Gastric Cancer (2018) 21:114–123
https://doi.org/10.1007/s10120-017-0704-y

ORIGINAL ARTICLE

A non-randomized confirmatory trial of an expanded indication for endoscopic submucosal dissection for intestinal-type gastric cancer (cT1a): the Japan Clinical Oncology Group study (JCOG0607)

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Received: 8 December 2016 / Accepted: 7 February 2017 / Published online: 21 February 2017

Abstract

Background Endoscopic resection has been limited to intestinal-type gastric cancer (cT1a) with a low risk of lymph node metastasis (T1a ≤2 cm, without ulcers). This single-arm confirmatory trial evaluated the efficacy and safety of endoscopic submucosal dissection (ESD) for >2 cm ulcer-negative and ≤3 cm ulcer-positive intestinal-type gastric cancer (cT1a).

Methods The eligibility criteria included endoscopically diagnosed cT1a, a single primary intestinal-type gastric adenocarcinoma, an ulcer-negative lesion of any size or a ≤3 cm ulcer-positive lesion, cN0M0, and no prior treatment. If ESD resulted in noncurative resection, surgical resection was added. The primary endpoint was the 5-year overall survival (OS) (planned sample size was 470, with a one-sided alpha level of 2.5%). The threshold 5-year OS was 86.1%.

Results We enrolled 470 early gastric cancer patients [median tumor size, 25 (5–130) mm] from 29 institutions between June 2007 and October 2010. These patients had 152 ulcer-negative lesions (>2 and ≤3 cm), 111 ulcer-negative lesions (>3 cm), and 207 ulcer-positive lesions (≤3 cm). The success rate for en block resection was 99.1% (466/470). Additional gastrectomy was conducted in 131 patients (28%) who did not fulfill the curative resection criteria. The 5-year OS of all patients was 97.0% (95% confidence interval, 95.0–98.2%), which was higher than the threshold 5-year OS (86.1%). The 317 patients who satisfied the curative resection criteria had no recurrence. There were no ESD-related grade 4 adverse events.

Conclusion ESD for early gastric cancers that met the expanded criteria for intestinal-type gastric cancer (cT1a) was acceptable and should be the standard treatment instead of gastrectomy.

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Keywords Endoscopy · Stomach neoplasms · Endoscopic submucosal resection · Gastrectomy

Introduction

Gastric cancer is one of the most common malignant diseases in the world. Clinical outcomes of gastric cancer have recently been improved due to early detection and curative resection. In Japan and Korea, the number of patients with T1 disease has increased since the establishment of a nationwide screening system; these patients now account for more than half of all gastric cancer patients. As early gastric cancer without lymph node and distant metastasis can be cured by limited local resection, endoscopic diagnostic and resection techniques have been rapidly developed [1–3]. However, considering that the clinical outcomes of endoscopic local resection should be comparable, not inferior, to those of surgical resection with lymph node dissection [4], endoscopic resection has been limited to patients with a very low risk of metastasis. In addition, since the pathological findings of resected specimens—such as histological differentiation, presence or absence of cancer cells at the cut end, and vessel invasion—are essential for estimating the risk of metastasis, en block resection is a very important technical issue when performing endoscopic resection [1, 5–8]. At present, the indication criteria for endoscopic resection of early gastric cancer recommended by the Japanese Gastric Cancer Association and the Japan Gastroenterological Endoscopy Society include (1) intestinal-type adenocarcinoma, (2) endoscopically diagnosed intramucosal cancer (cT1a), (3) tumor size $\leq$2 cm, and (4) no endoscopic findings of ulcer (UL) [1, 9–11].

Recently, a new endoscopic resection technique, endoscopic submucosal dissection (ESD), was developed. This technique enables endoscopists to cut into the submucosal layer in an intended direction and remove the mucosal cancer, regardless of its size and whether a UL is present [12]. Thus, ESD may potentially solve the technical problems associated with conventional endoscopic resection.

Previous data from surgically resected specimens suggest that the risk of lymph node metastasis of cT1a gastric cancer is less than 1% if the following criteria are satisfied: (1) intestinal (differentiated)-type gastric adenocarcinoma which is UL-negative >2 cm in size or which is UL-positive $\leq$3 cm in size or (2) diffuse (undifferentiated)-type gastric adenocarcinoma which is UL-negative and $\leq$2 cm in size [6, 7] This suggests that the indication for ESD can be expanded to these criteria for both intestinal and diffuse types of mucosal gastric adenocarcinoma. For intestinal-type gastric adenocarcinomas that satisfy the above criteria, the Japan Clinical Oncology Group (JCOG) conducted a multi-institution, single-arm, confirmatory trial (JCOG0607) to evaluate the efficacy and safety of ESD [13].

Patients and methods

Trial design and settings

This multi-institution, single-arm, confirmatory trial was conducted by the JCOG. The study protocol was reviewed and approved by the Protocol Review Committee of the JCOG and the institutional review board at each participating institution prior to initiation of the study. The study was conducted in accordance with the precepts established in the Declaration of Helsinki. Patients who were eligible for participation provided written informed consent before registration. This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (http://www.umin.ac.jp/ctr/index.htm), and the registration number was UMIN000000737.

Inclusion and exclusion criteria

The inclusion criteria were (1) histologically proven intestinal-type adenocarcinoma of the stomach by biopsy, (2) primary and single tumor, (3) endoscopically diagnosed as mucosal (cT1a) tumor, (4) UL-negative tumor >2 cm in size or UL-positive tumor $\leq$3 cm in size, (5) predicted to be completely removed by en bloc resection with ESD, (6) low risk of severe stenosis after ESD, (7) no lymph node or distant metastasis (cN0 and cM0) based on an abdominal computed tomography (CT) scan, (8) aged 20–75 years, (9) Eastern Cooperative Oncology Group performance status of 0 or 1, (10) no prior gastrectomy or endoscopic treatment for simultaneous or metachronous gastric cancer and no reconstructive surgery using the stomach after resection of esophageal cancer, (11) no prior chemotherapy or radiation therapy against any other malignancies, (12) sufficient organ function, and (13) written informed consent. Exclusion criteria included (1) regular use of anticoagulant or antiplatelet medication, (2) simultaneous or metachronous (within 5 years) malignancy other than carcinoma in situ or mucosal cancer, (3) pregnant or breastfeeding women, (4) severe mental disease, (5) systemic administration of corticosteroids, (6) active bacterial or fungal infection, (7) concurrent unstable angina or myocardial infarction within 3 months before registration, (8) unstable hypertension, (9) uncontrolled or insulin-controlled diabetes mellitus, or (10) severe respiratory disease requiring continuous oxygen therapy.

Endpoints

The primary endpoint was the 5-year overall survival (OS). OS was defined as the time from enrollment to death, irrespective of the cause, and it was censored at the last contact date for living patients. Secondary endpoints included recurrence-free survival (RFS), adverse events, and 5-year RFS with preserved stomach. RFS was defined as the time from registration to either the first event of recurrence or death from any cause, and it was censored at the last date when the patient was alive without recurrence. RFS with preserved stomach was defined as the time from registration to recurrence, gastrectomy, or death from any cause. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0.

Endoscopic submucosal dissection

Lesion resection was performed using the ESD technique by an endoscopist certified as having performed ESD on at least 100 patients or by an experienced staff member under the supervision of a certified endoscopist. The routine procedure involved marking around the lesion, performing a circumferential mucosal incision outside the marked points, and performing submucosal dissection starting from the circumferential incision to remove the lesion [14]. The ESD device was selected by each endoscopist and included the IT Knife® [15], Hook Knife®, and Flex Knife®, among others. Video recording was mandatory in all cases; some videos were reviewed at meetings of the study group to check that the technical quality of ESD was sufficiently high.

Gross and pathologic evaluation

Tumor size, location, and macroscopic types were endoscopically evaluated and classified by the Japanese Gastric Cancer Association Classification [16]. Intestinal (differentiated)-type gastric cancer was defined as papillary adenocarcinoma (pap), well-differentiated adenocarcinoma (tub1), or moderately differentiated adenocarcinoma (tub2). Diffuse (undifferentiated)-type gastric cancer was defined as a solid-type poorly differentiated adenocarcinoma (por1), non-solid-type poorly differentiated adenocarcinoma (por2), or signet-ring cell carcinoma. The depth of invasion, lymphatic and vascular involvement, and tumor involvement at the lateral and vertical margins were pathologically assessed.

Assessment of curability

Tumor removal in a single piece without macroscopically residual disease was defined as en bloc resection. En bloc resection showing lateral and vertical margins to be tumor-free on histological examination was defined as complete resection, and that showing cancer cells at the resection margin was defined as incomplete resection. Multiple fragment resection was also defined as incomplete resection, even if it resulted in tumor-free vertical margins with no macroscopic residual disease because the lateral margin could not be evaluated. Curative resection (CR) required the fulfillment of all of the following criteria on histological examination of the resected specimen: (1) intestinal-type adenocarcinoma, (2) pT1a(M) of any size or pT1b(SM1) (within 500 μm from the lamina muscularis mucosae) if $\leq$3 cm in size, (3) tumor-free at the vertical margin, (4) UL-negative tumor of any size or UL-positive tumor $\leq$3 cm in size, and (5) no lymphatic or vascular involvement. Curability was classified, according to the resection mode, as complete curative resection (CCR) or incomplete curative resection (ICR). If none of the criteria for CR were satisfied, the case was classified as noncurative resection (NCR).

While no additional treatment was required for CCR cases, surgical resection was recommended for NCR cases. For ICR cases, surgical resection was not mandatory, and either additional ESD or observation without additional treatment was permitted.

Complications

When symptoms of melena, hematochezia, or hematemesis were noted after ESD, all bleeding events were confirmed by emergency endoscopy. Perforation was diagnosed by observation of (1) mesenteric fat on endoscopy or (2) free air on abdomen radiography or CT scan.

Follow-up

Esophagogastroduodenoscopy at 2 months after ESD was performed to confirm healing of the artificial ulcer and to check for residual tumors. During follow up, esophagogastroduodenoscopy (to check for local recurrence and metachronous tumor) and abdominal CT (to detect lymph-node or distant metastasis) were repeated at least once a year for 5 years.

Statistical analysis

This trial was designed as a confirmatory trial to determine the efficacy and safety of ESD for cT1aN0M0 gastric cancer in terms of 5-year OS. The primary endpoint was the 5-year OS for all enrolled patients. At the planning phase, the expected 5-year OS was tentatively set at 90% based on the age- and sex-adjusted 5-year OS calculated from the 1991–2000 population using the abridged life tables for 2004 in Japan [17]. Prior to the primary analysis,

the expected 5-year OS was calculated based on the actual age and sex distribution of the enrolled patients, and the threshold 5-year OS was set at 85%, a value 5% lower than the expected 5-year OS. The initial planned sample size was 330, with a one-sided alpha level of 5% and a power of 80%. The protocol was amended to obtain a more precise estimate by increasing the sample size 1 year after the initiation of patient accrual because the patient accrual speed was better than expected. Thus, the sample size was increased from 330 to 470 patients with a one-sided alpha level of 2.5% and power of 90%. The Kaplan–Meier method was used to estimate survival curves, and the confidence interval (CI) was estimated by Greenwood's formula. If the lower limit of the 95% CI for 5-year OS exceeded the threshold 5-year OS, the primary endpoint was met. Adverse events were assessed according to Common Terminology Criteria for Adverse Events version 3.0. The JCOG Data Center was responsible for data management, central monitoring, and statistical analysis. None of the physicians administering the interventions were involved in data analysis. All statistical analyses were performed with an intention-to-treat principle using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients and clinicopathological characteristics

A total of 470 patients with early gastric cancer (cT1aN0M0) were enrolled from 29 institutions between June 2007 and October 2010. There were no ineligible cases. The median age was 65 years (range 40–75 years), and 85 (18.1%) patients were female. The macroscopic appearance type was protruded in 155 (33.0%), depressed in 258 (54.9%), and mixed (combined protruded and depressed) in 57 (12.1%) patients. A total of 71 (15.1%), 255 (54.3%), and 144 (30.6%) lesions were located in the upper, middle, and lower third of the stomach, respectively. The median lesion size was 25 mm (range 5–130 mm). The tumor characteristics were UL-negative and ≤3 cm in size in 152 (32.3%) patients, UL-negative and >3 cm in size in 111 (23.6%) patients, and UL-positive and ≤3 cm in size in 207 (44.1%) patients (Table 1).

Endoscopic submucosal dissection results

The median duration of ESD was 79 min (range 14–462 min), and the median size of the resected tissue was 50 mm (range 21–122 mm). Of 470 patients, 466 (99.1%, 95% CI, 97.8–99.8%) underwent en bloc resection. In 3 patients, tumors were resected by multiple fragments, and ESD was discontinued because of perforation in one patient. Curability judged by resection mode and pathological findings was CCR in 317 (67%) patients, ICR in 6 (1%) patients, and NCR in 146 (31%) patients (Table 2); 1 patient could not be evaluated because of emergent surgery for intraoperative perforation. Of the CCR patients, 34 patients had pT1a ≤2 cm and were UL-negative, 152 patients had pT1a >2 cm and were UL-negative, 105 patients had pT1a ≤3 cm and were UL-positive, and 26 patients had pT1b (SM1 <500 μm), ≤3 cm.

The causes of NCR and ICR are shown in Table 3. There were multiple causes in some cases; a total of 268 causes (NCR 262, ICR 6) were reported in 152 patients (NCR 146, ICR 6). These causes were categorized as diagnostic, pathological, or both. Diagnostic causes were considered to be due to pre-ESD underdiagnosis, and pathological causes were revealed only with post-ESD pathological assessment. Among the reported 268 causes, 115 (43%) were diagnostic (SM2 61, horizontal margin [+]

Table 1 Patient and tumor characteristics

Age		
Min–max	40–75	
Median	65	
Sex		
Male	385	
Female	85	
Ulcerative findings and size	≤3 cm	>3 cm
UL-negative	152	111
UL-positive	207	0
Tumor size (mm)		
Min–max	5–130	
Median	25	
Macroscopic type		
Protruded type (0-I, 0-IIa)	155	
Depressed type (0-IIb, 0-IIc, 0-III)	258	
Mixed type (0-IIa + IIc, 0-IIc + IIa)	57	
Tumor location		
Upper	71	
Middle	255	
Lower	144	
Tumor location (transverse section) (multiple choice)		
Lesser curvature	231	
Greater curvature	64	
Anterior wall	89	
Posterior wall	142	
Predominant histology		
Pap	6	
tub1	356	
tub2	108	

UL ulcerative, *Pap* papillary adenocarcinoma, *tub1* well-differentiated adenocarcinoma, *tub2* moderately differentiated adenocarcinoma

or [±] 22, vertical margin [+] or [±] 32), and 81 (30%) were pathological (dominantly undifferentiated-type 10, undifferentiated-type in SM invasion 20, lymphatic invasion 38, venous invasion 13), while 72 (27%) were both (UL-positive >3 cm: 44, pSM1 >3 cm: 28). A total of 132 patients, including 1 of 6 patients with ICR and 131 of 146 patients with NCR, underwent additional surgical resection (126 at the participating institutions and 6 at other hospitals), and 15 patients with NCR were followed up without additional treatment (Fig. 1). In the 132 patients with additional surgical resection, lymph node metastasis was pathologically detected in 7 (5%).

Complications

Perforation occurred in 12 patients (grade 2 and 3: 2.6%) during ESD (Table 4). Endoscopic closure by clipping was successful in 11 of these patients while emergent surgery was performed in 1 patient. Twenty-nine patients (grade 2 and 3: 6.2%) required endoscopic hemostasis after ESD (within 30 days), and 3 of those patients received a blood transfusion. Post-ESD secondary hemorrhage tended to be observed more frequently in patients with a resected tissue size >30 mm than in those with a resected tissue size ≤30 mm (10.9% vs. 4.7%, respectively, two-sided $P = 0.024$ by Fisher's exact test). While grade 3 or 4 adverse events were observed in 7 (5.3%) of 133 patients receiving additional surgical resection, grade 4 adverse events occurred in only 2 patients (acute pancreatitis and acute respiratory distress syndrome in 1 patient, central nervous system ischemia in 1 patient), both of whom recovered within a short period.

Clinical outcomes

The expected 5-year OS based on the actual age and sex distribution of enrolled patients was calculated as 91.1%. Thus, the threshold 5-year OS was found to be 86.1%. The number of patients lost to follow-up within 5 years was 22 (4.7%). With a median follow-up of 73.8 months (range 9.3–98.8) for all enrolled patients, the 5-year OS was 97.0% (95% CI, 95.0–98.2%) (Fig. 2a). The lower limit of the 95% CI of the 5-year OS was higher than the threshold 5-year OS (86.1%), and the primary endpoint was met. The 5-year RFS in all enrolled patients was 96.9% (95% CI 94.9–98.2%) (Fig. 2b). Among the 317 (67.4%) patients followed up after achieving CCR, no local or distant recurrence was observed and no deaths due to gastric cancer were encountered. In contrast, among the 146 (31.1%) patients with NCR, 3 (0.6%) patients (pSM2 depth of invasion after ESD in all 3 patients) developed a recurrence (liver only in 1 patient; left adrenal gland only in 1 patient; and lymph node, liver, lung, and bone in 1

Table 2 Operation details and pathological results of endoscopic submucosal dissection ($n = 470$)

Operation duration (minutes)	
Min–max	14–462
Median	79
ESD device	
IT knife, IT knife2	387
Hook knife	31
Flex knife	12
Needle knife	8
Flush knife	26
Other	6
Size of resected specimen (mm)[a]	
Median	50
Min–max	21–122
Technical assessment[a]	
Complete resection (en bloc)	431
Incomplete resection (cut into the lesion)	35
Incomplete resection (multiple fragments)	3
Predominant type[a]	
Pap	9
tub1	322
tub2	128
por1	5
por2	3
Sig	2
Depth of invasion[a]	
pM	346
pSM1	62
pSM2	59
SM invasive part undiff absent	102
SM invasive part undiff present	20
Ulcerative change[a]	
UL-negative	273
UL-positive	196
Tumor size (cm)[a]	
Median	2.8
Min–max	0.2–8.5
Lymphatic involvement[a]	
ly0	431
ly1	32
ly2	6
Vessel involvement[a]	
v0	456
v1	12
v2	1
Horizontal margin[a]	
Negative	447
Positive	9
Unknown	13
Vertical margin[a]	

Negative	437
Positive	13
Unknown	19
Curative assessment[a]	
Complete curative resection	317
Noncurative resection	146
Incomplete resection	6

ESD endoscopic submucosal dissection, *pap* papillary adenocarcinoma, *tub1* well-differentiated adenocarcinoma, *tub2* moderately differentiated adenocarcinoma, *por1* solid type of poorly differentiated adenocarcinoma, *por2* nonsolid type of poorly differentiated adenocarcinoma, *sig* signet-ring cell carcinoma, *UL* ulcerative

[a] One patient who underwent emergency surgery is missing from the data

patient) after additional surgical resection. These 3 patients subsequently received systemic chemotherapy, but all died of gastric cancer. In addition, the 5-year RFS with preserved stomach was 68.8% (95% CI 64.4–72.8%) in all patients and 95.8% (95% CI 92.9–97.5%) in those with CCR (Fig. 3a, b). Nine patients underwent gastrectomy for metachronous gastric cancer, and 1 patient underwent gastrectomy for a gastrointestinal stromal tumor after CCR. The 6 patients with ICR had no recurrence.

Discussion

This was the first multicenter confirmatory clinical trial evaluating the safety and efficacy of ESD for the expanded indication of intestinal-type gastric cancer (cT1a) including UL-negative tumor >2 cm in size or UL-positive tumor ≤3 cm in size. This trial demonstrated a good safety profile and good clinical outcomes in 470 patients with cT1aN0M0 for intestinal-type gastric adenocarcinoma. Complications associated with ESD were manageable, and the obtained lower limit of the 95% CI of the 5-year OS clearly exceeded the prespecified threshold. In this analysis, we used the survival rate of the general population adjusted for sex and age as a reference to determine the expected and threshold values of the 5-year OS. However, this study was biased as patients with preserved organ function and without severe complications were enrolled due to the eligibility criteria, resulting in a lower frequency

Table 3 Causes of noncurative resection and incomplete resection (there were multiple causes in some cases)

	Diagnostic			Pathological				Size	
	SM2	HM (+) or (±)	VM (+) or (±)	Dominant undiff type	Undiff type in SM invasion	ly+	v+	UL-positive >3 cm	pSM1 >3 cm
UL-negative >2 cm	34	13	19	5	12	25	6	21	25
UL-positive ≤3 cm	27	9	13	5	8	13	7	23	3
Total	61	22	32	10	20	38	13	44	28
	115			81				72	

HM horizontal margin, *SM* submucosal, *UL* ulcerative

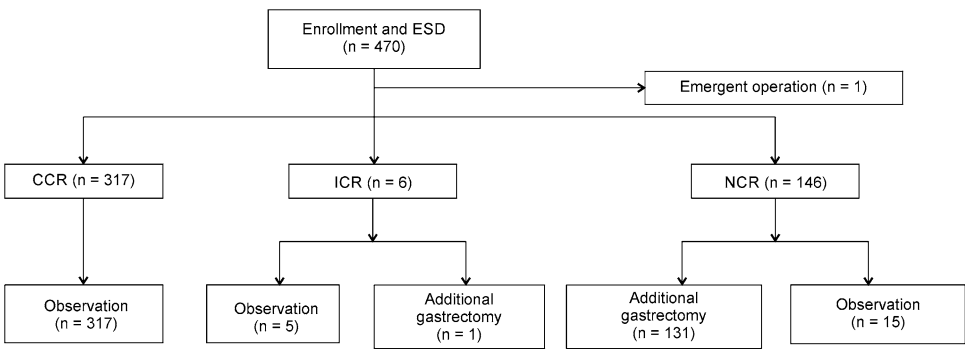

Fig. 1 Patient flow diagram. *ESD* endoscopic submucosal dissection, *CCR* complete curative resection, *ICR* incomplete curative resection, *NCR* noncurative resection

Table 4 Adverse events after endoscopic submucosal dissection

	G0	G1	G2	G3	G4	%G2–4	%G3–4	%G4	Total
Fever (>38 °C)	437	30	2	0	0	0.4	0	0	469
Aspiration	466	1	1	1	0	0.4	0.2	0	469
Appetite loss	457	11	1	0	0	0.2	0	0	469
Dysphagia	469	0	0	0	0	0	0	0	469
Heartburn	458	11	0	0	–	0	0	–	469
Nausea	454	14	1	0	0	0.2	0	0	469
Vomiting	461	6	2	0	0	0.4	0	0	469
Perforation: stomach	458	0	11	1	0	2.6	0.2	0	470
Pain: epigastric	417	43	9	0	0	1.9	0	0	469
Pain: throat	458	11	0	0	0	0	0	0	469
After bleeding: stomach	429	11	26	3	0	6.2	0.6	0	469

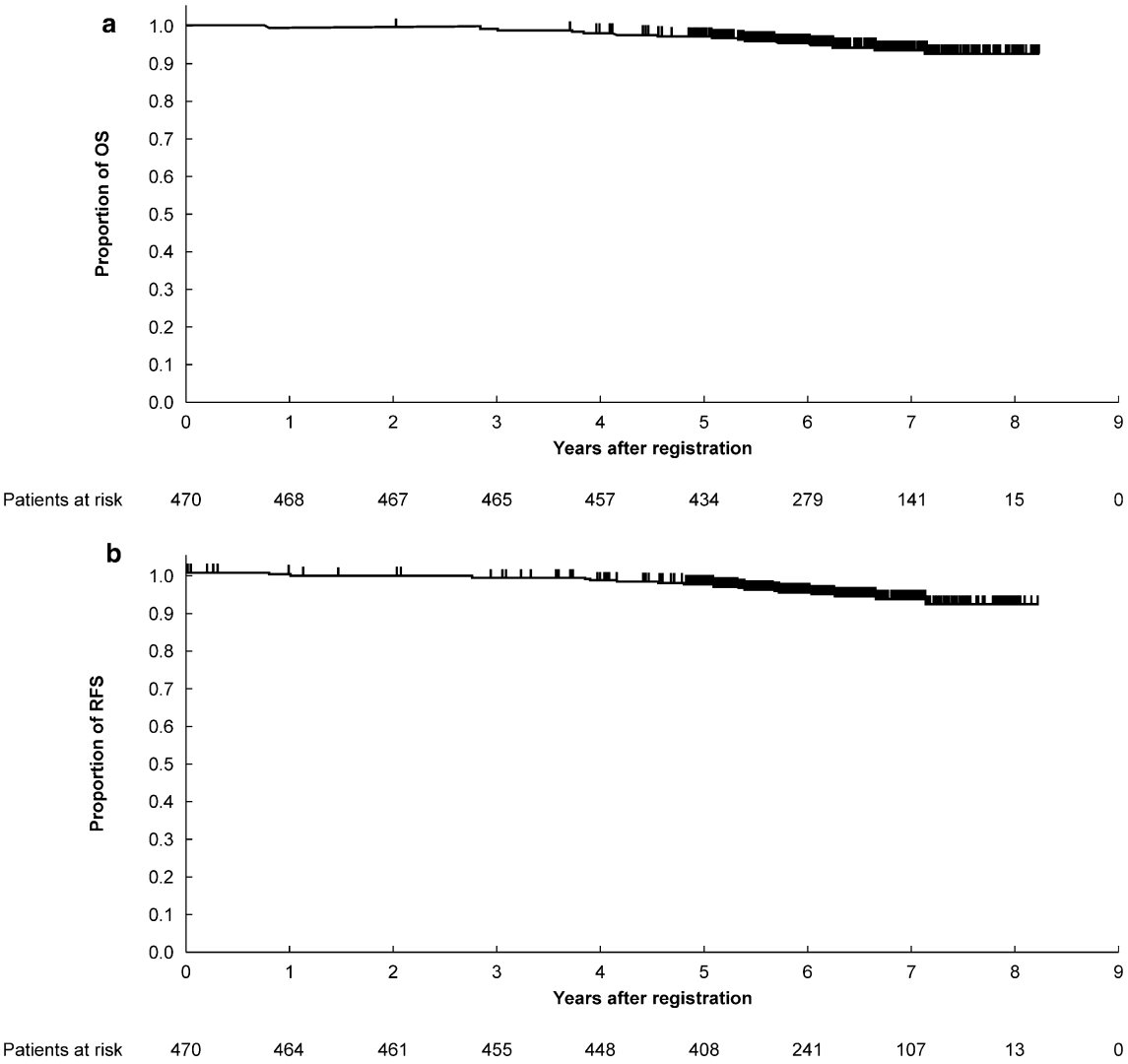

Fig. 2a–b Overall (**a**) and recurrence-free (**b**) survival for all enrolled patients. *OS* overall survival, *RFS* recurrence-free survival

of death due to other diseases compared to the general population. Another major limitation of this study is that it was not a randomized controlled trial. During the planning of this study, we expected it to be difficult to conduct a randomized phase III trial comparing surgical resection and ESD, which was very popular in Japan, so we designed this

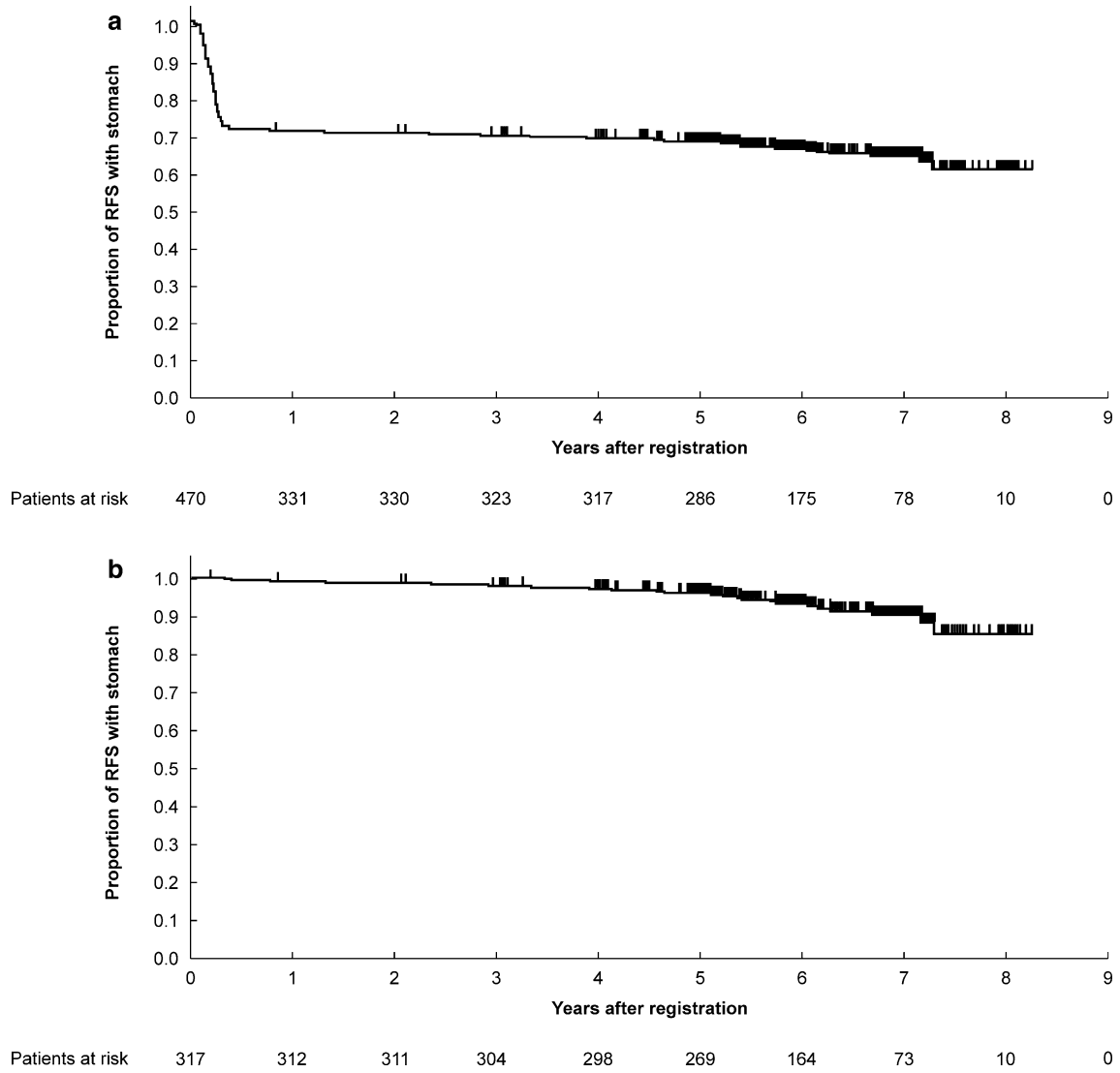

Fig. 3a–b Recurrence-free survival with preserved stomach for all enrolled patients (**a**) and complete curative resection patients (**b**). *RFS* recurrence-free survival

study as a confirmatory trial with a large sample size. However, there was no recurrence (100% curability) in 317 and 6 patients with CCR and ICR, respectively, and all but 3 of the 146 patients with NCR could be salvaged by performing additional surgery. While the 5-year RFS with preserved stomach for all cases was 68.8%, that for the patients with CCR was as high as 95.8%. Thus, the expanded indication for ESD can be accepted without a randomized controlled trial, given that it markedly improved the patients' quality of life. However, metachronous gastric cancer in the preserved stomach is another problem. In this study, 9 patients underwent gastrectomy for metachronous gastric cancer. The appropriate interval between endoscopic examinations needed to ensure that the patient's stomach is preserved throughout their life should be investigated in future trials.

One reason for the excellent outcomes obtained in our study was the endoscopists' technique in Japan. En bloc resection, which was obtained in 99.1% of the subjects, enables precise pathological evaluation. When planning this study, we believed that the ESD technique would be very important, as previous reports indicated an increased perioperative risk of complications and poor clinical outcomes due to lack of experience [6, 8, 8, 18–20]. In this study, only certified endoscopists that had performed more than 100 ESDs were allowed to perform ESD [3, 21, 22]. Endoscopist training for ESD is necessary to generalize the results of this study worldwide.

Another reason for the excellent outcomes attained in this study was the strict criteria applied for curative resection. The criteria for evaluating curability were determined based on previous reports of the frequency of lymph node

metastasis pathologically detected after gastrectomy, which suggested that CCR was associated with nearly 0% possibility of lymph node metastasis [6]. In other words, patients who did not satisfy the criteria for CCR had some risk of metastasis. Indeed, 3 patients (2%) with NCR died of gastric cancer after a recurrence with distant metastasis, even after additional surgical resection. Nevertheless, the outcome of additional surgery in this study was better than the previously reported 5-year OS of 89.3% for stage Ib gastric cancer [1, 3, 17, 23]. The good outcomes obtained after additional surgery partly contributed to the overall results of this study. However, the risk of lymph node metastasis in patients with NCR was estimated to be less than 10% in previous reports of surgical resection [24]. In fact, lymph node metastasis was detected in only 5% of the 131 patients with additional surgical resection. The present criteria for additional surgical resection after NCR may be too strict from a quality of life viewpoint because additional surgery would be considered overtreatment for more than 90% of patients without lymph node metastasis. New biomarkers predicting individual metastasis risk should be developed, in addition to pathological findings, to expand the indication for ESD and preserve the stomach in more patients.

Although CCR was attained in 67% of patients, in most of whom the stomach could be preserved, additional surgical gastrectomy was performed in 28% of the patients for whom ESD was not considered to be necessary. Among the causes of additional surgical resection, diagnostic causes—accounting for 43% of those patients—could be prevented by more accurate endoscopic diagnosis. In this study, each endoscopist decided which diagnostic tools to use, such as endoscopic ultrasound sonography. Generally, the accuracy rate when differentiating between mucosal and submucosal gastric cancer has been reported to be approximately 80% [25–28]. The relatively high rate of underdiagnosis in this study was likely due to the study population, as the extended indication criteria for ESD (such as large size and presence of UL) made depth diagnosis difficult. In the future, endoscopic diagnosis for tumor depth and spread should be improved by applying new image-enhanced endoscopy techniques such as narrow-band imaging.

As for the adverse events associated with ESD, Oka et al. noted that the incidence of perforation with ESD was significantly higher (53.8%) in cases of UL and advocated special measures for ESD of UL-positive lesions [4]. However, the overall incidence of perforation was as low as 2.6% in our study. This can be attributed to the fact that, in our expanded indication criteria, we limited the size of UL-positive lesions to $\leq$3 cm. This confirmatory trial indicates that the expanded indication criteria for ESD of intestinal-type gastric cancer (cT1a) do not notably increase the perforation risk [4, 21, 22, 29, 30]. Isomoto et al. [31] reported a perforation incidence of 4.6%, and that bleeding requiring a blood transfusion occurred in only a small percentage of patients. In this study, 6.2% of the patients required endoscopic hemostasis within 30 days after ESD, and 3 of these patients received a blood transfusion. These results highlight the good safety profile of the expanded ESD indication for intestinal-type gastric cancer (cT1a). However, it should be recognized that postoperative secondary hemorrhage tended to be more common in patients with a resected tissue size >3 cm.

In conclusion, this confirmatory clinical trial indicates that ESD for early gastric cancer that satisfies the expanded criteria of intestinal-type gastric cancer (cT1a) and UL-negative tumor >2 cm in size or UL-positive tumor $\leq$3 cm in size showed a 5-year OS of 97.0% and was associated with few adverse events, all of which were manageable. Furthermore, the 5-year RFS with preserved stomach was 68.8%. ESD is recommended for early gastric cancer that complies with the expanded criteria for intestinal-type gastric cancer (cT1a) instead of surgical gastrectomy.

Acknowledgements This study was supported by Grants-in-Aid for Cancer Research (17S-3, 17S-5, 20S-3, 20S-6, 23-A-16, 23-A-19, 26-A-4) and Health and Labour Sciences Research Grants for Clinical Cancer Research (17-12, 20-15) from the Ministry of Health, Labour and Welfare, Japan. Participating institutions: Japan Clinical Oncology Group (JCOG); Gastrointestinal Endoscopy Study Group; Hokkaido University Hospital; Federation of National Public Service Personnel Mutual Aid Associations, Tonan Hospital; Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital; Asahi General Hospital; Ishikawa Prefectural Central Hospital; Saku Central Hospital Advanced Care Center; Shizuoka Cancer Center; Aichi Cancer Center Hospital; Aichi Cancer Center, Aichi Hospital; Kyoto University Hospital; Osaka Prefectural Hospital Organization, Osaka Medical Center for Cancer and Cardiovascular Diseases; Osaka City General Hospital; Kobe University Graduate School of Medicine; Hyogo Cancer Center; National Hospital Organization Shikoku Cancer Center; Kochi Health Sciences Center; Tochigi Cancer Center; Yamagata Prefectural Central Hospital; Ibaraki Prefectural Central Hospital & Cancer Center; Showa University School of Medicine; Cancer Institute Hospital of Japanese Foundation for Cancer Research; Toranomon Hospital; Yokohama City University Medical Center; Kanagawa Cancer Center; Kitasato University School of Medicine; National Cancer Center Hospital East; Chiba Cancer Center; National Cancer Center Hospital; Iwate Prefectural Central Hospital.

Compliance with ethical standards

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The study protocol was reviewed and approved by the Protocol Review Committee of JCOG and the institutional review board at each participating institution prior to initiation of the study. Written informed consent was obtained from all patients before they were included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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