A nonrandomized, single-arm confirmatory trial of expanded endoscopic submucosal dissection indication for undifferentiated early gastric cancer: Japan Clinical Oncology Group study (JCOG1009/1010)

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Abstract

Background While endoscopic submucosal dissection (ESD) is recognized as a minimally invasive standard treatment for differentiated early gastric cancers (EGCs), it has not been indicated for undifferentiated EGC (UD-EGC) because of a relatively high risk of lymph node metastasis (LNM). However, patients with surgically resected mucosal (cT1a) UD-EGC ≤ 2 cm in size with no lymphovascular invasion or ulceration are reported to be at a very low risk of LNM. This multicenter, single-arm, confirmatory trial was conducted to evaluate the efficacy and safety of ESD for UD-EGC.

Methods The key eligibility criteria were endoscopically diagnosed cT1a/N0/M0, single primary lesion, size ≤ 2 cm, no ulceration and histologically proven components of undifferentiated adenocarcinoma on biopsy. Based on the histological findings after ESD, additional gastrectomy was indicated if the criteria for curative resection were not satisfied. The subjects of the primary analysis were patients with UD-EGC as the dominant component. The primary endpoint was 5-year overall survival (OS) of patients with UD-EGC.

Results Three hundred 46 patients were enrolled from 49 institutions. The proportion of *en bloc* resection was 99%. No ESD-related Grade 4 adverse events were noted. Delayed bleeding and intraoperative and delayed perforation occurred in 25 (7.3%), 13 (3.8%), and 6 (1.7%) patients, respectively. Among the 275 patients who were the subjects of the primary analysis, curative resection was achieved in 195 patients (71%), and 5-year OS was 99.3% (95% CI: 97.1–99.8).

Conclusions ESD can be a curative and less invasive treatment for UD-EGC for patients meeting the eligibility criteria of this study.

Keywords Endoscopy · Gastric cancer · Endoscopic submucosal dissection (ESD) · Gastrectomy · Undifferentiated type

Introduction

Gastrectomy with lymph node (LN) dissection has been the standard treatment for early gastric cancer (EGC) [1], resulting in an excellent curative rate, but post-operative quality of life sometimes deteriorates. Endoscopic resection (ER) is a minimally invasive curative treatment that can preserve the stomach. Initially, the indications for ER for EGC were limited to the differentiated (intestinal) type of intramucosal (cT1a) EGC and lesions ≤ 2 cm in size because of a low

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risk of LN metastasis and a technical probability of en bloc resection [2].

Subsequently, endoscopic submucosal dissection (ESD) was developed and is widely used to overcome the technical difficulty of en bloc resection [3], which enables the *en bloc* resection of lesions larger than 2 cm [4]. For differentiated-type EGC (differentiated-EGC), the ESD indications [5] have been expanded to mucosal cancer without ulceration (UL) regardless of the lesion size and mucosal cancer ≤ 3 cm with UL based on the favorable results of our previous clinical trial (Japan Clinical Oncology Group study, JCOG0607) [6].

In contrast, ESD is not indicated for undifferentiated-type (UD) EGC, and surgery has been the standard treatment because it is associated with a relatively high risk of LN metastasis and difficulty in diagnosing the horizontal margin due to discontinuous horizontal spread. However, Hirasawa et al. [7] reported that none of their 310 surgical cases of histologically diagnosed T1a UD-EGC ≤ 2 cm without lymphovascular invasion or UL showed an association with LN metastasis. In addition, Yamamoto et al. [8] reported excellent technical results with a one-piece resection rate of 98% and complete resection rate of 90% from a single-center retrospective study on ESD for UD-EGC. Based on these results, we conducted a multicenter, prospective, single-arm, confirmatory trial (JCOG1009/1010) [9] to evaluate the efficacy and safety of ESD within an indication specified for UD-EGC.

According to the Japanese Classification of Gastric Carcinoma [10], EGC showing a mixture of differentiated and UD components are classified based on the predominant histological type in the whole lesion. However, ESD indications should be determined by histological diagnoses of small biopsy specimens, which are sometimes different from those of resected specimens [11, 12]. Thus, in this study, patients with EGC showing UD components in biopsy specimens could be enrolled, regardless of the amount of UD components. The subjects of the primary analysis were patients who had UD-EGC as the dominant component histologically in ESD specimens.

Patients and methods

Trial design and settings

This is a multi-institutional, single-arm, confirmatory phase III trial conducted at 49 institutions in collaboration between the Gastrointestinal Endoscopy Study Group (GIESG) and the Stomach Cancer Study Group (SCSG) in the Japan Clinical Oncology Group (JCOG).

The study protocol was reviewed and approved by the Protocol Review Committee of JCOG in December 2010

and was approved by the Ethics Committee of Shizuoka cancer center (22-63-22-1) followed by the institutional review board at each participating institution prior to initiation of the study. This study was conducted in accordance with the precepts established in the Declaration of Helsinki, and patients provided written informed consent before undergoing any study procedure. This trial was registered with the UMIN Clinical Trial Registry [www.umin.ac.jp/ctr/] as UMIN000004995 and activated in February 2011.

Inclusion and exclusion criteria

The eligibility criteria for this study were as follows: (1) age of 20–80 years old, (2) performance status (ECOG) 0 and 1, (3) a primary single tumor of the stomach, (4) endoscopically diagnosed T1a (mucosal) disease with a size of 2 cm or less and without UL, (5) histologically proven gastric adenocarcinoma with components of UD adenocarcinoma (poorly differentiated adenocarcinoma (por) or signet-ring cell carcinoma (sig)) on biopsy, (6) confirmation of a cancer-free horizontal margin by biopsy taken at two or four points around the lesion, (7) a low risk of luminal stenosis after ESD, (8) clinical N0/M0 by abdominal CT, (9) sufficient organ function, (10) no prior gastrectomy and no reconstruction after esophagectomy, (11) no prior chemotherapy (including hormone therapy) or radiation therapy for any other malignancies, and (12) written informed consent.

The exclusion criteria were as follows: (1) simultaneous or metachronous (within 5 years) multiple cancers, except for intramucosal tumors curable with local therapy, (2) infectious disease requiring systemic therapy, (3) body temperature higher than 38 °C, (4) pregnancy or breast-feeding, (5) psychosis, (6) systemic steroid use, (7) a history of myocardial infarction within 6 months or unstable angina pectoris within 3 weeks, (8) uncontrolled hypertension, (9) severe respiratory disease requiring continuous oxygen therapy, (10) an inability to tolerate anticoagulant or antiplatelet medications, and (11) uncontrolled diabetes mellitus or the need for insulin.

Endpoints

The primary endpoint was the 5-year overall survival (OS). OS was defined as the time from registration to death from any cause. Patients lost to follow-up are censored at the last date of survival confirmation before loss to follow-up.

Secondary endpoints included relapse-free survival (RFS), RFS with stomach preservation, the proportion of en bloc resection with ESD, pathologically curative resection with ESD, and adverse events. RFS was defined as the time from registration to either the first event of recurrence or death from any cause, which was censored at the last date when a patient was alive without recurrence. Recurrence

included local recurrence and distant metastasis, excluding metachronous recurrence. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0. The criteria for pathologically curative resection are described in the ‘assessment of curability’ section.

ESD

ESD was performed within 30 days after registration. The routine procedure for ESD involved marking around the lesion, circumferential mucosal incision outside the marked points, and submucosal dissection until removal of the lesion [13]. The devices used for ESD were not specified. All ESD procedures were performed directly by certified endoscopists or by other investigators under supervision of the certified endoscopists. The criteria for certification required experience with ≥ 50 ESD procedures for gastric cancer. Video recording was mandatory in all cases; some selected videos were reviewed at the semiannual investigators’ meeting to assure the technical quality of ESD. The procedure time was counted from the start of marking to the completion of resection. All ESD technical assessments such as the procedure time and the proportion of en bloc resection were performed in all ESD-treated cases, including ineligible cases after registration.

Gross and pathological evaluation

All evaluations of the lesions were performed according to the Japanese Gastric Cancer Association Classification [10]. Tumor size, location, and macroscopic type were endoscopically evaluated and reported. After fixing in 10% formalin and serial sectioning at 2-mm intervals, the resected specimens were assessed histologically. UD gastric cancer was *por* or *sig*. Differentiated type gastric cancer was defined as papillary adenocarcinoma (*pap*), well-differentiated adenocarcinoma (*tub1*), or moderately differentiated adenocarcinoma (*tub2*). The depth of invasion, tumor size, lymphatic and vascular involvement, and tumor involvement at the horizontal and vertical margins were pathologically assessed. EGC showing a mixture of differentiated and UD components was classified based on the predominant histological type in the whole lesion, with classifications of UD-EGC or differentiated-EGC. Tumor size was also measured pathologically. Ancillary D2-40 immunostaining was strongly recommended to evaluate lymphatic invasion, especially in UD-EGC. The horizontal margin was judged as positive, if the distance from the tumor to the closest mucosal margin was less than 2 mm in

UD-EGC and 1 mm in differentiated-EGC. UL was judged as present if the muscularis propria was completely disrupted and if fibrosis in the submucosal layer was observed to be wider than the range of disrupted muscularis propria.

Assessment of curability

The curability of ESD was assessed in all eligible cases. *En bloc* resection, which was mandatory for accurate histological evaluation, was defined as tumor removal in a single piece without macroscopically residual disease. Complete resection was defined as *en bloc* resection with horizontal and vertical margins histologically confirmed to be tumor-free, and incomplete resection was defined when cancer cells were detected at the resection margin, including multi-piece resection even if vertical margins of the reconstructed lesion were tumor-free and no macroscopic residual disease was identified. The curability of ESD was different in some points between UD-EGC and differentiated-EGC. In both histological types, ESD was deemed ‘noncurative’ and additional gastrectomy was indicated if any of the following criteria were met in the histological diagnosis of the resected specimens:

- (A) Criteria of “noncurative” specific for UD-EGC.
 - (1) pT1b (submucosa, SM), (2) the presence of UL, and (3) tumor size > 2 cm.
- (B) Criteria of “noncurative” specific for differentiated-EGC
 - (1) pT1a with UL and a size > 3 cm, (2) pT1a with a size of the UD component > 2 cm, (3) pT1b invading ≤ 0.5 mm beyond the muscularis mucosae (SM1) and a size > 3 cm, (4) pT1b invading > 0.5 mm beyond the muscularis mucosae (SM2) regardless size, and (5) pT1b (SM1) with UD components in the most invaded area regardless of depth of invasion.
- (C) Common criteria of “noncurative” regardless of the histological type
 - (1) The presence of vascular or lymphatic invasion, (2) a positive or unevaluable histological vertical margin, (3) a positive or unevaluable histological horizontal margin, (4) intratumor incision found pathologically, and (5) a component of mucinous adenocarcinoma.

ESD is deemed ‘curative’ if none of the above criteria are met. ‘Curative’ cases required no additional treatment after ESD.

Complications

Adverse events during and after ESD were evaluated in all ESD-treated cases, including ineligible cases. When symptoms of melena, hematochezia, or hematemesis were noted after ESD, all bleeding events were confirmed by emergent endoscopy. Perforation was diagnosed by observation of (1) mesenteric fat on endoscopy or (2) free air on abdominal radiography or CT. The definition of delayed perforation in this study was cases in which perforations did not occur during the ESD procedure, but the abdominal radiography or CT showed free air, or subsequent endoscopy showed perforation in ESD ulcer bed. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 4.0.

Follow-up

At the beginning of this study, the follow-up duration was 5 years. However, we noticed that we should also be concerned about late recurrence beyond 5 years after ESD, so the protocol was amended from a follow-up duration of 5 years to a follow-up duration of 10 years. Although the primary analysis was conducted at the completion of the 5-year follow-up, the final analysis is planned to be performed at the 10-year follow-up. All enrolled patients were planned to be followed up for 10 years from the last patient's registration as specified in the study protocol. Follow-up examinations included evaluation of serum tumor markers (CEA and CA19-9), upper GI endoscopy, chest X-ray (or CT) and abdominal CT at least every 6 months for the first 3 years and then annually thereafter.

Central pathological review

To reduce institutional variation in pathological diagnoses, we had the investigators' meeting with pathologists of participating institutions to share the consensus regarding the pathological assessments of the ESD specimens prior to initiation of this study. Moreover, a central pathological review of all specimens resected by ESD was performed to confirm that there was no big difference between the local diagnosis and central review. The results of central review were reported to each institution, and if there was some difference of diagnosis, the physician discussed the case with the local pathologist and decided the final diagnosis.

Statistical analysis

This trial was designed as a confirmatory trial to determine the efficacy and safety of ESD for cT1a UD-EGC. The subjects of the primary analysis were all the eligible patients who had UD-EGC as the dominant component

histologically in ESD specimens because the efficacy and safety of ESD for differentiated-EGC satisfying the eligibility criteria of this study were already confirmed in our previous study. The expected and threshold values for 5-year OS were determined from the expected 5-year OS of the general population adjusted by sex and age.

At the time of planning this study, the expected 5-year OS was tentatively set at 93.2% based on the age- and sex-adjusted 5-year OS calculated in the 1994 to 2003 population using the abridged life tables for 2007 in Japan [14]. The threshold 5-year OS was 88.2% which was 5% lower than the expected value. The initial planned sample size for the patients with UD-EGC was 193 (expecting a total of 276 registered patients) with a one-sided alpha of 5% and a power of 70%. One year after the initiation of the study, the sample size was recalculated due to good patient accrual. The sample size was increased to 325 patients (to 259 patients with UD-EGC), providing 80% power under the hypothesis of an expected primary endpoint value of 94.7% and a threshold value of 89.7% using a one-sided alpha of 0.025. Five-year OS was estimated by the Kaplan–Meier method, and the confidence interval was estimated based on Greenwood's formula. At the time of the primary analysis, the expected 5-year OS was planned to be re-calculated based on the actual age and sex distributions of the enrolled patients, and the threshold 5-year OS was set to be lower by 5% than the “re-calculated” expected 5-year OS.

The JCOG Data Center was responsible for data management, central monitoring, and statistical analysis. None of the investigators who performed the protocol treatment participated in the data analysis. All statistical analyses were performed with an intention-to-treat principle using SAS version 9.4 (SAS Institute, Cary, NC, United States of America (USA)).

Results

Patients and clinicopathological characteristics (Table 1)

A total of 346 patients were enrolled from 49 institutions in Japan from February 2011 to May 2013. Excluding 9 ineligible patients ($n = 337$) (Supplementary Table 1), the median age was 62 years (range, 23–80 years), and 179 (53%) patients were male. The median size of the lesions was 12 mm (range, 3–20 mm). The predominant histological type by endoscopic biopsy was sig in 194 (58%), por in 102 (30%), tub1 in 4 (1%), and tub2 in 37 (11%) lesions (Table 1).

Table 1 Patient and tumor characteristics

	All eligible (<i>n</i> = 337)	UD-EGC (<i>n</i> = 275)
Age (y.o.)		
Median	62	61
(range)	(23–80)	(23–80)
Sex		
Male	179 (53%)	135 (49%)
Female	158 (47%)	140 (51%)
Tumor size (cm)		
Median	1.2	1.1
(range)	(0.3–2.0)	(0.3–2.0)
Macroscopic type		
Depressed (0–IIb, 0–IIc, 0–III)	320 (95%)	269 (98%)
Protruded (0–I, 0–IIa)	10 (3%)	3 (1%)
Mixed (0–IIa + IIc, 0–IIc + IIa)	7 (2%)	3 (1%)
Predominant histological type (biopsy)		
Undifferentiated		
sig	194 (58%)	183 (67%)
por	102 (30%)	80 (29%)
Differentiated		
tub1	4 (1%)	0 (0%)
tub2	37 (11%)	12 (4%)
pap	0 (0%)	0 (0%)
Tumor location		
Upper	27 (8%)	16 (6%)
Middle	196 (58%)	175 (64%)
Lower	114 (34%)	84 (31%)
Tumor location (transverse section) (multiple choice)		
Lesser curvature	88 (26%)	68 (25%)
Greater curvature	129 (38%)	110 (40%)
Anterior wall	63 (19%)	56 (20%)
Posterior wall	72 (21%)	55 (20%)

UD undifferentiated, EGC early gastric cancer, y.o. years old, sig signet-ring cell carcinoma, por poorly differentiated adenocarcinoma, tub1 well-differentiated adenocarcinoma, tub2 moderately differentiated adenocarcinoma, Pap papillary adenocarcinoma

ESD technical results (Table 2)

In all eligible patients (*n* = 337), the median ESD procedure time was 65 min (range, 12–459 min), and the proportion of a procedure time longer than 180 min was 5%. The median resected specimen size was 4.5 cm (range 0.5–8.6 cm). Of 337 patients, 332 (99%) underwent en bloc resection (Table 2). Among the five remaining patients,

the lesions were removed in one piece, but the specimen was cut inside the marking in four patients, and ESD was discontinued due to perforation in one patient who underwent emergent surgery.

Pathological results (Tables 3 and 4 and Fig. 1)

According to the pathological evaluation of the ESD specimens, 275 patients were diagnosed with UD-EGC, 55 patients had differentiated-EGC, and 7 patients had no

Table 2 ESD technical results ($n = 337$)

	All eligible ($n = 337$)	UD-EGC ($n = 275$)
Operation time (mins)		
Median	65	61
(range)	(12–459)	(12–374)
≥ 180 min	17 (5%)	11 (4%)
Electrosurgical knife (ESD device)		
IT knife series	262 (78%)	213 (77%)
Others	75 (21%)	62 (23%)
Resected specimen size (cm)		
Median	4.5	4.4
(range)	(0.5–8.6)	(0.5–8.6)
Technical assessment		
En bloc (complete)	332 (99%)	271 (99%)
En bloc with cut inside	4 (1%)	3 (1%)
Piecemeal resection	0	0
NE (not evaluated) ^a	1 (< 1%)	1 (< 1%)

ESD endoscopic submucosal dissection, UD undifferentiated, EGC early gastric cancer

^aThe data of one patient who underwent emergency surgery are missing

findings of cancer in the resected specimens.

The baseline characteristics and ESD technical results of the patients with UD-EGC, who were the subjects of the primary analysis, are shown in Tables 1 and 2. The predominant histological type of UD-EGC by biopsy was sig in 183 (67%) patients and por in 80 (29%) patients (Table 1). In cases of ESD for UD-EGC ($n = 275$), the median procedure time was 61 min (range 12–374 min), and 271 (99%) patients underwent en bloc resection (Table 2). In the patients with UD-EGC, curative resection was achieved in 195 patients (71%) and was not evaluable in 1 patient due to emergent surgery for perforation during ESD (Table 3).

The factors resulting in noncurative resection in all treated patients are shown in Table 4. Among the patients with noncurative ESD for UD-EGC, the major factors were SM invasion in 33 patients, presence of UL in 21 patients, and tumor size > 2 cm in 37 patients. Of the 79 patients with noncurative resection among all eligible patients with UD-EGC, 73 patients underwent additional treatment by gastrectomy (Fig. 1) and 1 patient had LN metastasis (1.4%).

In the differentiated-EGC group, curative resection was achieved in 41 patients (75%), and 12 of the 14 patients with noncurative resection underwent additional surgery. The concordance rate between local diagnosis and central review was 91.4%.

Table 3 Pathological results of UD-EGC ($n = 275$)

	UD-EGC ($n = 275$)
Depth of invasion	
pT1a(M)	242 (88%)
pT1b(SM)	33 (12%)
Ulceration (UL)	
UL0	254 (92%)
UL1	21 (8%)
Tumor size	
≤ 2 cm	239 (87%)
> 2 cm	36 (13%)
Lymphatic invasion (Ly)	
Ly0	266 (97%)
Ly1	9 (3%)
Venous invasion (V)	
V0	273 (99%)
V1	2 (1%)
Horizontal margin (HM)	
HM0	267 (97%)
HM1	7 (3%)
HMX	1 (< 1%)
Vertical margin (VM)	
VM0	262 (95%)
VM1	9 (3%)
VMX	4 (1%)
Curability	
Curative	195 (71%)
Noncurative	79 (29%)
NE	1 ^a (< 1%)

^aThe data of one patient who underwent emergent surgery are missing
UD undifferentiated, EGC early gastric cancer, UL ulceration, NE not evaluated

Table 4 Causes of noncurative resection and incomplete resection (with multiple causes in some cases)

	UD-EGC <i>n</i> = 80	Differentiated-EGC <i>n</i> = 15
(A) Criteria of “noncurative” specific for UD-EGC (any of the following (i)–(iii) are applicable)	71	–
(i) pT1b (submucosa, SM)	33	–
(ii) presence of UL	21	–
(iii) Tumor size > 2 cm	37	–
(B) Criteria of “noncurative” specific for differentiated-EGC (any of the following (i)–(v) are applicable)	–	11
(i) pT1a (M) with UL when size > 3 cm	–	0
(ii) pT1a (M) with the size of UD component > 2 cm	–	8
(iii) pT1b1 (SM1) and tumor size > 3 cm	–	0
(iv) pT1b2 (SM2) or more regardless size	–	7
(v) pT1a (SM1) with UD component in the most invading area	–	0
(C) Common criteria of “noncurative” regardless histological type		
(i) Presence of vascular or lymphatic invasion (ly+ and/or v+)	10	9
(ii) VM1 or VMX (histological vertical margin positive or unevaluable)	13	2
(iii) HM1 or HMX (histological horizontal margin positive or unevaluable)	8	0
(iv) Intratumor incision found pathologically	3	1
(v) Presence of mucinous adenocarcinoma component	1	0

UD undifferentiated, EGC early gastric cancer, UL ulceration

Fig. 1 Patient flow diagram. ESD endoscopic submucosal dissection, NE not evaluated, UD undifferentiated, EGC early gastric cancer

Complications (Table 5)

Perforation during ESD occurred in 13 patients (Grade 2/3: 3.9%, 95% CI 2.1%–6.5%), 12 of whom were successfully treated by endoscopic closure with clipping, while emergent surgery was performed in 1 patient (0.3%, 95% CI 0.0–1.6%). 25 patients required endoscopic hemostasis after ESD (within 30 days), but none of them required blood transfusion (Grade 2: 6.8%, 95% CI 4.4–10.1%). Delayed perforation occurred in six patients (Grade 2/3:

1.8%, 95% CI 0.7–3.8%). Two patients were treated by endoscopic closure, and three patients improved without any additional treatment, while one patient underwent emergent surgery. No ESD-related Grade 4 adverse events were noted (Table 5).

Clinical outcomes (Figs. 2a, b, 3a, b)

The expected 5-year OS based on the actual age and sex distributions of all eligible patients was re-calculated to be 94.9%.

Table 5 Adverse events after ESD ($n = 337$)

	G0	G1	G2	G3	G4	%G2–4	%G3–4	% G4	total
Fever ($> 38^{\circ}\text{C}$)	325	11	1	0	0	0.3	0	0	337
Aspiration	337	0	0	0	0	0	0	0	337
Appetite loss	333	3	1	0	0	0.3	0	0	337
Dysphagia	337	0	0	0	0	0	0	0	337
Heartburn	327	10	0	0	–	0	0	–	337
Nausea	336	1	0	0	0	0	0	0	337
Vomiting	331	–	5	1	0	1.8	0.3	0	337
Perforation-stomach	337	0	0	0	0	0	0	0	337
Gastric stenosis	303	30	3	1	–	1.2	0.3	–	337
Pain-epigastric	336	1	0	0	–	0	0	–	337
Pain-throat	312	2	23	0	0	6.8	0	0	337
Postoperative bleeding-stomach	325	11	1	0	0	0.3	0	0	337

Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 4.0

G Grade

Thus, the threshold 5-year OS was set to be 89.9%. With a median follow-up of 69.9 months (range: 16.0–87.0) among 275 eligible patients with UD-EGC, the 5-year OS was 99.3% (95% CI, 97.1–99.8%) (Fig. 2a). The lower limit of the 95% CI of 5-year OS was higher than the threshold 5-year OS (97.1% $>$ 89.9%). Thus, the primary endpoint was met. The 5-year RFS among eligible patients with UD-EGC was 98.9% (95% CI, 96.5–99.6%) (Fig. 2b). Among 275 eligible patients with UD-EGC, 5 deaths occurred (4 due to other diseases, 1 due to gastric cancer). In one patient who had UD-EGC with deep SM invasion underwent additional surgery, and no LN metastasis was identified in surgically resected specimens; however, recurrence of LN metastasis was detected 38 months after ESD. The 5-year RFS with stomach preservation among eligible patients with UD-EGC was 70.9%. Among the 195 patients followed after achieving curative resection of UD-EGC, no local or distant recurrence were observed, and no deaths due to gastric cancer were encountered.

Among all 337 eligible patients, the 5-year OS was 98.8% (95% CI, 96.8–99.5%) (Fig. 3a), and the 5-year RFS was 98.5% (95% CI, 96.4–99.4%) (Fig. 3b). Among all eligible patients, two patients developed recurrence after noncurative ESD, one of whom is described above, while the other patient had differentiated-EGC with deep SM invasion. This patient refused additional surgery, and intragastric recurrence was detected 12 months after ESD. Among the patients who were followed after achieving curative ESD (195 with UD-EGC and 41 with differentiated-EGC), no cases of local or distant recurrence were observed, and no deaths due to gastric cancer were encountered.

Discussion

This is the first report of a multicenter, prospective, confirmatory clinical trial evaluating the safety and efficacy of ESD for UD-EGC. The results demonstrated that the complications associated with ESD were clinically manageable, and that the 5-year OS of 275 patients with histologically confirmed UD-EGC with no metastasis detectable by image diagnosis was excellent at 99.3% (95% CI, 97.1–99.8%). Abe et al. and Okada et al. reported the proportion of curative resection and long-term outcomes after ESD for UD-EGC [15, 16]. In those studies, the proportions of curative resection were 63.9% and 82.5%, and the 5-year OS after curative resection were 93.0% and 96.1%, respectively. Although these reports were retrospective single-center studies with a small number of patients (46 and 83 patients, respectively), the clinical outcomes of ESD for UD-EGC appeared to be consistently good. Because this multicenter prospective study was well designed with a large sample size and a sufficient follow-up period, it provides strong evidence for the safety and efficacy of ESD for UD-EGC.

From the intention-to-treat point of view, the 5-year OS was 98.8% (95% CI, 96.8–99.5%), and the 5-year RFS was 98.5% (95% CI, 96.4–99.4%) among all 337 eligible patients. Actually, 275 patients were diagnosed with UD-EGC, and 55 patients had differentiated-EGC, and 7 patients had no findings of cancer. These 55 patients with differentiated-EGC were good candidates who satisfied the classical narrow indication for ESD and also showed an excellent 5-year survival of 96.4% (95% CI, 86.2–99.1%). Considering that all 337 eligible patients should have received surgical

Fig. 2 Overall (a) and recurrence-free (b) survival of patients with UD-EGC. *OS* overall survival, *RFS* recurrence-free survival

resection if ESD had not been performed according to the preset treatment guideline, ESD could contribute to preservation of their quality of life without decreasing the chance of cure.

Our study also showed the excellent technical results for ESD. Notably, the proportion of en bloc resection was 99%, and the median procedure time was approximately 60 min. Moreover, before this study, the difficulty of diagnosing the lateral extent was considered one problem of ESD for UD-EGC. In this study, as a result of mandatory biopsies from outside the lesion before ESD, the proportion of horizontal

margin positivity was only 3%. Recently, the indication for ESD for differentiated-EGC has been expanded to larger and ulcerative lesions based on our previous clinical trial (JCOG0607) in which the en bloc resection rate was 99.1%, and the median procedure time was 79 min [6]. Although a larger size and fibrosis associated with UL render ESD technically difficult, this histological type may not cause technical difficulty in ESD. Furthermore, because this study and our previous study, which consistently showed excellent technical results, were multi-institutional investigations all

Fig. 3 Overall (a) and recurrence-free (b) survival of all eligible patients. *OS* overall survival, *RFS* recurrence-free survival

over Japan, ESD can be considered a technically feasible standard treatment for EGC in Japan.

In this study, among the patients achieving curative resection after ESD, no cases of recurrence or gastric cancer-related death were noted. On the other hand, among the patients with noncurative ESD, two patients developed recurrence after ESD. In another large multicenter, retrospective study, among the patients who refused immediate additional surgery, salvage surgery after recurrence was very

difficult to perform and resulted in a poor prognosis [17]. Therefore, when the ESD is judged as noncurative, we have to recommend that the patient undergo immediate additional surgery.

The pathological evaluation is critical to evaluate whether ESD is curative or noncurative. Surgically resected specimens are generally sectioned with an interval of 5 mm or more for pathological evaluation. In contrast, ESD specimens are sectioned at an interval of 2 mm. Thus, the

pathological evaluation of ESD specimens is more precise than that of surgical specimens. In other words, pathological evaluation of ESD specimens with thicker sections might miss noncurative factors such as lymphovascular invasion, leading to worse clinical outcomes of ESD. Moreover, ancillary D2-40 immunostaining was strongly recommended for UD-EGC in the protocol of this study, which may have contributed to a more accurate diagnosis of lymphatic invasion. Therefore, based on the results when we expand the indication for ESD for UD-EGC, pathological evaluation of ESD specimens should be standardized worldwide.

While this study shows excellent results for OS, the proportion of curative resection after ESD was only 71% in the patients with UD-EGC. Major reasons for noncurative resection might be difficulty in the endoscopic evaluation of the indication for ESD because the clinical diagnostic accuracies of tumor depth, the presence or absence of UL, and tumor size were 88%, 92%, and 87% in UD-EGC group, respectively. Improving the accuracy of clinical diagnosis is important for improving the proportion of curative resection with ESD.

This study has several limitations. First, survival following ESD was not directly compared with that after surgery. Theoretically, a randomized controlled study would be ideal for that purpose; however, obtaining informed consent might be difficult because the level of invasiveness is quite different between surgery and ESD. However, among the patients with UD-EGC, the proportion of 5-year OS was excellent, and no cases of recurrence were identified among 195 patients treated with curative ESD, and all of the 79 patients except for one patient treated with noncurative ESD could be salvaged by additional surgery. All metachronous gastric cancers that developed during the follow-up period except one could be curatively resected with repeated ESD (data not shown), and 5-year RFS with stomach preservation was quite high. Thus, due to the high proportion of survival and stomach preservation, ESD for UD-EGC can substantially contribute to improved patient quality of life and can be accepted as a standard treatment. Another limitation is that because EGC may grow very slowly, late recurrence more than 5 years after ESD cannot be ruled out. Therefore, we have already extended the follow-up period to 10 years after ESD.

In conclusion, this confirmatory clinical trial indicates that ESD can be a standard treatment for UD-EGC (cT1a) (intramucosal cancer ≤ 2 cm in size without UL) patients instead of surgical gastrectomy.

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Compliance with ethical standards

Conflict of interest Kohei Takizawa has received personal fees from Takeda Pharmaceutical, Otsuka Pharmaceutical, EA Pharma, Boston Scientific, AstraZeneca, Taiho Pharmaceutical. Hiroyuki Ono has received personal fees from Otsuka Pharmaceutical, Daiichi-Sankyo, EA Pharma, Boston Scientific, AstraZeneca, Olympus. Keiko Minashi has received research funding from Ono Pharmaceutical, MSD K.K., Mediscience Planning Inc, Merck Biopharma Co., Ltd, and Astellas Pharma Inc. Narikazu Boku has received research funding from Ono Pharmaceutical, Takeda Pharmaceutical and personal fees from Ono Pharmaceutical, Taiho Pharmaceutical, and Bristol-Myers Squibb. Ry-oji Kushima has received personal fees from Takeda Pharmaceutical, EA Pharma, AstraZeneca, Otsuka Pharmaceutical, Novartis, and Chugai Pharmaceutical. Hiroshi Katayama has received personal fees from Johnson & Johnson. Haruhiko Fukuda has received personal fees from Chugai Pharmaceutical. Tomonori Yano has received research funding from Olympus, FUJIFILM and personal fees from Olympus. Shin-ichiro Hori has received personal fees from FUJIFILM Corporation, FUJIFILM Medical Co., Ltd., and Kaneka Medix Corporation. Hisashi Doyama has received personal fees from Otsuka Pharmaceutical, EA Pharma, AstraZeneca, Daiichi Sankyo, Olympus medical systems. Ryu Ishihara has received personal fees from EA Pharma, AstraZeneca, Ono Pharmaceutical, MSD, Olympus, and FUJIFILM. Satoshi Tanabe has received personal fees from AstraZeneca, Takeda Pharmaceutical, EA Pharma. Masanori Terashima has received personal fees from Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Yakult Honsha, Takeda Pharmaceutical, Eli Lilly, Pfizer, and Daiichi Sankyo. Manabu Muto has received research funding from Olympus and Ono Pharmaceutical for clinical trial. All remaining authors have declared no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration of 1964 and later versions. This study was approved by the institutional review boards of all participating hospitals. Informed consent was obtained from all patients.

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