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Long-term outcomes after non-curative endoscopic submucosal dissection for early gastric cancer according to hospital volumes in Japan: a multicenter propensity-matched analysis

Osamu Dohi[1] · Waku Hatta[2] · Takuji Gotoda[3] · Yuji Naito[1] · Tsuneo Oyama[4] · Noboru Kawata[5] · Akiko Takahashi[4] · Shiro Oka[6] · Shu Hoteya[7] · Masahiro Nakagawa[8] · Masaaki Hirano[9] · Mitsuru Esaki[3,10] · Mitsuru Matsuda[11] · Ken Ohnita[12] · Ryo Shimoda[13] · Motoyuki Yoshida[14] · Jun Takada[15] · Keiko Tanaka[16] · Shinya Yamada[17] · Tsuyotoshi Tsuji[18] · Hirotaka Ito[19] · Hiroyuki Aoyagi[20] · Tooru Shimosegawa[2]

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Abstract

Background There is a lack of data regarding the long-term outcomes of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) without curative resection, and the relationship of these outcomes with hospital volumes remains unclear. This study evaluated long-term outcomes of patients who underwent ESD for EGC without curative resection according to hospital volumes in Japan.

Methods This multicenter retrospective study evaluated 1,969 patients who did not meet the criteria of the Japanese Gastric Cancer Association for curative resection between January 2000 and August 2011. Hospitals were classified according to the annual number of ESD procedures: low- and medium-volume group (LMVG), high-volume group (HVG), and very high-volume group (VHVG). Clinicopathological features, overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were compared across groups after a generalized propensity score matching analysis.

Results In 495 pairs of generalized propensity score-matched patients, the 5-year OS, DSS, and RFS rates were 81.5%, 97.9%, and 97.6% for LMVG; 86.9%, 98.2%, and 97.0% for HVG; and 85.4%, 98.5%, and 97.6% for VHVG, respectively. The 5-year DSS and RFS rates did not significantly differ among the three groups. However, 5-year OS was significantly worse in the LMVG than in the HVG and VHVG ($P < 0.001$ and $P = 0.008$, respectively).

Conclusions DSS and RFS in patients with EGC who did not meet the criteria for curative resection did not differ across hospital volumes in Japan. Even in cases in which ESD for EGC involved non-curative resection, the procedure is feasible across Japanese hospitals with different volumes.

Keywords Hospital volume · Long-term outcome · Endoscopic submucosal dissection · Early gastric cancer · Propensity score matching

Gastric cancer is the second most common cause of cancer-associated death worldwide [1]. Since Gotoda and Hirasawa et al. reported the features of early gastric cancer (EGC) with no lymph node metastasis from a large database including patients who underwent gastrectomy with lymph node dissection [2, 3], endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have become widely accepted treatments for EGC without lymph node metastasis. According to the current guidelines of the Japanese Gastric Cancer Association [4], ESD is a feasible treatment for EGC with absolute and expanded indication [5].

In high-volume Japanese institutions, ESD for EGCs with absolute and expanded indications have been reported to have excellent outcomes and acceptable complication rates compared with EMR in the short [6–10] and long term [11, 12]. Short-term outcomes of ESD for EGCs at low-volume institutions were as good as those at high-volume institutions at 31 Japanese institutions [13]. By contrast, high-volume institutions had a better short-term outcome of ESD for patients with EGC in the upper third of the stomach

✉ Waku Hatta
waku-style@festa.ocn.ne.jp

Extended author information available on the last page of the article

compared with low-volume institutions as per the national administrative database of Japan [14].

However, insufficient data are available regarding the long-term outcomes of ESD for patients who do not meet the criteria of the Japanese Gastric Cancer Association for curative resection of EGC and their relationship with hospital volumes. Therefore, the aim of this study was to compare long-term outcomes of EGC among very high-, high-, and low- and medium-volume institutions in Japan using a retrospective cohort design.

Methods

Patients and participating institutions

We conducted a multicenter retrospective study at 19 institutions in Japan (Fig. 1); all institutions were members of the Establishment of Accommodation of Early Stomach Cancer Treatment (EAST) study group [15]. Of 15,785 consecutive patients who underwent ESD for EGC between January 2000 and August 2011, 2526 patients who did not meet the criteria of the Japanese Gastric Cancer Association for curative resection [16] were enrolled in this study. Patients with the following characteristics were excluded: (1) differentiated-type EGC with a positive horizontal margin as the only unsatisfactory curative factor; (2) synchronous EGC that did not meet the curative criteria for ESD; (3) ESD in the remnant stomach; (4) additional treatment except for surgical resection (e.g., chemotherapy, photodynamic therapy, or argon plasma coagulation); (5) invasion of the muscularis propria or deeper in the surgically resected specimen; (6) synchronous or metachronous advanced cancer; (7) missing data; and (8) patients with a follow-up period of < 3 years, except those who died, since previous studies [17–19] have reported frequent recurrence within 3 years after endoscopic or surgical resection.

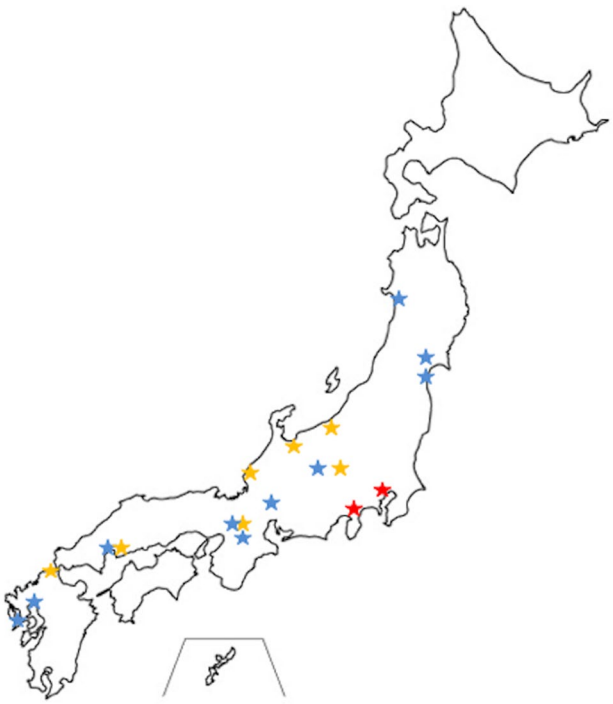

Fig. 1 Map of 19 institutions in Japan included in this multicenter retrospective study (each indicated by a star). Blue star: low- and medium-volume group, yellow star: high-volume group, red star: very high-volume group. (Color figure online)

This study was approved by the Ethical Review Committee of each institution and was carried out in accordance with the Helsinki Declaration of the World Medical Association. All patients provided written informed consent before ESD.

Hospital volume

Hospital volumes were defined according to the average annual number of ESD procedures per hospital between January 2000 and August 2011 as follows: low- and medium-volume group (LMVG; low-volume: < 50/year and medium-volume: 50–99/year, $n = 685$), high-volume group (HVG; 100–200/year, $n = 714$), and very high-volume group (VHVG; > 200/year, $n = 570$). These categories were based on cutoff values that resulted in a similar number of patients in each group. Hospital type was classified as academic or community [14]. Hospital size was defined according to the number of hospital beds as small (< 200 beds), medium (200–600 beds), or large (> 600 beds) [14]. Hospital region was also classified into two categories: metropolis (population ≥ 1,000,000) and provincial city (population < 1,000,000).

Procedure

After endoscopic diagnosis, ESD was performed using a high-frequency diathermy knife, typically under moderate sedation. Clinicopathological features such as patient age, sex, tumor location, tumor size, macroscopic type, recurrence, and prognosis were collected at the time of ESD at each institution. Lymph node metastasis was also reviewed in patients who underwent radical surgery. Radical curative surgical resection with D1–2 lymph node dissection was recommended after ESD for all patients who did not meet the criteria of the Japanese Gastric Cancer Association for curative resection. All the radical surgeries were performed by board-certified surgeons in Gastroenterology of the Japanese Society of Gastroenterological Surgery in all institutions. Finally, additional treatment was decided by physicians in each institution. Therefore, the patients who agreed to radical surgery with lymph node dissection

were included. However, those who did not undergo surgery owing to older age, the presence of severe comorbidities, or individual preference were followed up with no additional treatment. According to guidelines [4], patients who underwent radical surgery were typically followed up by annual esophagogastroduodenoscopy (EGD) and computed tomography (CT). Those who were followed up with no additional treatment also underwent scheduled surveillance via EGD and CT with a follow-up interval of 6–12 months.

Pathological diagnosis

ESD and surgically resected specimens of all lesions were fixed in 10% formalin and pathologically evaluated under a microscope using hematoxylin–eosin and immunohistochemical staining. At each institution, highly experienced gastrointestinal pathologists who were certified pathologists of the Japanese Society of Pathology evaluated the pathological diagnoses according to the Japanese Classification of Gastric Carcinoma proposed by the Japanese Gastric Cancer Association [20]. The depth of submucosal invasion was classified as SM1 (tumor invasion into submucosa < 500 μm from the muscularis mucosa) or SM2 (tumor invasion into submucosa ≥ 500 μm from the muscularis mucosa).

Definitions

The resection is considered as curative when all of the following conditions are fulfilled [4]: En bloc resection, HM0, VM0, ly(−), v(−), and

(1) Tumor size ≤ 2 cm, histologically of differentiated type, pT1a, UL(−).
(2) Tumor size > 2 cm, histologically of differentiated type, pT1a, UL(−).
(3) Tumor size ≤ 3 cm, histologically of differentiated type, pT1a, UL(+).
(4) Tumor size ≤ 2 cm, histologically of undifferentiated type, pT1a, UL(−).
(5) Tumor size ≤ 3 cm, histologically of differentiated type, pT1b (SM1, < 500 micron from the muscularis mucosae).

Resection that does not satisfy any of the above criteria is considered non-curative.

Local recurrence was defined as pathologically proven tumor relapse at the site of ESD. Lymph node recurrence was defined as radiologically or pathologically in the lymph nodes, and distant recurrence was defined as radiologically or pathologically in the distant other organs after a series of treatments for EGC.

Overall survival (OS) was determined from the date of ESD to death. Disease-specific survival (DSS) was determined from the date of ESD to death from gastric cancer. Recurrence-free survival (RFS) was determined from the date of ESD to the first relapse or death with evidence of recurrence.

Statistical analysis

The chi-squared test was used to compare the two groups. OS, DSS, and RFS were calculated by the Kaplan–Meier method. Differences in survival were examined by the log-rank test. *P* values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Moreover, we performed a generalized propensity score matching analysis among three groups to reduce the effect of selection bias for hospital volumes. The propensity score matching method was proposed to evaluate statistically causal effects free from confounding effects by mathematically refashioning an observational study into a randomized study; therefore, studies using the propensity score approach are occasionally considered pseudo-randomized studies [21]. Propensity scores were estimated by using a logistic regression model of the following covariates: patient age and sex, tumor size, macroscopic type, location, invasion depth, ulceration, and histological type of the tumor. By using these generalized propensity scores, patients were individually matched among the three groups (a 1:1:1 matching). The matched data sets were thoroughly checked for balance in terms of an absolute standardized difference (ASD) near 0 and variance ratios near 1.

Results

Clinicopathological characteristics

Among 2526 patients who did not meet the criteria of the Japanese Gastric Cancer Association for curative resection, 557 patients who did not fulfill this study protocol were excluded, and a total of 1969 patients were enrolled in this study: 685 patients in the LMVG, 714 patients in the HVG, and 570 patients in the VHVG. A study flowchart and the distribution of generalized propensity scores are shown in Fig. 2. After generalized propensity score matching, there were 495 matched pairs of patients who did not meet the criteria for curative resection among the three groups.

The characteristics of the hospitals are shown in Table 1. There was no significant difference based on hospital type, size, or region among the three groups. However, the proportion of curative resections in the VHVG was significantly lower than that in the LMVG and HVG ($P < 0.001$). Table 2 shows the clinicopathological features of all patients and generalized propensity-matched patients according to

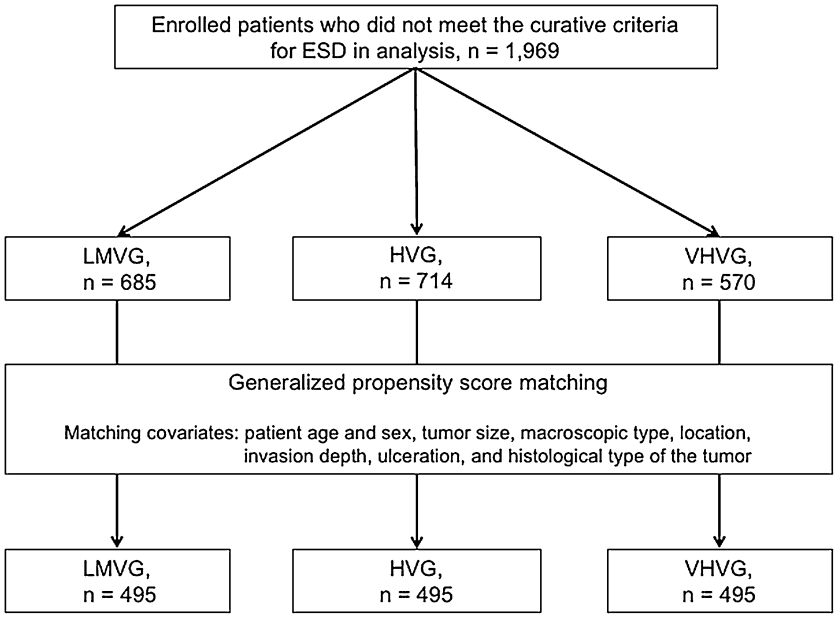

Fig. 2 Flowchart of patient enrollment. *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer, *LMVG* low- and medium-volume group, *HVG* high-volume group, *VHVG* very high-volume group

Table 1 Characteristics among hospital volumes

Variables	LMVG	HVG	VHVG	*P* value
No. of hospitals	10	7	2	
Hospital type, *n* (%)				0.076
Academic hospital	7 (70.0)	1 (14.3)	1 (50.0)	
Community hospital	3 (30.0)	6 (85.7)	1 (50.0)	
Hospital size, *n* (%)				0.669
Small-sized hospital	0	0	0	
Medium-sized hospital	3 (30.0)	2 (28.6)	0	
Large-sized hospital	7 (70.0)	5 (71.4)	2 (100)	
Hospital region, *n* (%)				0.795
Metropolis	3 (30.0)	3 (42.9)	1 (50.0)	
Provincial city	7 (70.0)	4 (57.1)	1 (50.0)	
No. of patients				< 0.001
Curative resection	4467 (82.9)	5934 (86.4)	2858 (80.8)	
Others	919 (17.1)	931 (13.6)	676 (19.2)	

LMVG low- and medium-volume group, *HVG* high-volume group, *VHVG* very high-volume group

hospital volume. Sex ratio, tumor location, and histological type were not significantly different across the three groups. The mean age in the VHVG was significantly younger than that in the LMVG and HVG ($P = 0.003$). The mean tumor size in the HVG was significantly smaller than that in the LMVG and VHVG ($P < 0.001$). The proportion of depressed-type cancers in the VHVG was significantly higher than that in the LMVG and HVG ($P < 0.001$). The proportion of intramucosal cancers in the VHVG was significantly higher than that in the LMVG and HVG ($P = 0.004$). The presence of ulceration in the VHVG was significantly higher than that in the LMVG and HVG ($P < 0.001$). In addition, patients in the LMVG had higher rates of lymphatic invasion ($P = 0.035$) and vascular invasion ($P < 0.001$) than those in the HVG and VHVG. The rate of radical surgery was nearly 55% among the three groups, with no significant difference among the groups. Clinical outcomes, such as lymph node metastasis and recurrence, were not significantly different among the three groups. Follow-up duration was significantly longer in the HVG than that in the LMVG and VHVG ($P < 0.001$).

In the 495 pairs of generalized propensity score-matched patients, the baseline characteristics of the three groups were comparable. The ASDs for all matched covariates were < 0.1, suggesting a substantial balance across the three groups. After matching, the difference in lymphatic invasion was no longer present among the three groups. However, the differences in vascular invasion ($P = 0.004$) and follow-up duration ($P < 0.001$) remained after matching.

Long-term outcomes

During the follow-up period, gastric cancer recurred in 12 patients (2.4%) from the LMVG, 15 patients (3.0%) from the HVG, and 12 patients (2.4%) from the VHVG after a generalized propensity score matching. Table 3 shows recurrences of gastric cancers in all patients and generalized propensity-matched patients who were followed up and those who underwent radical surgery after non-curative ESD for EGC according to hospital volume. There was no significant

Table 2 Clinicopathological characteristics of gastric cancers

Variables	Overall					Propensity score-matched				
	LMVG	HVG	VHVG	ASD	*P* value	LMVG	HVG	VHVG	ASD	*P* value
	n = 685	*n* = 714	*n* = 570			*n* = 495	*n* = 495	*n* = 495		
Sex, *n* (%)				0.04	0.283				0.01	0.972
Male	528 (77.1)	548 (76.8)	457 (80.2)			391 (79.0)	393 (79.4)	394 (79.6)		
Female	157 (22.9)	166 (23.2)	113 (19.8)			104 (21.0)	102 (20.6)	101 (20.4)		
Age, years, mean ± SD[e]	71.4 ± 9.4	71.2 ± 9.9	69.7 ± 9.8	0.08	0.003	70.9 ± 9.3	71.2 ± 9.7	70.2 ± 9.2	0.04	0.284
Tumor size (mm), mean ± SD	33.7 ± 19.5	29.3 ± 18.2	33.8 ± 18.9	0.11	< 0.001	32.1 ± 18.6	30.6 ± 17.1	32.8 ± 17.3	0.05	0.138
Location, *n* (%)				0.04	0.099				0.04	0.313
Upper third	206 (30.1)	201 (28.2)	157 (27.6)			149 (30.1)	143 (28.9)	147 (29.7)		
Middle third	284 (41.4)	272 (38.1)	251 (44.0)			193 (39.0)	198 (40.0)	219 (44.2)		
Lower third	195 (28.5)	241 (33.7)	162 (28.4)			153 (30.9)	154 (31.1)	129 (26.1)		
Tumor morphology, *n* (%)				0.08	< 0.001				0.03	0.574
Elevated/flat	206 (30.1)	209 (29.3)	134 (23.5)			143 (28.9)	142 (28.7)	122 (24.6)		
Depressed	323 (47.2)	387 (54.2)	346 (60.7)			272 (54.9)	272 (54.9)	290 (58.6)		
Mixed	156 (22.7)	118 (16.5)	90 (15.8)			80 (16.2)	81 (16.4)	83 (16.8)		
Histological type, *n* (%)				0.03	0.490				0.02	0.938
Differentiated	455 (66.4)	448 (62.7)	360 (63.1)			315 (63.6)	319 (64.4)	327 (66.1)		
Undifferentiated	59 (8.6)	74 (10.4)	50 (8.8)			46 (9.3)	43 (8.7)	44 (8.9)		
Mixed type	171 (25.0)	192 (26.9)	160 (28.1)			134 (27.1)	133 (26.9)	124 (25.0)		
Depth, *n* (%)				0.06	0.004				0.04	0.322
Intramucosal	132 (19.3)	135 (18.9)	153 (26.8)			101 (20.4)	85 (17.2)	110 (22.2)		
Submucosa superficial	157 (22.9)	177 (24.8)	123 (21.6)			112 (22.6)	123 (24.8)	106 (21.4)		
Submucosa deep	396 (57.8)	402 (56.3)	294 (51.6)			282 (57.0)	287 (58.0)	279 (56.4)		
Ulceration, *n* (%)				0.09	< 0.001				0.05	0.206
Absence	497 (72.6)	547 (76.6)	360 (63.2)			357 (72.1)	367 (74.1)	342 (69.1)		
Presence	188 (27.4)	167 (23.4)	210 (36.8)			138 (27.9)	128 (25.9)	153 (30.9)		
Lymphatic invasion, *n* (%)				0.06	0.035				0.04	0.359
Positive	255 (34.4)	229 (32.1)	176 (30.9)			182 (36.8)	163 (32.9)	164 (33.1)		
Negative	430 (65.6)	485 (67.9)	394 (69.1)			313 (63.2)	332 (67.1)	331 (66.9)		
Vascular invasion, *n* (%)				0.10	< 0.001				0.09	0.004
Positive	153 (22.3)	96 (13.4)	111 (19.5)			108 (21.8)	70 (14.1)	101 (20.4)		
Negative	532 (77.7)	618 (86.6)	459 (80.5)			387 (78.2)	425 (85.9)	394 (79.6)		
R0 resection, *n* (%)				0.05	0.060				0.01	0.909
R0	539 (78.7)	591 (82.8)	475 (83.3)			402 (81.2)	406 (82.0)	407 (82.2)		
R1/RX	146 (21.3)	123 (17.2)	95 (16.7)			93 (18.8)	89 (18.0)	88 (17.8)		
Additional therapy, *n* (%)				0.03	0.428				0.04	0.374
Follow-up	308 (45.0)	342 (47.9)	255 (44.7)			214 (43.2)	235 (47.5)	219 (44.2)		
Radical surgery	377 (55.0)	372 (52.1)	315 (55.3)			281 (56.8)	260 (52.5)	276 (55.8)		
Lymph node metastasis, *n* (%)				0.06	0.135				0.08	0.072
Absent	354 (93.9)	335 (90.1)	287 (91.1)			265 (94.3)	232 (89.2)	248 (89.9)		
Present	23 (6.1)	37 (9.9)	29 (9.2)			16 (5.7)	28 (10.8)	28 (10.1)		
Recurrence, *n* (%)				0.02	0.559				0.02	0.789
Absent	664 (96.9)	689 (96.5)	556 (97.5)			483 (97.6)	480 (97.0)	483 (97.6)		
Present	21 (3.1)	25 (3.5)	14 (2.5)			12 (2.4)	15 (3.0)	12 (2.4)		
Follow-up (months), mean ± SD	63.9 ± 27.8	77.4 ± 34.2	71.1 ± 27.1	0.19	< 0.001	64.2 ± 27.7	77.5 ± 33.0	70.5 ± 27.2	0.18	< 0.001

LMVG low- and medium-volume group, *HVG* high-volume group, *VHVG* very high-volume group, *ASD* absolute standardized difference, *SD* standard deviation

Table 3 Recurrence of gastric cancers in patients who were followed up and those who underwent radical surgery

Recurrence	Overall				Propensity score-matched			
	LMVG	HVG	VHVG	*P* value	LMVG	HVG	VHVG	*P* value
Radical surgery	*n* = 377	*n* = 332	*n* = 354		*n* = 281	*n* = 260	*n* = 276	
Follow-up	*n* = 308	*n* = 382	*n* = 216		*n* = 214	*n* = 235	*n* = 219	
Local, *n* (%)								
Radical surgery	0 (0)	0 (0)	0 (0)	1	0 (0)	0 (0)	0 (0)	1
Follow-up	10 (3.2)	10 (2.6)	9 (4.2)	0.59	4 (1.9)	8 (3.4)	6 (2.7)	0.60
Lymph node, *n* (%)								
Radical surgery	2 (0.5)	3 (0.9)	2 (0.6)	0.80	2 (0.7)	1 (0.4)	1 (0.4)	0.80
Follow-up	6 (1.9)	7 (1.8)	7 (3.2)	0.49	2 (0.9)	5 (2.1)	3 (1.4)	0.57
Distant other organ, *n* (%)								
Radical surgery	5 (1.3)	5 (1.5)	3 (0.8)	0.72	5 (1.8)	3 (1.2)	2 (0.7)	0.52
Follow-up	11 (3.6)	3 (0.8)	7 (3.2)	0.06	5 (2.3)	3 (1.3)	4 (1.8)	0.70

LMVG low- and medium-volume group, *HVG* high-volume group, *VHVG* very high-volume group

difference in the rate of local, lymph node, and distant recurrences of gastric cancers in generalized propensity-matched patients among the three groups.

In the propensity-matched patients, local recurrence was shown in 3.9% of the follow-up patients with R1 resection (13/337) among all the hospitals. Local recurrences were occurred in four patients (2.9%; 4/138) from LMVG, six patients (5.8%; 6/104) from the HVG, and three patients (3.2%; 3/95) from the VHVG, with no significant difference ($P = 0.71$). In multivariable analysis, there was no independent factor associated with increased risk of R1 resection (Table 4).

Gastric cancer-related death occurred in nine patients (1.8%) from LMVG, seven patients (1.4%) from the HVG, and six patients (1.2%) from the VHVG. Death from other diseases occurred in 111 patients from the LMVG, 89 patients from the HVG, and 89 patients from the VHVG. The Kaplan–Meier survival curves for OS, DSS, and RFS are presented for the three groups after a generalized propensity score matching in Fig. 3. The 5-year OS, DSS, and RFS rates were 81.5%, 97.9%, and 97.6% for the LMVG; 86.9%, 98.2%, and 97.0% for the HVG; and 85.4%, 98.5%, and 97.6% for the VHVG, respectively. The 5-year DSS and RFS rates were not significantly different among the three groups; however, the 5-year OS rate was significantly poorer in the LMVG than in the HVG and the VHVG ($P < 0.001$ and $P = 0.008$, respectively) due to deaths from other diseases.

Table 4 Risk factors for R1/RX resection in stratified Cox regression analysis (propensity score-matched cohort)

Variables	Multivariable		
	HR	95% CI	*P* value
Tumor size			
> 30	1.06	0.82, 1.36	0.667
≤ 30	1	Reference	
Location			
Upper third	1.10	0.85, 1.43	0.467
Middle/lower third	1	Reference	
Ulceration			
Present	1.09	0.83, 1.44	0.529
Absent	1	Reference	
Dominant histological type			
Differentiated	1.16	0.82, 1.63	0.339
Undifferentiated	1	Reference	
Depth			
Submucosa deep	1.24	0.95, 1.61	0.112
Intramucosa/submucosa superficial	1	Reference	
Hospital volume			
HVG/VHVG	1.25	0.98, 1.60	0.073
LMVG	1	Reference	

HR hazard ratio, *CI* confidence interval, *HVG* high-volume group, *VHVG* very high-volume group, *LMVG* low- and medium-volume group

Risk factors of OS, DSS, and recurrence

The risk factors for all-cause death, disease-specific death, and the recurrence of gastric cancer in patients who did not meet the criteria of the Japanese Gastric Cancer Association for curative resection in the propensity score-matched cohort are shown in Tables 5, 6, and 7. In univariable analysis, radical surgery (hazard ratio [HR] 0.33, 95% confidence interval [CI] 0.25–0.42, $P < 0.001$), VHVG (HR 0.68, 95% CI 0.51–0.89, $P = 0.006$), and HVG (HR 0.56, 95% CI 0.42–0.74, $P < 0.001$) were significantly associated with decreased risk of all-cause death. In multivariable analysis, R1/RX resection was significantly associated with increased risk of all-cause death (HR 1.65, 95%

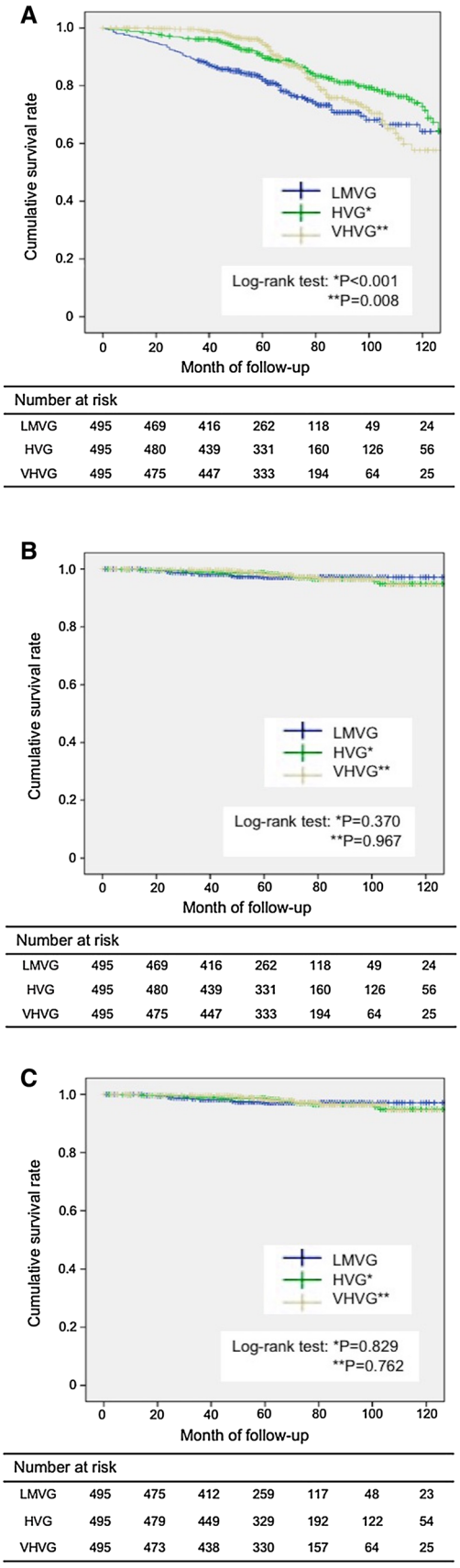

Fig. 3 Kaplan–Meier survival curves for overall survival (**A**), disease-specific survival (**B**), and recurrence-free survival (**C**) among three groups. *LMVG* low- and medium-volume group, *HVG* high-volume group, *VHVG* very high-volume group. **P* and ***P* compared to the LMVG

CI 1.24–2.20, $P=0.001$), while radical surgery (HR 0.30, 95% CI 0.23–0.38, $P<0.001$), VHVG (HR 0.69, 95% CI 0.52–0.91, $P=0.008$), and HVG (HR 0.53, 95% CI 0.40–0.71, $P<0.001$) were significantly associated with decreased risk of all-cause death in these patients (Table 5).

In univariable analysis, positive vascular invasion (HR 2.73, 95% CI 1.13–6.58, $P=0.025$) and R1/RX resection (HR 5.79, 95% CI 2.49–13.51, $P<0.001$) were significantly associated with increased risk of disease-specific death. In multivariable analysis, R1/RX resection (HR 6.38, 95% CI 2.66–15.29, $P<0.001$) and radical surgery (HR 0.40, 95% CI 0.16–0.96, $P=0.040$) were significantly associated with increased and decreased risk, respectively, of disease-specific death (Table 6).

In univariable analysis, R1/RX resection (HR 7.23, 95% CI 3.76–16.90, $P<0.001$) and radical surgery (HR 0.30, 95% CI 0.15–0.60, $P=0.001$) were significantly associated with the recurrence of gastric cancer. In multivariable analysis, R1/RX resection (HR 9.82, 95% CI 5.00–19.26, $P<0.001$) and radical surgery (HR 0.19, 95% CI 0.09–0.38, $P<0.001$) were also significantly associated with the recurrence of gastric cancer in those patients (Table 7).

Discussion

This is the first comparative report of long-term outcomes after ESD among patients with EGC who did not meet criteria for curative resection according to hospital volume. Across Japanese hospitals with different volumes, ESD is widely accepted as an alternative to surgery for the treatment of EGC that meets the absolute or expanded criteria. However, no comparative study has investigated the long-term outcomes after ESD for patients with EGC who do not meet criteria for curative resection according to hospital volumes, and it is difficult to conduct a well-designed prospective study to compare the long-term outcomes for these patients between hospitals of different volumes in clinical situations. Therefore, we conducted a retrospective cohort study on the outcomes of ESD for EGC using generalized propensity score matching to adjust for significant differences in baseline characteristics across hospitals with different volumes.

In the overall patient cohort, the rates of depressed-type cancer, ulceration, and intramucosal cancers were significantly higher in the VHVG than that in the LMVG and HVG. In particular, the proportion of lesions with

Table 5 Risk factors for all-cause death in stratified Cox regression analysis (propensity score-matched cohort)

Variables	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Lymphatic invasion						
Positive	1.01	0.79, 1.30	0.922	1.12	0.87, 1.46	0.379
Negative	1	Reference		1	Reference	
Vascular invasion						
Positive	1.12	0.82, 1.51	0.482	1.12	0.81, 1.53	0.501
Negative	1	Reference		1	Reference	
R0 resection						
R1/RX	1.32	0.99, 1.75	0.055	1.65	1.24, 2.20	0.001
R0	1	Reference		1	Reference	
Additional therapy						
Radical surgery	0.33	0.25, 0.42	< 0.001	0.30	0.23, 0.38	< 0.001
Follow-up	1	Reference		1	Reference	
Hospital volume						
VHVG	0.68	0.51, 0.89	0.006	0.69	0.52, 0.91	0.008
HVG	0.56	0.42, 0.74	< 0.001	0.53	0.40, 0.71	< 0.001
LMVG	1	Reference		1	Reference	

HR hazard ratio, *CI* confidence interval, *VHVG* very high-volume group, *HVG* high-volume group, *LMVG* low- and medium-volume group

Table 6 Risk factors for disease-specific death in stratified Cox regression analysis (propensity score-matched cohort)

Variables	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Lymphatic invasion						
Positive	1.63	0.70, 3.81	0.256	1.47	0.59, 3.69	0.411
Negative	1	Reference		1	Reference	
Vascular invasion						
Positive	2.73	1.13, 6.58	0.025	2.21	0.85, 5.74	0.103
Negative	1	Reference		1	Reference	
R0 resection						
R1/RX	5.79	2.49, 13.51	< 0.001	6.38	2.66, 15.29	< 0.001
R0	1	Reference		1	Reference	
Additional therapy						
Radical surgery	0.64	0.28, 1.49	0.299	0.40	0.16, 0.96	0.040
Follow-up	1	Reference		1	Reference	
Hospital volume						
VHVG[c]	0.58	0.21, 1.64	0.306	0.65	0.23, 1.85	0.420
HVG	0.60	0.22, 1.63	0.315	0.63	0.22, 1.77	0.381
LMVG	1	Reference		1	Reference	

HR hazard ratio, *CI* confidence interval, *VHVG* very high-volume group, *HVG* high-volume group, *LMVG* low- and medium-volume group

ulceration was higher in the VHVG than in the other groups, and we speculate that these lesions were referred to high-volume hospitals due to the difficulty of the ESD procedures. On the other hand, the rate of R0 resection in the LMVG was lower than that in the VHVG although the LMVG had less ulcerated lesions. This may be influenced by technical inferiority and the high rate of SM cancer in the LMVG compared to the VHVG.

Among generalized propensity score-matched patients, the baseline characteristics of the three groups were comparable. However, the differences in vascular invasion and follow-up duration remained among the three groups. Vascular

Table 7 Risk factors for the recurrence of gastric cancers in stratified Cox regression analysis (propensity score-matched cohort)

Variables	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Lymphatic invasion						
Positive	1.38	0.72, 2.62	0.333	1.73	0.86, 3.50	0.126
Negative	1	Reference		1	Reference	
Vascular invasion						
Positive	1.95	0.96, 3.96	0.064	1.61	0.74, 3.50	0.232
Negative	1	Reference		1	Reference	
R0 resection						
R1/RX	7.23	3.76, 16.90	< 0.001	9.82	5.00, 19.26	< 0.001
R0	1	Reference		1	Reference	
Additional therapy						
Radical surgery	0.30	0.15, 0.60	0.001	0.19	0.09, 0.38	< 0.001
Follow-up	1	Reference		1	Reference	
Hospital volume						
VHVG	0.86	0.39, 1.93	0.720	0.89	0.40, 2.01	0.784
HVG	0.99	0.46, 2.13	0.981	0.96	0.44, 2.11	0.924
LMVG	1	Reference		1	Reference	

HR hazard ratio, *CI* confidence interval, *VHVG* very high-volume group, *HVG* high-volume group, *LMVG* low- and medium-volume group

invasion is usually identified based on conventional hematoxylin-eosin staining. However, the immunohistochemical identification of vascular invasion is useful for increasing the accuracy of its diagnosis. In this study, the assessment of vascular invasion was not standardized across all institutions. Therefore, the rate of vascular invasion might have significantly differed due to different assessment methods across the three groups [22]. The follow-up duration was shorter in the LMVG than in the other groups, which may be the result of ESD for the treatment of EGC being introduced later in the LMVG than in the HVG and VHVG.

Our study demonstrated no significant difference in the rate of radical surgery across hospital volumes in both the overall and generalized propensity score-matched cohorts. These findings suggest that radical surgery may be recommended after non-curative ESD for all patients according to Japanese gastric cancer treatment guidelines despite different hospital volumes. Moreover, there was no significant difference in DSS and RFS across hospital volumes in a generalized propensity score-matched cohort of patients with EGC lesions that did not meet the criteria for curative resection. Therefore, even if ESD for EGC involved non-curative resection, there was no significant difference in the prognosis of gastric cancer death according to hospital volume in Japan. The 5-year OS rate was significantly poorer in the LMVG than in the HVG and VHVG among the propensity score-matched cohort. The lower OS rate in the LMVG was due to the high incidence of deaths from other diseases. It is speculated that the rate of patients with comorbidities in the LMVG was higher than that in the HVG and VHVG.

We did not compare the long-term outcomes between low-volume, medium-volume, and high-volume hospitals according to propensity score matching because only two hospitals were low-volume (< 50/year) hospitals. Therefore, the hospital volume is relatively large in this study compared to previous reports [13, 14]. In Western countries, long-term outcomes after ESD for EGC in low-volume hospitals were comparable to those in the LMVG of our study [23, 24]. However, there were a small number of patients with EGC who did not meet the criteria for curative resection in Western countries. Further research will be necessary to compare long-term outcomes after non-curative ESD for EGC between low-volume and high-volume hospitals in Western countries.

Our study has some limitations. First, this was a retrospective cohort study. Therefore, a generalized propensity score matching was performed to minimize differences in baseline clinical and lesion characteristics between the three groups. However, vascular invasion and follow-up duration were significantly different among three groups, even after propensity score matching. Second, the pathological diagnoses were performed by gastrointestinal pathologists in each institution, not on central review. Third, although our sample size was large, we cannot rule out the possibility that some differences were overlooked among the three groups because underlying conditions of the patients, such as comorbidities and performance status, were not assessed in our study. Fourth, the study was conducted only in Japanese institutions and may lack generalizability around the world. Lastly, the LMVG group is quite heterogeneous, where 10 different

centers are included. However, no significant difference was shown in the baseline characteristics of the patients, except histological types of EGC, between LVG and MVG. In addition, when MVG, instead of LMVG, was used in the propensity score matching analysis, similar results were shown.

Conclusions

DSS and RFS in patients with EGC who did not meet criteria for curative resection did not differ across hospital volumes in Japan. Even if ESD for EGC involved non-curative resection, ESD for EGC patients is feasible across Japanese hospitals with different volumes.

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Compliance with ethical standards

Disclosure Osamu Dohi, Waku Hatta, Takuji Gotoda, Yuji Naito, Tsuneo Oyama, Noboru Kawata, Akiko Takahashi, Shiro Oka, Shu Hoteya, Masahiro Nakagawa, Masaaki Hirano, Mitsuru Esaki, Mitsuru Matsuda, Ken Ohnita, Ryo Shimoda, Motoyuki Yoshida, Jun Takada, Keiko Tanaka, Shinya Yamada, Tsuyotoshi Tsuji, Hirotaka Ito, Hiroyuki Aoyagi, and Tooru Shimosegawa have no conflicts of interest or financial ties to disclose.

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Affiliations

Osamu Dohi[1] · Waku Hatta[2] · Takuji Gotoda[3] · Yuji Naito[1] · Tsuneo Oyama[4] · Noboru Kawata[5] · Akiko Takahashi[4] · Shiro Oka[6] · Shu Hoteya[7] · Masahiro Nakagawa[8] · Masaaki Hirano[9] · Mitsuru Esaki[3,10] · Mitsuru Matsuda[11] · Ken Ohnita[12] · Ryo Shimoda[13] · Motoyuki Yoshida[14] · Jun Takada[15] · Keiko Tanaka[16] · Shinya Yamada[17] · Tsuyotoshi Tsuji[18] · Hirotaka Ito[19] · Hiroyuki Aoyagi[20] · Tooru Shimosegawa[2]

1 Department of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan

2 Department of Gastroenterology, Graduate School of Medicine, Tohoku University, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan

3 Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

4 Division of Endoscopy, Saku Central Hospital Advanced Care Center, Nagano, Japan

5 Division of Endoscopy, Shizuoka Cancer Center, Shizuoka, Japan

6 Department of Gastroenterology and Metabolism, Hiroshima University Hospital, Hiroshima, Japan

7 Department of Gastroenterology, Toranomon Hospital, Tokyo, Japan

8 Department of Endoscopy, Hiroshima City Hospital, Hiroshima, Japan

9 Department of Internal Medicine, Niigata Prefectural Central Hospital, Joetsu, Japan

10 Department of Gastroenterology, Kitakyushu Municipal Medical Center, Kitakyushu, Japan

11 Department of Internal Medicine, Toyama Prefectural Central Hospital, Toyama, Japan

12 Department of Gastroenterology and Hepatology, Nagasaki University Hospital, Nagasaki, Japan

13 Department of Internal Medicine and Gastrointestinal Endoscopy, Saga Medical School, Saga, Japan

14 Department of Gastroenterology and Endocrinology and Metabolism, Nara Medical University, Nara, Japan

15 Department of Gastroenterology, Gifu University Graduate School of Medicine, Gifu, Japan

16 Department of Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan

17 Department of Gastroenterology and Hepatology, Japanese Red Cross Society Kyoto Daiichi Hospital, Kyoto, Japan

18 Department of Gastroenterology, Akita City Hospital, Akita, Japan

19 Department of Gastroenterology, Osaki Citizen Hospital, Osaki, Japan

20 Department of Gastroenterology, Fukui Prefectural Hospital, Fukui, Japan