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Non-cardia early gastric cancer in Central Vietnam: noticeable uncommon background mucosa and results of endoscopic submucosal dissection

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ABSTRACT

Background and study aims Gastric cancer (GC) is one of the leading causes of malignancy-related death in Vietnam, with increasing incidence of non-cardia early gastric cancer (N-EGC). Data on accurate diagnosis of EGC and treatment by endoscopic submucosal dissection (ESD) in Vietnam are very sparse. The aim of this study was to describe the characteristics of N-EGC and evaluate the effectiveness and the safety of ESD in Central Vietnam.

Patients and methods We prospectively enrolled patients with N-EGC detected by magnified chromoendoscopy from December 2013 to August, 2018 in Central Vietnam. Selected cases of N-EGC received standardized ESD technique and have been following up carefully as in protocol.

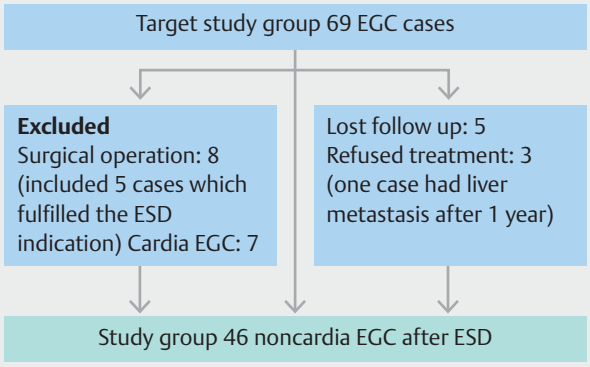
Results Among 606 GC patients, 46 had N-GEC and underwent ESD. The depth of invasion was pT1a in 33 (71.7%), pT1b1 in 10 (21.7%), and pT1b2 in three cases (6.6%). Mild chronic atrophic gastritis, most being C2 (63%), and gastritis-like EGC that did not appear malignant was the predominant type. ESD achieved a 97.8% en bloc resection rate; the mean procedure time was 76 ± 22 minutes (range 24–155), and mean endoscopic tumor size was 23 ± 5 mm (range 13–52) and ESD sample size was 28 ± 7 mm (range 16.5–60). Complications consisted of two patients with bleeding and one with a minor perforation, all of which were successfully managed by endoscopy. The longest and the mean follow-up times were 84 and 64 months, respectively, with no recurrence.

Conclusions A significant proportion patients with N-EGC have a background mucosa of mild chronic atrophic gastritis. Our results 7 years after starting ESD demonstrate early promising outcomes with the procedure.

Introduction

Gastric cancer (GC) was ranked in 2020 as the fifth most common cancer worldwide, with 1,089,103 new cases and 768,793 deaths. GC in Vietnam, with 17,906 new cases in 2020 and an age-standardized incidence and mortality rates of 15.5 and 12.6, respectively, for both sexes, is the highest among countries in Southeast Asian nations. GC is one of the leading causes of malignancy-related death, with increasing incidence of the

non-cardia type [1,2]. Cardia and non-cardia GC have different pathogenesis, risk factors, and prognosis. In Vietnam, patients who are infected with *Helicobacter pylori* with Vacuolating cytotoxin A (VacA) m1 genotype have an increased risk of non-cardia GC. Unfortunately, the majority of GCs in Vietnam have been diagnosed at an advanced stage [3,4], and data about diagnosis and treatment by endoscopic submucosal dissection (ESD) for non-cardia early gastric cancer (N-EGC) in our country are very limited. Central Vietnam is an area with more than 25 million inhabitants and, in general, faces more difficulties in terms of available health care facilities and endoscopy equipment. Hue University Hospital is a teaching institute for Central Vietnam, where we have been trying to systemically establish diagnostic and treatment protocols for EGC since December 2013. Being the first report in Vietnam about the diagnosis of EGC and its treatment by ESD, this study aims to describe the characteristics of N-EGC and evaluate the effectiveness and safety of ESD.



▶ **Fig. 1** Diagram of patient selection process, in which there were 69 EGC cases. Fifteen patients were excluded: eight had undergone surgery that fulfilled the ESD indication and seven had cardia EGC. Five patients were lost to follow up and three refused treatment (one patient had liver metastasis more than 1 year later). Forty-six patients with non-cardia EGC were treated with ESD.

Patients and methods

Patients

Patients diagnosed with N-EGC were recruited and they came mostly from the Central and Highland area of Vietnam, but some lived in Hanoi or Ho Chi Minh, the largest city. Patients with EGC who refused treatment or underwent surgery despite fulfilling ESD indications were not eligible for the study, as shown in ▶ **Fig. 1**. All patients underwent diagnostic and interventional endoscopy at the Gastrointestinal Endoscopy Center, Hue University Hospital, Vietnam, from December 2013 to August 2018. The study protocol was approved by the Institutional Review Board on June 5, 2013 and all patients gave written informed consent for ESD or study enrollment.

Testing prior to ESD

Diagnostic endoscopy procedures

Before ESD, we systemically evaluated all gastric lesions by magnified chromoendoscopy using ZW530 zoom scopes (Fujifilm, Tokyo, Japan) and Indigo carmine 0.2%. The atrophic mucosal background was evaluated according to the Kimura Takemoto classification, in which the atrophic level is classified into closed type (C1-C3) and opened type (O1-O3) according to how wide the atrophic area spreads along the lesser curvature to cardia and the greater curvature [5]. We classified the location and macroscopic type of EGC based on the Japanese classification of gastric carcinoma [6]. Among them, "gastritis-like" appearance is denotes that the EGC is not well demarcated and difficult to identify among lesions in the spreading inflammatory background mucosa. Moreover, the EGC lesions can be partially covered by non-cancerous gastritis mucosa [7].

We determined the indication of ESD for these N-EGC before the procedure based on endoscopic and biopsied findings according to Japanese GC treatment guidelines [8].

Tissue biopsies were taken in all cases prior to ESD to confirm the malignant diagnosis and to test for *H. pylori* with rapid urease and histopathological examination. Patients were considered *H. pylori* positive if at least one of two tests was positive.

Laboratory testing

All routine tests were performed as before surgery. In three patients, ESD had to be postponed when testing revealed severe chronic renal failure and acute hepatitis.

Diagnostic imaging

All patients were evaluated with abdominal ultrasound, chest X-ray, and abdominal contrast- enhanced multi-slice computed tomography scan. In addition, endoscopic ultrasound was performed in patients in whom submucosal invasion was suspected.

ESD technique

All steps in ESD procedures were performed in standard fashion as per protocol of Japanese experts [9].

All patients were sedated by anesthetists using propofol 10 mg/mL.

Initially, we performed magnified chromoendoscopy using Indigo carmine 0.2% to determine the lateral margin of EGC lesions by zoom scope. Then we switched to therapeutic scope (530 CT), and started the ESD by circumference marking with a needle knife (KD-1L-1, Olympus, Tokyo, Japan) or Flush ball tip (BT) knife (Fujifilm, Tokyo, Japan). The oral site of lesions was marked by two dots (double marking), to aid in directing pathological analysis. We raised the submucosa with a mixed solution of hyaluronic acid 0.1% in tear drops (Mucoseup with higher hyaluronic acid concentration, as used in Japan, was not available), NaCl 0.9%, Indigo carmine 0.2% and adrenaline 1/1000 at the fixed rate. When the submucosal layers were adequately injected, we performed the initial incision, 3 to 5 mm outside the marking circle, by needle type knife. Circumference cutting and submucosal dissection were done by either Flush BT knife (Fujifilm, Tokyo, Japan) or Insulated Tip 2 (IT2) knife,

Dual knife (Olympus, Tokyo, Japan). When the tumor was resected en bloc, we carefully inspected the site for risk of bleeding and cauterized using Coagrasper (Olympus, Tokyo, Japan). Finally, ESD samples were retrieved by Roth Net and fixed by pins in a specific rubber pad, put into 10 % formalin boxes and transported to the Pathology Department. ESD procedure duration was defined as the time of from scope introduction into a patient's mouth to the end of the procedure.

The main ESD-related complications included bleeding and perforation. The former refers to vessel damage in the dissection field that occurred during or post ESD and required additional intervention such as clipping to achieve hemostasis. The latter was defined as penetration of the serosa leading to leakage of gas and gastric contents into the abdominal cavity.

Pathological examination

All biopsied and ESD samples were examined histopathologically according to the Vienna Classification [10]. Carcinoma in the biopsied samples of all cases was confirmed by two pathologists before considering treatment. The ESD specimens were cut every 2 mm for examination as per guidance from Japan [6]. Histopathological examinations were done by experienced pathologists on the attending physician level. The vertical and horizontal margins and lymphovascular involvement were carefully examined.

Care and follow up after ESD

After ESD, patients were placed on a fasting diet, intravenous nutrition, high-dose proton pump inhibitor (PPI) as for peptic ulcer bleeding, and vital signs were continuously monitored until the following day when the second-look endoscopy was done.

Complete blood count (CBC) and C-reactive protein were checked 6 hours after the procedure if there was no earlier sign of a complication. If the second-look endoscopy on the day after ESD detected no sign of bleeding, patients were fed liquid foods and started on oral PPI the following 2 to 3 days.

Three to 5 days post ESD, stable patients were discharged and scheduled for a follow-up endoscopy at 1, 3 and 6 months, and then annually if there was no evidence of recurrence.

At time of follow-up endoscopy, we checked CBC, abdominal ultrasound, and chest X- ray. We also performed histopathological examinations and CT scan in cases of suspected recurrence or where metachronous lesions were noted.

Patients were considered "lost to follow-up" if they did not return for clinical and endoscopy examination.

Statistical analysis

Statistical analysis of the data was performed with the Microsoft Excel (Microsoft Office 2013), and SPSS 16.0 for Windows (Statistical Product and Service Solutions, Chicago, IL, USA). Categorical data between the two groups were compared by chi-squared test with Fisher's exact test. Continuous variables were expressed as mean ± standard deviation (SD) and ranges (min-max), and were compared by the Student's *t*-test. $P < 0.05$ was considered statistically significant.

Results

Patient demographics and clinical features

After excluding all ineligible EGCs and those lost to follow-up, our study group consisted of 46 patients with N-EGC who had undergone ESD. The longest follow up was 7 years post diagnosis. The specific data are presented in ▶ **Table 1**. Among them, men were predominant with 32 cases (69.5 %). The age ranged from 39 to 83 and the mean age was 55 ± 10 years old. The clinical symptoms were usually nonspecific. However, there were three remarkable anemia cases, two cases due to chronic renal failure with hemoglobin (Hb) < 7 g/dL, and one case was detected by routine health check with Hb = 7.2 g/dL.

EGC characteristics

Characteristics of EGC lesions are shown in ▶ **Table 2**. In total, there were 606 GC cases in the same time period as the study, giving an EGC rate of 7.6 %. Of note, gastritis-like EGC was common (65.2 %) and most patients had mild to moderate (C1-O1) atrophic background mucosa with the highest atrophic level being C2 (63 %). There were only two cases of the open type. There was no detected EGC lesion in the setting of pan-atrophic background mucosa. The *H. pylori* infection rate was 80.4 % (37/46).

Regarding the locations of EGC, most cases were in the atrophic area (39/46; 84.8 %), including 25 lesions in the antrum plus 14 lesions in the corpus. The number of EGCs on atrophic border in the corpus was five. The two patients in whom the EGC had been found in the non-atrophic area in the corpus both had poorly differentiated disease on histopathological examination (▶ **Fig. 2**).

▶ **Table 1** Patient demographics and clinical features.

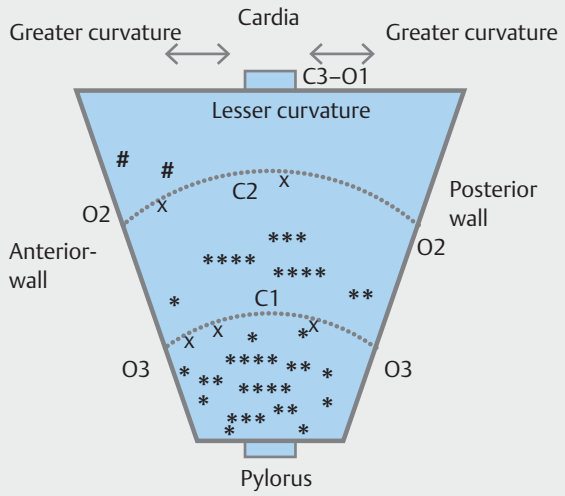
Variable	n (%)	Variable	n (%)
Male	32 (69.5 %)	Noticeable anemia	3 (6.5 %)
Female	14 (30.5 %)	Remarkable weight loss	2 (4.3 %)
Mean age (year)	55 ± 10		
Family history of GC	4 (8.7 %)	Severe Comorbidity	3 (6.5 %)

GC, gastric cancer.

▶ **Table 2** EGC characteristics.

Variable	N (%)	Variable	N (%)
Mucosal background		Background	
Atrophy		▪ Gastritis-like	30 (65.2%)
▪ C1	6 (13%)	▪ H. pylori (+)	37 (80.4%)
▪ C2	29 (63%)	Location	
▪ C3	9 (19.6%)	▪ In all atrophic areas	39 (84.8%)
▪ O1	1 (2.2%)	▪ +antrum	25 (54.3%)
▪ O2	1 (2.2%)	▪ +corpus	14 (30.5%)
EGC morphological type		▪ At the atrophic borderline	5 (10.9%)
▪ 0-I	5 (10.9%)	▪ Outside of atrophic area	2 (4.3%)
▪ 0-IIa+c	29 (63%)	Tumor depth	
▪ 0-IIa	2 (4.3%)	▪ pT1a (m)	33 (71.7%)
▪ 0-IIb	4 (8.6%)	▪ pT1b1 (sm1)	10 (21.7%)
▪ 0-IIc	7 (15.2%)	▪ pT1b2 (sm2)	3 (6.6%)

EGC, early gastric cancer.



▶ **Fig. 2** Association between the endoscopically assessed atrophic mucosa and the locations of 46 EGC lesions. An asterisk indicates EGC located within an atrophic area, an X indicates EGC located at the atrophic border, and an # indicates EGC located outside the atrophic area.

Moreover, there were three patients with pT1b2 tumors, beyond the indication for ESD, but the patients and their families expressed willingness to undergo ESD under an expanded indication in the setting of age >80 years and severe morbidity. Fortunately, up to this point in time, we have found no recurrence in these cases.

ESD outcomes

The main outcomes of ESD are shown in ▶ **Table 3**. Up to December 2020, the longest follow-up time was 84 months with a mean of 64±6 months. The mean endoscopic tumor size was 23±5 mm (13–52), the average ESD size was 28±7 mm (16.5–60), with the largest sample measuring 6 cm. ESD time was 76±22 minutes (range 24–155). We found no lymphatic or vascular invasion in conventional pathological examination of any ESD specimens. There was one patient in whom we could not complete en bloc resection, due to large size and bleeding during ESD. There were 97.8% of cases in which R0 ultimately was achieved (there were two who had high-grade dysplasia tissue remaining at the lateral margin, but after reexamination, that was possibly be due to burning effect; the follow-up at 5 years after ESD showed no recurrence). Endoscopic and pathological images of EGC characteristics and ESD outcome are shown in ▶ **Fig. 3**.

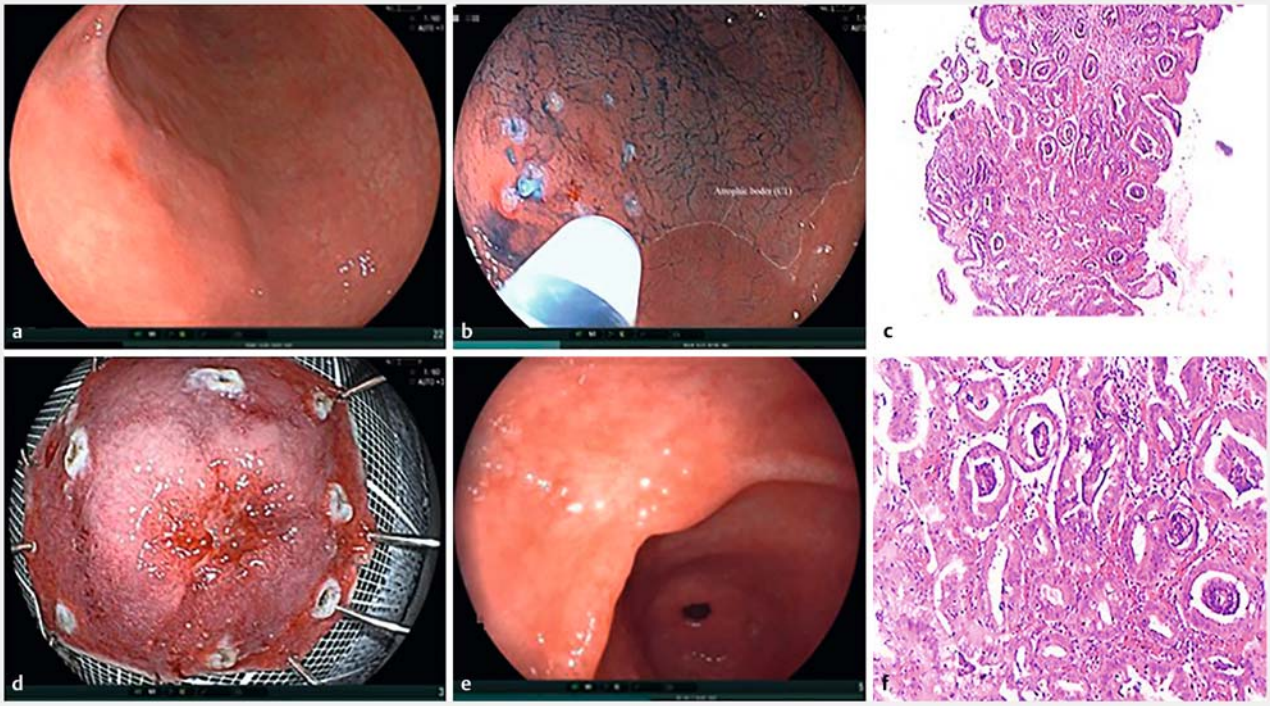
With respect to complications, there were two patients with bleeding that required endoscopy intervention at night and both were controlled by clipping and coagulation using Coagrasper. There was one case of perforation that was successfully controlled with conservative treatment by clipping and antibiotics. Fortunately, as of December 2020, no recurrences had been found on follow-up and all patients were alive with no GC-related manifestations.

We analyzed the association of ESD time to ESD size, as shown in ▶ **Fig. 4** (chart 1), and noted a regressive correlation, with $r=0.67$, $P<0.01$, although there were some small lesions that required longer ESD process due to submucosal fibrosis or bleeding.

▶ **Table 3** Main outcomes of ESD.

Variable	N (%)	Variable	N (%)
ESD size	28 ± 7 (16.5–60) mm	Complications	
ESD time	76 ± 22 (24–155) minutes	Bleeding	2 (4.3 %)
		Perforation	1 (2.2 %)
		Recurrence	0
En bloc resection rate	45/46 (97.8 %)		
R0	46/46 (100 %)		

ESD, endoscopic submucosal dissection.

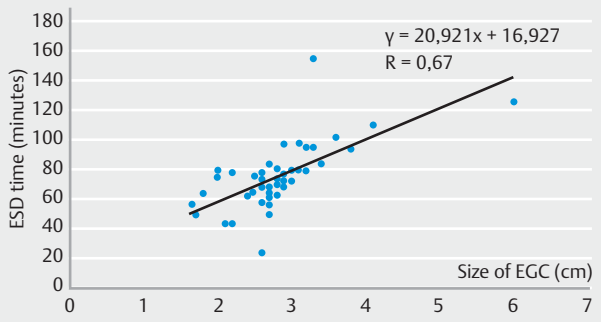


▶ **Fig. 3** **a** red, 0-IIa EGC lesion in the antrum, inside the atrophic area. **b** Gastritis-like EGC lesions after marking for ESD; the C1 atrophic border line is the white marked line and the background mucosa have multiple gastritis erosions, which were clearer after performing chromoendoscopy with Indigo carmine. **d** (HE, ×100) and (HE, ×400) pathological results (Slide number: 8577) show carcinoma insitu in the mild atrophic gastritis background mucosa. **e** ESD sample. **f** ESD scar after 3 years of follow up.

Discussion

Patient demographic and clinical features

Concerning clinical and demographic features of the study group, although there were several patients who had early-onset GC as defined by age up to 45 years old [11], the average onset age of this EGC was quite late (55 ± 10). These results were consistent with one study about advanced non-cardia GC in Ho Chi Minh city, Vietnam [4] and other epidemiological data [12]. According to Nagini et al, incidence of non-cardia GC increases with age, and peaks after the 5th decade of life. *H. pylori* infection, lifestyle and environmental factors may influence this trend [13]. As shown in ▶ **Table 2**, the *H.pylori*-positive rate in our study reached 80.4 %. As Eckardt et al reported, EGC patients in Europe had an age range and clinical features similar to those with symptoms of benign gastric ulcer, unlike presentations in patients with advanced GC. Also according to this study, where there were 51 EGC and 190 patients with advanced GC in a 10-year period, the EGC detection rate was 21.2 % [14]. We also found no common typical clinical symptoms of advanced GC in our EGC group. However, there were three moderate anemia cases with Hb level around 7 g/dL, of which two cases could be explained by severe chronic renal failure. The third was a 44-year-old female patient who came for a routine health check and was subsequently shown to have a typical 0-IIc EGC at the greater curvature. This patient also re-



▶ **Fig. 4** EGC lesion size and time were regressively correlated, with r = 0.67, $P < 0.01$.

ported a weight loss of 4 kg 2 months prior to diagnosis. Everett SM et al showed that in Europe, EGC can manifest with warning signs like weight loss (3.9 % to 40 %) or anemia (5.3 % to 15 %) [15]. In the Mexican National Cancer Institute study, 21 EGCs were retrospectively studied. The mean age of the patients was 58.1 years (range 33 to 84) with a female predominance (57.1 %), and one- third had symptoms of weight loss. There were 66.4 % of these patients who survived at 5 years post diagnosis [16]. Overall, the mean age of patients with EGC appears quite similar, while there were differences in gender distribution and clinical manifestation.

The EGC rate in our study was only 7.6 %, which was lower ($P = 0.18$) than in Eckardt's study, although his data were published in 1990 and were not statistically significant due to the limited sample size. Our results are similar to those found in Chile where most GC cases were diagnosed late (12 % identified after death, 20 % were inoperable) and only 6 % were diagnosed early (stages I or II) [17]. Another report outside Japan (where the EGC has been diagnosing over 50 %, top in the world), was published by Chinese authors, and showed the EGC rate at 13.8 % [18], somewhat more promising than ours.

Characteristics of EGC

Eckardt et al stated that Western presented EGC subtypes were predominantly 0-IIc or III, and were located in the greater curvature in more than 60 % of patients [14]. In our study, the most common morphological types of EGC were 0-IIa + IIc at 63 %, and most lesions were distributed in the antrum and lesser curvature. However, we calculated only N-EGC while the former author analyzed all EGC. Interestingly, the predominant background mucosa of our EGC patients is mild to moderate atrophy with gastritis-like appearance lesions. The EGC lesions were not well demarcated and difficult to identify among other lesions in the spreading inflammatory background mucosa. The most common atrophic level was C2 (63 %) and there was no O3 case, only one O1 and one O2 case. In contrast, Song JH et al showed in 2017 that during follow-up of more than 2000 Korean subjects, the incidences of gastric neoplasm were 1.6 %, 5.2 %, 12.0 % in mild atrophic gastritis, moderate atrophic gastritis and severe atrophic gastritis, respectively, (r = 0.184, $P < 0.001$) [19]. Moreover, Naomi Uemura et al reported in a long-term follow up of 1526 Japanese patients that severe gastric atrophy resulted in a significantly higher risk for GC [20]. Our results indicate that we should also pay enough attention to screen EGC even in mild atrophic chronic gastritis patients.

Also, in our study, 65.2 % of lesions had a gastritis-like appearance, leading to difficulty in endoscopic detection of EGC. Saka et al found that narrow-band imaging magnifying endoscopic findings showed a gastritis-like appearance within the cancerous area in 54.2 % of EGC cases and confirmed that the superficial lesions that look like gastritis were very difficult to diagnose [7]. This may partially explain the low EGC detection

▶ **Table 4** Comparison of ESD data in other countries.

	Italy [22]	France [23]	Southeast Asia [24]	Vietnam
Study period	2005–2011	2010–2013	2009–2015	2013–2018
Study method	Retrospective	Prospective	Retrospective	Prospective
No. cases	20	319	35	46
Size (mm)	Median 29	39 ± 23	Median 20 (5–60)	28±7 (16.5–60)
ESD time (minutes)	Medial 119.1	108.2 ± 62	Median 105 (15–480)	76 ±22 (24–155)
ESD knives	IT knife	Dual knife,	IT knife	IT2 knife
	Hook knife	Flush knife	Hybrid knife	Flush knife
En bloc resection rate	NA	91.5 %	32/35 (91.4 %)	45/46 (97.8 %)
R0 rate	18/20 (90 %)	71.2 %	27/35 (77.1 %)	44/46 (95.7 %)
Complications				
▪ Severe bleeding	0	15 (4.7 %)	1 (2.9 %)	2 (4.3 %)
▪ Perforation	3/20 (15 %)	26 (8.1 %)	0	1 (2.2 %)

ESD, endoscopic submucosal dissection.

rate in Vietnam. Moreover, we detected two superficially spreading lesions with a diameter that reached 6 cm. According to Imai et al, 69 of 1,062 EGCs had superficial spreading morphology [21]. This result was not significantly different from our findings ($P = 0.55$).

ESD results

Although we recently started doing ESD, by following a careful preparation process, the primary results seem quite promising. There were few complications, and these were well controlled by conservative treatment. There has been no recurrence found so far, with the longest duration of follow-up being 7 years. The technical indicators such as ESD time and en bloc resection rate were comparable with other studies. The details are presented in ▶ **Table 3** and the comparison with other studies, which were conducted in areas with similar ESD development, is demonstrated in ▶ **Table 4** [22–24].

Looking at this table, we can see that average ESD sample size in the French study is larger than ours but the ESD time in our results was shorter than that of the former research [23]. The R0 rate in our study was higher than that of the study in Southeast Asia, and may be due to the previous analyzed ESD outcomes being not only in EGC but also in submucosal tumors [24]. There were no significant differences in en bloc resection, bleeding, and perforation rates among the above compared studies.

However, our study had some limitations. Even though the outcomes showed the favorable results of ESD without recurrence, we have not been able to compare the data to those for surgical treatment using our own data. Moreover, only 46 patients were included, and the cases were not randomly selected. A large multicenter study needs to be conducted in the near future.

Conclusions

In Central Vietnam, N-EGC with gastritis-like lesions is common and most patients in the present study had mild to moderate atrophic background mucosa. The results in these patients 7 years of starting ESD treatment suggest that the procedure is highly effective and relatively safe.

Acknowledgments

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Competing interests

The authors declare that they have no conflict of interest.

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CORRECTION

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In the above-mentioned article its title was corrected to “Non-cardia early gastric cancer in Central Vietnam: noticeable uncommon background mucosa and results of endoscopic submucosal dissection.” The legends of figures 3 and 4 were switched. This was corrected in the online version on 23 August 2022.