective	SM	45	31.10%	38	7.90%
Hanaoka, 2009 [77]	Single-center, retrospective	SM	63	36.50%	80	15.00%

LNM = lymph node metastasis; EGC = early gastric cancer; UD = undifferentiated; M = cancer confined to mucosa; SM = cancer invading submucosa.

conducted in a single center [80]. Thus, further studies are required to develop an accurate diagnosis before resection of mixed-type EGC.

Regarding the clinicopathological characteristics of pure UD-EGC, the long-term outcomes of ER do not differ between PDA and SRC [20]. However, the biological behavior is considered to be altered between the two. PDA is associated with a higher risk of LNM, while SRC is associated with a lower risk of LNM than other histological types [20,81,82]. PDA also tends to involve the vertical margin, while SRC tends to involve the horizontal margin more frequently when non-curatively resected with ER [20,54]. This tendency can be a result of the different growth patterns of PDA and SRC, as PDA exhibits a more infiltrative growth pattern, while SRC is known to have a subepithelial spreading type, which is more prevalent in cases of atrophy or intestinal metaplasia [83,84].

FUTURE PERSPECTIVES

The frequency of LNM in patients who undergo additional surgery after non-curative ER is reported to be relatively low (5.2%–11.0%), although the data are mainly related to D-EGC [85–89]. Thus, recommending additional surgery for all patients with non-curative ER can be excessive. Hatta et al. developed a risk-scoring system (eCura system) for the risk stratification of LNM in patients undergoing non-curative ESD for EGC [89]. This system was established using a large cohort of patients with EGC, particularly 1,101 patients who underwent additional gastrectomy after non-curative ESD. In this system, weighted points are assigned for five pathological characteristics (lymphatic invasion, venous invasion, tumor size >30 mm, positive vertical margin, and SM2; deep submucosal invasion $\geq 50 \mu\text{m}$) based on the risk of LNM and patients are categorized into three LNM risk groups: low (2.5% risk), intermediate (6.7% risk), and high (22.7%). However, only few UD-EGC cases were used in the development cohort in this system. Thus, the validity of the eCura system must be confirmed or a new scoring system for UD-EGC must be developed.

With continued growth of the aging population, the proportion of elderly patients with GC has been increasing, despite its primary application to D-GC as it is more common in younger populations than D-GC [90]. In elderly patients who undergo gastrectomy after non-curative ER, not only the risk of LNM for EGC but also the risk of non-GC related mortality and impaired quality of life should be considered, as gastrectomy can be too invasive for patients in poor condition or with several comorbidities. Therefore, a new indication for ESD (including both UD-EGC and D-EGC) in elderly patients is currently under investigation in a multicenter prospective study (JCOG1902) in Japan [91]. This study aimed to determine whether watchful waiting after ESD is acceptable for EGC with an LNM risk of <10% in men ≥ 75 years and women ≥ 80 years. If the non-inferiority of the 5-year OS after ESD to that after gastrectomy for these populations is confirmed, the indications for ESD in elderly patients may be expanded in the future.

CONCLUSION

The indication for ER of UD-EGC has expanded, and UD-EGC ≤ 2 cm with ULO is involved in 'absolute indications' in the latest Japanese guidelines, according to the favorable results of a prospective multicenter study (JCOG 1009/1010). However, further discussions are needed to

generalize this indication outside Japan, as the levels of evidence grades and recommendations for ER of UD-EGC in Korea and Western countries differ from those in Japan.

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