Clinico-pathologic determinants of non-e-curative outcomes following *en*-bloc endoscopic submucosal dissection in patients with early gastric neoplasia

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Abstract

Background:

Endoscopic submucosal dissection (ESD) is gaining enormous popularity in the treatment of early gastric cancers (EGCs) across many institutions in the world. However, appropriate selection of patients for endoscopic resection is crucial to sufficiently mitigate non-e-curative (NEC) resection. This study aims at identifying the various clinico-pathologic factors that independently predict the depth of submucosal invasion and NEC resection following ESD in patients with EGCs.

Methods:

Multiple logistic regression analysis was applied to investigate factors that independently predict the level of submucosal invasion and NEC resection in patients with early gastric neoplasia. Statistical Packages for the Social Sciences version 23 was used for analysis.

Results:

A total of 162 EGCs underwent *en*-bloc ESD for which the rate of complete resection and non-e-curative outcomes were 95% and 22.2%, correspondingly. Multivariate analysis depicted that tumor location in the upper two third of stomach (odds ratio [OR] 5.46, confidence interval [CI] 95%, 1.65–18.12, $p = 0.006$), tumor size > 2 cm (OR 7.63, CI 95%, 2.29–25.42, $p = 0.001$), histologically undifferentiated tumor (OR 15.54, CI 95%, 1.65-146.22, $p = 0.001$), and tumors with 0-IIa/0-IIc or their mixed variants with predominant 0-IIa/0-IIc (OR 9.77, CI 95%, 1.23–77.65, $p = 0.031$) were all independent predictors of NEC resection for early gastric tumors. Additionally, location in the upper two third of stomach (OR 8.88, CI 95%, 2.90-27.17, $p < 0.001$), ulcerated lesions (OR 3.70, CI 95%, 1.15–11.90, $p = 0.028$), lesions with > 2 cm (OR 2.94, CI 95%, 1.08–8.02, $p = 0.036$) and those with poor differentiation (OR 6.51, CI 95%, 2.23–18.98, $p = 0.001$) were found to have significant association with submucosal invasion.

Conclusions:

Tumors located in the upper two third of stomach having larger size (> 2 cm), poor histo-differentiation and a gross type of 0-IIa/0-IIc or their mixed variants with predominant 0-IIa/0-IIc are significantly associated with a risk of NEC after ESD procedure. Thus, early gastric tumors displaying these features need to be handled carefully during endoscopic resection. Our findings may provide some insights about the factors that determine non-curability outcomes in patients with EGC in relation to ESD procedure.

Background

Gastric cancer remains to be the fifth most common malignancy and the third leading cause of cancer-related deaths across the globe, and exhibits a significant epidemiological variation as a function of age and geography [1]. This malignant neoplastic disorder is two times higher in males than in females and the East Asian countries possess a comparatively higher burden of GC cases than North American, European and African continents [1, 2]. A subset of these cancers that do not invade beyond the submucosal layer are called early gastric cancers (EGC) irrespective of lymph node metastasis [3].

According to the Japanese Gastric Cancer Association (JGCA) [3] classification scheme, EGCs belong to class zero ('0'), which are further subdivided in to specific subtypes. These class '0' lesions include protruding type (0-I), superficial lesions with elevation (0-IIa), superficial flat (0-IIb), superficial depressed (0-IIc) and the last type encompasses excavated lesions (0-III). In real practice, however, the occurrence of combined macroscopic features is not uncommon where the more dominant type is written first followed by the other [4].

Despite being a gold standard method in the treatment of early stage gastric cancers for the last many decades, gastrectomy has nowadays been replaced by a relatively less invasive therapeutic endoscopy that has promising clinical outcomes [8, 9]. Endoscopic approach of tissue resection has shown dramatic change over the last four decades. It started in the form of Endoscopic Mucosal Resection (EMR) in the early 1980s, and subsequently, Endoscopic Submucosal Dissection (ESD) came in to play and now has proven itself as a very popular means of resecting EGCs [10].

In accordance with Japanese guidelines, patients with EGC without lymph node involvement are given specific criteria for diagnosis [11, 12]. Hence, absolute indication is considered in patients with less than 2 cm size, differentiated EGCs intra-mucosal location and devoid of ulcer. And indications are expanded for early stage gastric lesions which measure greater than 2 cm in size, not extending beyond the mucosal layer, having differentiated histology and lacking ulceration or less than 3 cm if ulceration is present, and undifferentiated lesions if size is less than 2 cm. Lympho-vascular involvement, however, should not be present in both absolute and expanded indications [11, 12]. The above-mentioned indications were established after evaluating the likelihood of metastasis to lymph nodes in specimens obtained from gastrectomy [13].

There is a general agreement that during selection of patients with superficial gastric neoplasia for endoscopic treatment, complete removal of a lesion has to be assured with no lymph nodes involved and the margins' status has to be clear [3, 14]. However, the definition applied for EGCs at the present fails to take account of lymph node status [15–17] and, hence, nothing is said about lymph node involvement after microscopic evaluation of specimens obtained from endoscopic resection [18, 19]. To make matters worse, there is no any single imaging modality to date that can preoperatively decide on lymph node status with full confidence [20–22]. Yet, metastasis to lymph nodes is seen in patients with EGCs that varies according to the extent of invasion (intra-mucosal vs submucosal) where the risk is lower in the former (less than 3%) compared to the latter (up to 20%) [13, 23–25].

If regional lymph nodes remain involved after endoscopic resection, it implies that the endoscopic treatment is suboptimal and patients would end up having additional interventions on top of ESD [26]. The ultimate goal of ESD, nevertheless, is to attain curability which can be assessed by microscopic evaluation of resected specimens using a set of inclusion criteria (absolute and expanded) [3]. And the post-ESD clinical results are similar for all patients not exceeding the expanded criteria as could be indicated by many studies conducted in the Asian continent [27–31].

It is worthwhile to adopt an *en*-bloc means of resection for EGC in order to obtain a specimen that has appropriate histologic details for reliable assessment and potential reduction in the emergence of recurrent lesions [3, 32]. The attainment of complete resection is declared when an *en*-bloc resected lesion lacks both margin positivity and lympho-vascular invasion.

Following ESD procedure, patients who do not conform to the inclusion criteria are rendered to have non-e-curative (NEC) outcomes and may require further intervention depending on the situation due to fear of metastasis to lymph nodes as well as for having bad prognostic behavior [13, 16]. Nonetheless, the risk of lymph node metastasis in patients who received NEC resection treatment after undergoing gastrectomy was found to be less than 10% [3, 33–35]. In addition to this, there is a growing number of elderly patients with or without concomitant illnesses making them unfit for operation [36]. Hence, the need to identify tumor associated factors which determine oncologic outcome in ESD is indispensable in order to have appropriate selection of candidates for subsequent surgical intervention. Of note, there is an ever-changing trend in the technical aspects as well as indications for patients with early gastric neoplasia in the setting of ESD. Thus, the goal of our study is to investigate the potential clinico-pathologic parameters that lead to NEC endoscopic resection following ESD. Likewise, we have investigated various tumor-associated factors and their role in submucosal invasion in patients with EGC.

Methods

Study subjects

Figure 1, illustrates the general enrolment process of patients with early gastric neoplasia in to our study. Accordingly, there were a total of 301 patients who underwent *en*-bloc resection by ESD, after meeting absolute or expanded indications before ESD at our institution from January 2010 to October 2019. In this study, we excluded 148 patients who had the following features; I) Detailed data was unavailable (n = 80), II) Neoplastic lesions with non-epithelial origin (n = 2), III) Non-neoplastic epithelial lesions (n = 21), and IV) Gastric low-grade dysplasia (n = 45). After exclusion of the above-mentioned cases, a total of 162 early gastric neoplastic lesions (153 patients) were retained for subsequent descriptive, comparative and logistic regression analysis. In this study, we made analysis of risk factors based on individual neoplastic lesions as some of the study subjects had multiple tumors resected by *en*-bloc ESD.

Study design and period

The present study is a single center of retrospective design, which involved patients diagnosed as early gastric epithelial neoplasia for whom ESD resection was consecutively performed at a tertiary hospital (Tongji Hospital, Wuhan, China). The study period ranges from January 2010 to October 2019.

Study setting

This study was conducted in the Institute of Pathology at Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China.

Data collection

The demographic information of patients including age and gender was obtained from previous medical records in the computer system. Similarly, data related to endoscopic tumor characteristics such as macroscopic type, location, tumor size, and ulcerative findings were gleaned from previous records of endoscopic examination by experts in the field. The processed tissue specimens in the form of slides were searched in an archive according to the identification number of each recruited patient in its respective shelf. After collecting all the slides, we arranged them serially in accordance with the corresponding year of ESD resection. After that, we began microscopic evaluation of all slides from enrolled patients and the data pertaining to each parameter was recorded.

For difficult cases, proper consultation to senior experts was done to re-evaluate cases under multi-headed microscope to avoid discordance in the final histopathologic assessment. A new slide preparation was requested from reserved tissue blocks (formalin fixed paraffin embedded) as needed, especially, for older slides in which case evaluation was difficult owing to poor slide quality. In such instance, a thin slice of specimen (4 μm thick) was prepared through sectioning by a microtome, and routine hematoxylin and eosin staining was carried out after which microscopic evaluation of slides was done. We made meticulous histopathologic evaluation of ESD-resected specimens with necessary discussions and consultations to minimize intra-observer bias.

Definitions and clinico-pathologic assessment

On the whole, 153 patients with early gastric neoplasia were enrolled in our study, all of whom received an *en*-bloc ESD in accordance with the indications established by JGCA [3]. Hence, none of the study participants underwent a piecemeal type of resection. The JGCA classification system was adopted in our study to categorize all the endoscopically assessed as well as those microscopically assessed tumor-associated factors during our evaluation. Accordingly, the study patients were grouped as e-curative and NEC based on their respective clinical and pathological characteristics.

As per the JGCA (Fig. 1), indications for curative resection include EGCs that conform to both absolute and expanded criteria for ESD. Patients with absolute indication are required to have differentiated morphology, size of two centimeters or below and tumor has to be confined to the mucosal region. Additionally, curative resection is considered for patients with expanded indications that include; 1) Differentiated intra-mucosal tumor of any size that has no ulceration, 2) Ulcerated intra-mucosal cancer with differentiated histology having maximum diameter of ≤ 30 mm, 3) A tumor size ≤ 30 mm with

submucosal invasion of < 500 μm as measured from the muscularis mucosa, 4) An intra-mucosal tumor of ≤ 20 mm diameter with undifferentiated histology and is devoid of ulcer. On top of satisfying the absolute and expanded indications, the type of resection has to be *en*-bloc, both horizontal and vertical margins negative, and lympho-vascular involvement should also be negative. The NEC group are those who do not fulfill the above-mentioned criteria.

Three intra-gastric tumor locations namely upper, middle and lower one-thirds will be considered during analysis. Tumors seen during endoscopic inspection were classified based on macroscopic features as; protruding (0-I), purely superficial elevated (0-IIa) or mixed type with predominant superficial elevated, purely superficial flat (0-IIb) or mixed with predominant superficial flat type and purely superficial depressed (0-IIc) or mixed with predominant superficial depressed types (indicated in Fig. 2). There were no lesions belonging to excavated (0-III) macroscopic variant in this study. For the purpose of analysis, tumors were divided in to two groups with respect to their macroscopic type. 'Group 1' constituted protruding (0-I), purely superficial flat (0-IIb) and mixed variants of superficial flat lesions, and 'Group 2' included purely superficial elevated or depressed lesions (0-IIa or IIc) and/or their corresponding mixed variants where the superficial elevated or depressed is a predominant feature. The maximum diameter of each lesion (in centimeter) was taken in to account during microscopic visualization, and ulceration status was thoroughly evaluated with dichotomous result (absence vs presence). Diagnostic decision on ulcerative findings was dependent on histologic evaluation of a tissue but information from endoscopic examination was also incorporated to provide a final conclusion. Further evaluation of the remaining parameters depended on histopathological examination of the ESD resected specimen. The degree of histologic tumor differentiation was divided as differentiated (D) type in which case a well or moderately differentiated tubular or papillary adenocarcinoma is identified. On the contrary, if tumor showed poor differentiation or a signet ring cell type of carcinoma or mucinous type adenocarcinoma, it was regarded as having undifferentiated (UD) histology. If a single tumor lesion displays both histologic variants of differentiated and undifferentiated histology, the type that is quantitatively predominant will be considered.

The Lauren's classification scheme was also used to classify EGCs as intestinal, diffuse and mixed. The extent of tumor invasion for the superficial gastric lesions was assessed by taking the muscularis mucosa as land mark (shown in Fig. 3). Hence, there were three groups of patients in relation to tumor invasion, in one group the tumor is confined to the mucosa (M), in the second group, invasion extends deep in to the submucosa but hardly exceeds 500 μm as measured from the muscularis mucosa (SM1) and the last set included patients with greater or equal to 500 μm submucosal penetration from the muscularis mucosa (SM2). But during our analysis, we grouped patients in to two as mucosal and submucosal (SM1 and SM2) with respect to depth of tumor invasion as the number of lesions with submucosal invasion was low. In addition, we assessed the lymphatic and vascular invasion characteristics where the expected outcome fell into either absent or present. Likewise, we tried to determine the margin clearance status (both horizontal and vertical margins) falling in to two-tier class as positive or negative.

Statistical analysis

Relevant data was initially entered in to an Excel Spreadsheet and then imported in to Statistical Package for the Social Sciences version 23 for final analysis. While executing descriptive analysis, continuous variables were calculated as mean ± standard deviation, and categorical variables were expressed using frequency and percentages. A chi-squared test or Fisher's exact probability test (as appropriate) and student's *t*-test were used to investigate possible differences among categorical and continuous variables, respectively. In an attempt to investigate whether tumor-related factors have predictive effect on curability and depth of tumor invasion, a logistic regression model was applied. To that end, each variable was first tested using univariate analysis. Subsequently, all the variables that showed significance in univariate analysis were retained for multivariate analysis in order to investigate the factors that were independently associated with NEC resection and submucosal infiltration after ESD. Two-tailed $p < 0.05$ was considered statistically significant. And we also made calculation of both odds ratios (OR) and the 95% confidence intervals (95% CI) in order to estimate the relative risk of NEC outcomes and depth of submucosal invasion following ESD resection as well as to measure the degree of association with different clinico-pathologic factors.

Results

Baseline characteristics of study patients following ESD procedure

In this study, all of the 162 early gastric neoplastic lesions (153 patients) received an *en*-bloc type of ESD resection. Table 1 provides a summarized background information of recruited patients including frequency distribution and their corresponding clinical parameters. The rate of completeness of resection and NEC outcome were 95% and 22.2%, respectively. Three fourth of the participants (74.1%) were males and the mean age (± standard deviation) of the study population was 61.10 ± 8.76 years.

Majority of the neoplastic lesions (58.6%) were located in the lower one third of the stomach and 71.6% of all the tumors had a macroscopic type belonging to the group with purely superficial elevated or depressed lesions (0-IIa or 0-IIc) and/or their corresponding mixed variants where the superficial elevated or depressed is a predominant feature (Group 2). All other macroscopic lesions such as protruding (0-I), purely superficial flat (0-IIb) and mixed variants of superficial flat constituted for 28.4% (Group 1).

Table 1 Overall frequency distribution of patients with early gastric neoplasia after ESD procedure

Clinico-pathologic parameter	Total number of EGC lesions (n=162)	Percentage
Mean Age in years (±SD)	61.10 ± 8.76	-
Gender		
Female	42	25.9%
Male	120	74.1%
Tumor location		
Lower one third	95	58.6%
Middle or Upper third	67	41.4%
Gross tumor type		
Group 1	46	28.4%
Group 2	116	71.6%
Ulceration status		
Absent	135	83.%
Present	27	16.7%
Size of tumor		
≤ 2 cm	111	68.5%
> 2 cm	51	31.5%
Differentiation		
Differentiated	129	79.6%
Undifferentiated	33	20.4%
Lauren's category		
Intestinal	129	79.6%
Diffuse/Mixed	33	20.4%
Level of tumor invasion		
Intra-mucosal tumor	132	81.5%
Submucosal tumor	30	18.5%
Horizontal margin		
Negative	159	98.1%
Positive	3	1.9%
Vertical margin		
Negative	158	97.5%
Positive	4	2.5%
Lympho-vascular invasion		
Absent	159	98.1%
Present	3	1.9%
Resection type (*en*-bloc)	162	100%
Curability outcomes (non-e-curative)	36	22.2%
Complete resection	154	95%

ESD = Endoscopic Submucosal Dissection, *EGC* = Early Gastric Cancer, *SD* = Standard Deviation, *Group 1* = lesions with Protruding (0-I), Purely superficial flat (0-IIb) and Mixed variants with 0-IIb predominant, *Group2* = Purely superficial elevated (0-IIa) or depressed (0-IIc) or mixed variants with either 0-IIa or 0-IIc predominant.

A large proportion of gastric lesions showed a size ≤ 2 cm (68.5%, 111 lesions), absence of ulceration (83.0%, 135 lesions), and differentiated type of histology (79.6%, 129 lesions).

According to Lauren's classification of gastric tumors, a total of 129 lesions (79.6%) displayed an intestinal-type morphology whereas nearly 20% were non-intestinal (diffuse/mixed histology). In terms of depth of tumor invasion, there were higher number of intra-mucosal lesions as compared to the submucosa, 81.5% and 18.5%, respectively. The horizontal margin was positive in three lesions (1.9%), and four lesions (2.5%) had positive vertical margin. Positive lympho-vascular invasion was found in three lesions (1.9%).

The baseline characteristics of patients with regard to depth of tumor invasion (mucosal vs submucosal) are shown in table 4. Out of 162 lesions, 18.5% (30 lesions) had invasion in to the submucosal layer. Considering tumor location and macroscopic endoscopic features, tumors in the upper two third of stomach and those having 0-IIa/0-IIc or their mixed types with 0-IIa/0-IIc predominant accounted for a great proportion of cases with submucosal invasion (80% and 90%, correspondingly). In terms of histologic differentiation, the number of cases in each differentiated and undifferentiated groups exhibiting submucosal invasion were equal (50% each).

Factors that contributed to NEC resection after ESD procedure

Table 2 summarizes the demographic and clinico-pathologic factors of patients with early gastric neoplasia in relation to the post-ESD curability outcome. Accordingly, all patients were divided in to two groups (e-curative vs non-e-curative). Overall, there were 126 early gastric lesions (77.8%) that received curative ESD resection whereas 35 lesions had a NEC resection (22.2%). We tried to compare between e-curative and NEC group, in terms of their demographic and clinico-pathologic factors using a chi squared independent test or Fisher's exact test and student *t*-test applied as appropriate. Hence, there was significant difference in curability outcome among tumor-associated factors such as tumor location, differentiation, size of tumor, and depth of tumor invasion (all with $p < 0.001$).

Table 2 Baseline characteristics of patients and their difference in curability outcomes following ESD

Patient Parameter	All EGCs lesions (n = 162) [No. (%)]	E-curative (n = 126) [No. (%)]	Non-e-curative (n = 36) [No. (%)]	p*-value
Mean age in years (±SD)	61.10 (± 8.76)	60.37 (± 8.27)	63.67 (± 10.0)	**0.046**
Gender				0.472
Female	42 (25.9)	31 (24.6)	11 (30.6)	
Male	120 (74.1)	95 (75.4)	25 (69.4)	
Tumor location				**< 0.001**
Lower third	95 (58.6)	84 (66.7)	11 (30.6)	
Middle or Upper third	67 (41.4)	42 (33.3)	25 (69.4)	
Gross tumor type				**0.002**
Group 1	46 (28.4)	43 (34.1)	3 (8.3)	
Group 2	116 (71.6)	83 (65.9)	33 (91.7)	
Ulceration status				**0.011**
Absent	135 (83.3)	110 (87.3)	25 (69.4)	
Present	27 (16.7)	16 (12.7)	14 (30.6)	
Size of tumor				**< 0.001**
≤ 2 cm	111 (68.5)	98 (77.8)	13 (36.1)	
> 2 cm	51 (31.5)	28 (22.2)	23 (63.9)	
Differentiation				**< 0.001**
Differentiated	129 (79.6)	115 (91.3)	14 (38.9)	
Undifferentiated	33 (20.4)	12 (9.5)	21 (60.0)	
Lauren's category				
Intestinal	129 (79.6)	115 (91.3)	14 (38.9)	
Diffuse/ Mixed	33 (20.4)	11 (8.7)	22 (61.1)	
Level of tumor invasion				**< 0.001**
Intra-mucosal tumor	132 (81.5)	124 (98.4)	8 (22.2)	
Submucosal tumor	30 (18.5)	2 (1.6)	28 (77.8)	
Horizontal margin				**0.010**
Negative	159 (98.1)	126 (100)	33 (91.7)	
Positive	3 (1.9)	0 (0.0)	3 (8.3)	
Vertical margin				**0.002**
Negative	158 (97.5)	126 (100)	32 (88.9)	
Positive	4 (2.5)	0 (0.0)	4 (11.1)	
Lympho-vascular invasion				**0.010**
Absent	159 (98.1)	126 (100)	33 (91.7)	
Present	3 (1.9)	0 (0.0)	3 (8.3)	

ESD = Endoscopic Submucosal Dissection, *EGC* = Early Gastric Cancers, *SD* = Standard Deviation, *Group 1* = lesions with Protruding (0-I), Purely superficial flat (0-IIb) and Mixed variants with 0-IIb predominant, *Group2* = Purely superficial elevated (0-IIa) or depressed (0-IIc) or mixed variants with either 0-IIa or 0-IIc predominant.
*Chi-squared independent test/Fisher's exact test of probability and Student t-test as appropriate

Likewise, a significant difference was found between these groups of patients with regard to macroscopic tumor type (p = 0.002), ulcerative finding (p = 0.011), horizontal margin (p

= 0.011), vertical margin (p = 0.002) and lympho-vascular invasion (p = 0.010) following endoscopic resection. On the contrary, no significant difference was seen with respect to gender of patients (p = 0.472) and the difference in age was only marginally significant (p = 0.046).

Subsequently, the predictive impact of all clinico-pathologic factors of enrolled patients with early gastric cancer following ESD procedure was investigated using logistic regression analysis as depicted in table 3. Initially, the role of each tumor-associated variable was examined separately for curability outcome in a univariate analysis. As a result, significant effect on non-curability was obtained in association with tumors located in the upper two third, larger tumor size (> 2 cm), undifferentiated histology and a tumor that belonged to diffuse or mixed by Lauren's classification (all with $p < 0.001$). In addition, univariate analysis revealed significant associations with NEC resection when lesions; were ulcerated (p = 0.001), had purely superficial elevated or depressed or their mixed counterparts (p = 0.006), and when patients had advanced age (p = 0.049).

Finally, a multivariate logistic regression analysis was carried out (table 3) in which all the clinico-pathologic factors were considered together in order to further investigate factors that independently predict a NEC outcome. Thus, tumor location in the upper two third of stomach (odds ratio [OR] 5.46, confidence interval [CI] 95%, 1.65-18.12, p = 0.006), tumor size greater than 2 cm (OR 7.63, CI 95%, 2.29-25.42, p = 0.001), microscopically undifferentiated tumor (OR 15.54, CI 95%, 1.65-146.22, p = 0.001), and old age (OR 1.08, CI 95%, 1.01-1.17, p = 0.029) were found to have independent predictive influence on NEC resection of early gastric tumors.

In a similar fashion, purely superficial elevated or depressed or mixed gross type lesions with either elevated or depressed component predominating, independently contributed to a NEC outcome (OR 9.77, CI 95%, 1.23-77.65, p = 0.031). The presence of ulceration (OR 2.39, 95% CI, 0.59-9.65, p = 0.223) and non-intestinal (diffuse or mixed) tumors by Lauren's classification (OR 3.29, 95% CI, 0.36-31.40, p = 0.300) did not show significant contribution to no-curability after multivariate analysis.

Table 3 **Factors that contributed to non-e-curative outcomes in patients with early gastric cancers after ESD**

Clinico-pathologic parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p*-value**	**OR** (95% CI)	***p*-value**
Age (in years)	1.05 (1.00-1.09)	**0.049**	1.08 (1.01-1.17)	**0.029**
Tumor location				
Lower one third	1 (Reference)		1 (Reference)	
Middle or Upper third	4.55 (2.04-10.12)	**< 0.001**	5.46 (1.65-18.12)	**0.006**
Gross tumor type				
Group 1	1 (Reference)		1 (Reference)	
Group 2	5.70 (1.65-19.65)	**0.006**	9.77 (1.23-77.65)	**0.031**
Ulceration status				
Absent	1 (Reference)			
Present	4.38 (1.87-10.25)	**0.001**	2.39 (0.59-9.65)	0.223
Size of tumor				
≤ 2 cm	1 (Reference)			
> 2 cm	6.19 (2.79-13.77)	**< 0.001**	7.63 (2.29-25.42)	**0.001**
Differentiation				
Differentiated	1 (Reference)		1 (Reference)	
Undifferentiated	16.43 (6.60-40.89)	**< 0.001**	15.54 (1.65-146.22)	**0.016**
Lauren's category				
Intestinal	1 (Reference)		1 (Reference)	
Non-intestinal	16.43 (6.60-40.89)	**< 0.001**	3.29 (0.36-31.40)	0.300

ESD = Endoscopic Submucosal Dissection, *OR* = Odds Ratio, *CI* = Confidence Interval, *Group 1* = lesions with Protruding (0-I), Purely superficial flat (0-IIb) and Mixed variants with 0-IIb predominant, *Group2* = Purely superficial elevated (0-IIa) or depressed (0-IIc) or mixed variants with either 0-IIa or 0-IIc predominant.

Factors associated with submucosal invasion in patients with EGC after receiving ESD

Herein, we conducted both comparative and multiple logistic regression analysis of clinico-pathologic factors with respect to the depth of invasion as illustrated in table 4 and table 5, respectively. Accordingly, a significant difference was obtained in tumors located in the upper two third vs lower third ($p < 0.001$), macroscopic type of 0-IIa/0-IIc or their mixed types with 0-IIa/0-IIc predominant gross type vs 0-I/0-IIb and mixed with 0-IIb dominant ($p = 0.013$), lesions with ulcerative finding vs non-ulcerated ($p = 0.001$), size ≥ 2 cm vs size < 2 cm ($p = 0.001$) and undifferentiated vs differentiated histology ($p < 0.001$).

Table 4 Baseline characteristics of patients with EGC and their difference in terms of depth of invasion following ESD procedure

Patient Parameters	All EGCs lesions (*n* = 162) [No. (%)]	Mucosal lesion (*n* = 132) [No. (%)]	Submucosal (*n* = 30) [No. (%)]	*p**-value
Mean age in years (±SD)	61.10 (± 8.76)	60.33 (± 8.38)	64.53 (± 9.70)	0.563
Gender				0.981
Female	42 (25.9)	34 (25.8)	8 (26.7)	
Male	120 (74.1)	98 (74.2)	22 (73.3)	
Tumor location				**< 0.001**
Lower third	95 (58.6)	89 (67.4)	6 (20.0)	
Middle or Upper third	67 (41.4)	43 (32.6)	24 (80.0)	
Gross tumor type				**0.013**
Group 1	46 (28.4)	43 (32.6)	3 (10.0)	
Group 2	116 (71.6)	89 (67.4)	27 (90.0)	
Ulceration status				**0.001**
Absent	135 (83.3)	116 (87.9)	19 (63.3)	
Present	27 (16.7)	16 (12.1)	11 (36.7)	
Size of tumor in				**0.001**
≤2 cm	111 (68.5)	98 (74.2)	13 (43.3)	
>2 cm	51 (31.5)	34 (25.8)	17 (56.7)	
Differentiation				**< 0.001**
Differentiated	129 (79.6)	114 (86.4)	15 (50.0)	
Undifferentiated	33 (20.4)	18 (13.6)	15 (50.0)	
Horizontal margin				0.088
Negative	159 (98.1)	131 (99.2)	28 (91.7)	
Positive	3 (1.9)	1 (0.8)	2 (8.3)	
Vertical margin				**0.001**
Negative	158 (97.5)	132 (100)	26 (86.7)	
Positive	4 (2.5)	0 (0.0)	4 (13.3)	
Lympho-vascular invasion				**< 0.001**
Absent	159 (98.1)	132 (100)	27 (90.0)	
Present	3 (1.9)	0 (0.0)	3 (10.0)	

ESD = Endoscopic Submucosal Dissection, *EGC* = Early Gastric Cancers, *Group 1* = lesions with Protruding (0-I), Purely superficial flat (0-IIb) and Mixed variants with 0-IIb predominant, *Group 2* = Purely superficial elevated (0-IIa) or depressed (0-IIc) or mixed variants with either 0-IIa or 0-IIc predominant.
*Chi-squared independent test/Fisher's exact test of probability and Student t-test

Subsequently, factors that had significant difference were analyzed using univariate and then multivariate logistic regression was carried out (table 5). In a univariate analysis, submucosal infiltration was significantly related with tumors of upper two third location,

gross type 0-IIa/0-IIc or their mixed types with 0-IIa/0-IIc predominant, ulcerated lesions, lesions with ≥ 2 cm size and undifferentiated histology (all with $p < 0.05$). A multivariate logistic regression analysis revealed that the following tumor-related factors were independent predictors of submucosal invasion; location in the upper two third of stomach (Odds ratio [OR] 8.88, Confidence interval [CI]) 95%, 2.90-27.17, $p < 0.001$), ulcerated lesions (OR 3.70, CI 95%, 1.15-11.90, $p = 0.028$), lesions with greater than 2 cm (OR 2.94, CI 95%, 1.08-8.02, $p = 0.036$) and those with poor differentiation (OR 6.51, CI 95%, 2.23-18.98, $p = 0.001$).

Table 5 Risk factors for submucosal invasion in patients with early gastric cancer following Endoscopic Submucosal Dissection

Clinico-pathologic parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Tumor location				
Lower one third	1 (Reference)		1 (Reference)	
Middle or Upper third	8.28 (3.15-21.75)	**< 0.001**	8.88 (2.90-27.17)	**< 0.001**
Gross tumor type				
Group 1	1 (Reference)		1 (Reference)	
Group 2	4.35 (1.25-15.13)	**0.021**	3.59 (0.84-15.45)	0.086
Ulceration status				
Absent	1 (Reference)			
Present	4.20 (1.69-10.41)	**0.002**	3.70 (1.15-11.90)	**0.028**
Size of tumor				
≤ 2 cm	1 (Reference)			
> 2 cm	3.77 (1.66-8.57)	**0.002**	2.94 (1.08-8.02)	**0.036**
Differentiation				
Differentiated	1 (Reference)		1 (Reference)	
Undifferentiated	6.33 (2.65-15.14)	**< 0.001**	6.51 (2.23-18.98)	**0.001**

OR = Odds Ratio, *CI* = Confidence Interval, *Group 1* = lesions with Protruding (0-I), Purely superficial flat (0-IIb) and Mixed variants with 0-IIb predominant, *Group2* = Purely superficial elevated (0-IIa) or depressed (0-IIc) or mixed variants with either 0-IIa or 0-IIc predominant.

Results of gastrectomy specimens for patients who had NEC outcome following ESD

Parallel to evaluation of ESD resected specimens, we tried to look at some of the gastrectomy specimens together with their lymph node dissections for patients who had a NEC with an attempt to determine the presence of residual tumor and lymph node metastasis (Figure 1). Hence, out of the total 36 lesions that satisfied the criteria for NEC

outcome, 17 patients received additional surgical treatment. Fifteen of those patients who received additional surgery showed evidence of mucosal defect with chronic ulcerative and inflammatory changes or/and granulation tissue. But not cancerous cells were detected in the resected lymph nodes and surrounding tissues. Residual cancer was found in two of the patients who underwent surgery but none of them exhibited metastatic disease in the dissected lymph nodes.

Discussion

A timely detection of early gastric cancers and selection of appropriate means of their treatment is very crucial as it results in favorable prognostication and reduced mortalities [14]. A remarkably high rate (95%) of 5-year survival has been reported in patients with early gastric cancer who underwent ESD fulfilling the indications for expanded criteria [38, 39].

Despite the curative intent of ESD procedure, there is an inevitable NEC resection in about 11.9%-21.4% of EGC patients who might require additional surgical treatment depending on their overall situation [40–45]. Unlike those tumor-associated factors such as location, size and macroscopic type, it is difficult to accurately predict the depth of tumor invasion and lympho-vascular involvement using endoscopy-based pre-ESD evaluations [46]. Recent studies indicated that conventional endoscopic methods had about 72%-78% accuracy in predicting the level of tumor infiltration in EGCs. Likewise, a similar precision rate (67–85%) in extent of invasion has been reported for ultra-sonographic endoscopy, which is a common means of evaluation in several institutions [20–22].

Whatsoever the case, appropriate selection of candidates for subsequent additional surgery is essential in the setting of non-curability following ESD resection. This is in order to obviate the possibility of local recurrence and metastasis to lymph nodes that are potentially associated with NEC endoscopic resection. Additionally, it helps to eliminate unnecessary ESD procedure on patients if they finally have to end up doing surgery following NEC outcome. Our study indicated that the rate of complete resection and non-curability were 95% and 22.2%, respectively, which is in harmony with several previous reports [40–45].

The utilization of ESD for management of early gastric lesions has attained tremendous popularity and the need for expansion of the indication criteria for resection is also increasing. Therefore, sufficient and reliable data on factors that are associated with non-curability following endoscopy-based gastric tumor resection is vital for better clinical outcomes. In terms of respectability, the *en*-bloc means of resection provides a better curative outcome as compared to a piecemeal method [47]. Therefore, in this particular study, we aimed to investigate the demographic and tumor-associated parameters that predict submucosal infiltration and a NEC outcome in patients with early gastric neoplasia who received *en*-bloc ESD resection.

Overall, the results of our multivariate analysis indicated that the following factors were independently associated with both submucosal invasion and NEC outcomes; 1) Upper tumor location (upper two third of stomach), 2) Large tumor size (> 2 cm) and 3) Tumors with undifferentiated histologic pattern. Tumors with purely superficial elevated (0-IIa) or depressed (0-IIc) or mixed gross type with predominant superficial elevated or depressed component (mixed with 0-IIa or 0-IIc dominant) and advanced age were also identified as independent predictors of non-e-curability. In addition to that, ulcerated lesions showed significant association with submucosal infiltration.

Many studies have shown that upper tumor location, enlarged tumor size and undifferentiated microscopic feature independently predict for NEC outcomes, which is consistent with the present study [43, 44, 48–50]. Others reported that tumors located in the upper two third of stomach had higher rate of submucosal invasion and hence a greater frequency of NEC resection as opposed to tumors of the lower third (antrum), which is in line with our study [51, 52]. Similarly, it was clearly described that proximally located gastric tumors behave more aggressively and have a worse prognosis compared to distal counterparts [52–57]. EGCs located in the middle and upper third are not detected as early, owing to the technical difficulty faced during endoscopic evaluation and hence it compromises diagnostic yield from forceps biopsy. This is because maintaining a front view of endoscopy is challenging and it has to be used in its retroflexed fashion [58]. Additionally, there is a difference in thickness of submucosal layer between body and antrum, with the former being thinner as compared to the latter [59]. At last but not least, relatively abundant lymphatic vessels are found in the lamina propria of cardia region as opposed to lower regions of the stomach [60]. By combining all these evidences, EGCs situated in the upper portion of stomach are likely to result in NEC resection and hence, special caution is needed while dealing with tumors in this location.

The real impact of tumor size on ESD outcome has been debated by many researchers. One large-scale study [61] indicated that the size of tumor has nothing to do with curability outcome after ESD. On the contrary, the present study has shown a significant contribution of larger tumor size (> 2 cm) for NEC outcome in a multivariate analysis. In line with our study, Imagawa et al. reported a significant difference ($p < 0.0001$) in curability outcome between lesions of ≤ 2 cm and > 2 cm, 59% vs 89%, respectively. Lee et al. indicated that there was a correlation between depth of tumor invasion and its size ($p < 0.001$). And as a rule of thumb, the bigger the lesion is, the more extensive the vascular bed will be, and excess bleeding is anticipated that might interfere with ESD procedure. Moreover, data on a large series of cases [13] demonstrated that tumors with larger than 3 cm are significantly correlated with an increased risk of metastasis to lymph nodes. For the aforementioned reasons, the post-ESD outcome is likely to be influenced by large size EGCs.

Our study demonstrated that EGCs with undifferentiated histology are significantly associated with NEC outcome in a multivariate analysis. The morphologic patterns of both differentiated and undifferentiated gastric adenocarcinoma are somewhat dissimilar. According to several recent studies, the rate of curative resection in EGCs was low with tumors exhibiting undifferentiated microscopic pattern as opposed to differentiated tumors [62–65]. Another peculiar behavior of gastric adenocarcinoma displaying

undifferentiated histology (mainly the signet-ring cell carcinoma) is the tendency to extend along the sub-epithelial plane [66]. Hence, a wider safety margin of the surrounding mucosa has to be considered for tumors with poor differentiation.

Regarding macroscopic type of tumors, majority of published data consider the three-tier grouping system of Paris classification; elevated, flat and depressed gross types [67]. But in reality, lesions with mixed endoscopic appearances are commonly seen in clinical practice as shown in Fig. 2. The Japanese classification system [3] provides a better and wider macroscopic description for early gastric neoplasia that includes all pure and mixed variants in their respective category (0-I, 0-II [a,b,c], 0-III and mixed with any one of the types predominating).

In our study we adopted the Japanese guidelines for macroscopic classification of the EGCs to investigate their association with non-curability after ESD. In concordance with a study done by Ohara et al. [68], our multivariate analysis depicted that EGCs with purely superficial elevated (0-IIa) or depressed (0-IIc) or their mixed gross types with predominant elevated or depressed component (Mixed with 0-IIa or 0-IIc dominant) were significantly associated with NEC resection. In a univariate analysis, Abe et al. [69] recently reported that superficial depressed and/or elevated lesions were found to be indicative of submucosal invasion ≥ 500 μm, even though, their finding was lacking significance in a multivariate regression analysis. Similarly, Yamada et al. found that EGCs with superficial elevated and depressed endoscopic features were greatly linked with submucosal as well as invasion of lympho-vascular structures [70]. The above-mentioned studies are consistent with our results in that superficial elevated or depressed macroscopic types have a predilection to invade the submucosal layer and hence leading to non-curability after endoscopic resection.

It is well known that metastasis to lymph nodes is a very critical issue in determining curability following resection of EGCs. And several previous researchers had confirmed that EGCs invading deep in to the submucosal layer and lympho-vascular structures are independently associated with metastasis to lymph nodes [23, 71–74]. Thus, taking all these ideas together, we can infer that EGCs with superficial elevated or depressed gross type are likely to have metastasis to lymph nodes. And great care is needed while encountering EGCs with purely superficial elevated (0-IIa) or depressed (0-IIc) or their mixed gross types with predominant elevated or depressed component (mixed with 0-IIa or 0-IIc dominant).

In the present study, presence of ulcerative finding was associated with NEC resection in a univariate analysis and it was found to be an independent predictor of submucosal infiltration in patients with EGCs after ESD as shown in multivariate analysis (Table 5). In a multivariate analysis, Ohnita et al. [48] reported that absence of ulceration significantly predicted curative outcomes following ESD ($p = 0.002$). In a similar way, other studies demonstrated the interference of ulcer in curability of endoscopically resected lesions [75, 76]. It has been reported that presence of ulceration, mainly in those with greater than 2 cm size, caused technical difficulty during removal procedure leading to incomplete resection of EGCs [77]. Hence, the procedure of ESD might not be smooth in the setting of ulceration, thus, hindering proper dissection along the submucosal plane resulting in NEC resection.

The present study had a number of shortcomings. Firstly, it was a retrospective study and, hence, large-scale multi-center prospective cohort data is needed for external validation. Secondly, the number of enrolled subjects was relatively small, especially those cases who had ulceration, positive margins and positive lympho-vascular structures. With regard to lympho-vascular involvement, we didn't use immunohistochemistry for better identification and that could possibly increase the number of missed cases with positive LVI. We could not get data related to patients' follow up and lymph node status. As such, it was difficult to deal with post-ESD tumor recurrences and disease survival conditions.

Conclusions

Our study demonstrated that certain tumor-associated factors such as location in upper two third, larger tumor size (> 2 cm) and undifferentiated histology are significantly associated with submucosal invasion and NEC outcomes. Hence, great care is needed while handling EGCs with these clinico-pathologic features. There is very little in literature regarding endoscopic macroscopic feature of tumors and their role in curability after ESD by using the JGCA classification. In this study, we discovered that tumors with macroscopic type of purely superficial elevated (0-IIa) or depressed (0-IIc) or mixed gross type with predominant 0-IIa or 0-IIc are highly linked with non-e-curability. Therefore, the findings of our study may shed light on the consideration of certain clinico-pathologic features such as location and macroscopic types in the indication criteria for ESD.

Abbreviations

CI: Confidence Interval; D: Differentiated; EGC: Early Gastric Cancer; EMR: Endoscopic Mucosal Resection; ESD: Endoscopic Submucosal Dissection; JGCA: Japanese Gastric Cancer Association; M: Mucosal; NEC: Non-e-curative; OR: Odds Ratio; SD: Standard Deviation; SM: Submucosal; T1a: Intra-mucosal Tumor; T1b: Submucosal Tumor; U: Ulcer; UD: undifferentiated

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (Medical Ethics Committee of Tongji Hospital) of Tongji Medical College, Huazhong University of Science and Technology. No specific IRB reference number is available. The data related to this work were obtained from the hospital's registry and statistical data as part of patients' care and support. No consent to participate was sought from the study participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflicts of interests.

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Authors' contributions

KSE, CZ and XW conceived and designed the study. KSE performed the microscopic evaluation, analyzed data, interpreted results, and drafted the manuscript. CZ performed the microscopic evaluation, provided the HE images and revised the manuscript. All authors reviewed the manuscript and approved the submitted version.

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Figures

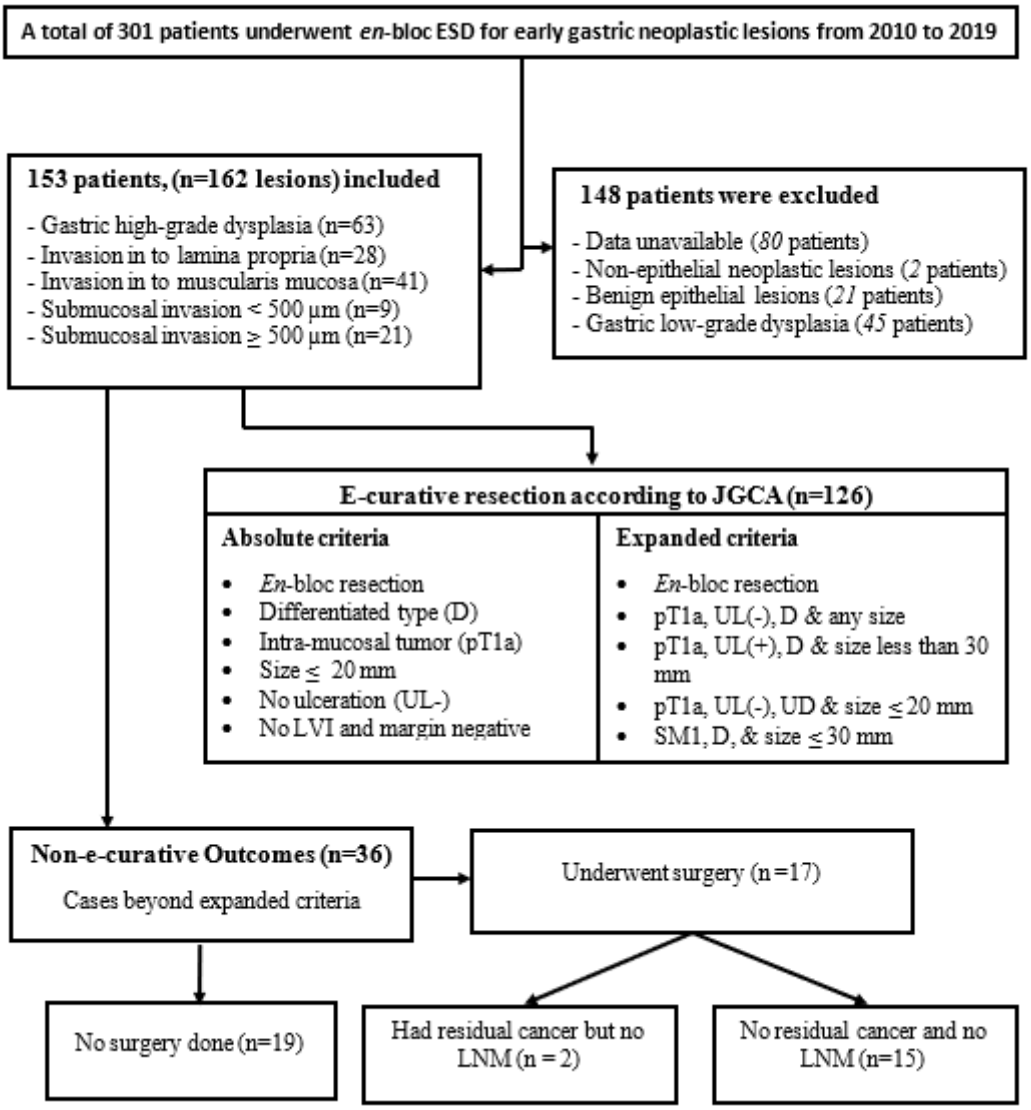

Figure 1

Flowchart for patients with early gastric neoplasia who underwent ESD ESD = Endoscopic submucosal Dissection, EGC = early gastric cancer, JGCA = Japanese Gastric Cancer Association, UD = Undifferentiated, U = Ulcer, SM1= Submucosal invasion < 500 µm LVI = Lympho-vascular invasion, UL= Ulceration, LNM = lymph node metastasis type

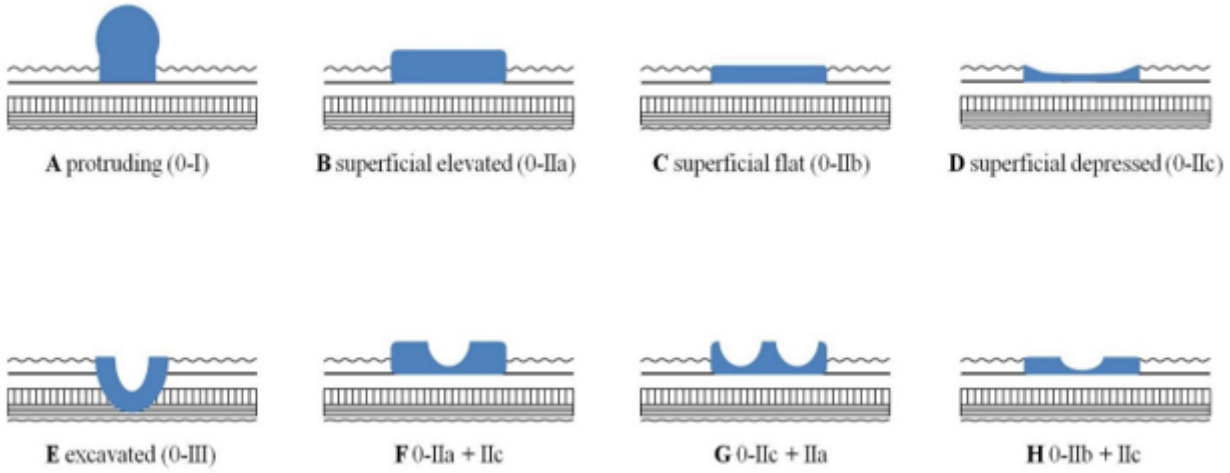

Figure 2

Endoscopy-based macroscopic sub-classification of type '0' early gastric lesions (A) Protruding [0-I], with ≥ 3 mm elevation. (B) Superficial elevated [0-IIa], with < 3 mm elevation. (C) Superficial flat lesions [0-IIb], tumors with no elevation or depression. (D) Superficial depressed [0-IIc], tumors with slight depression. (E) Excavated [0-III], tumors which are deeply depressed. (F) Superficial elevated and depressed lesions with predominant elevated type [0-IIa + IIc] and. (G) Superficial elevated and depressed lesions with predominant superficial depressed type [0-IIc + IIa]. (H) Superficial flat and depressed lesions with predominant superficial flat type [0-IIb + IIc].

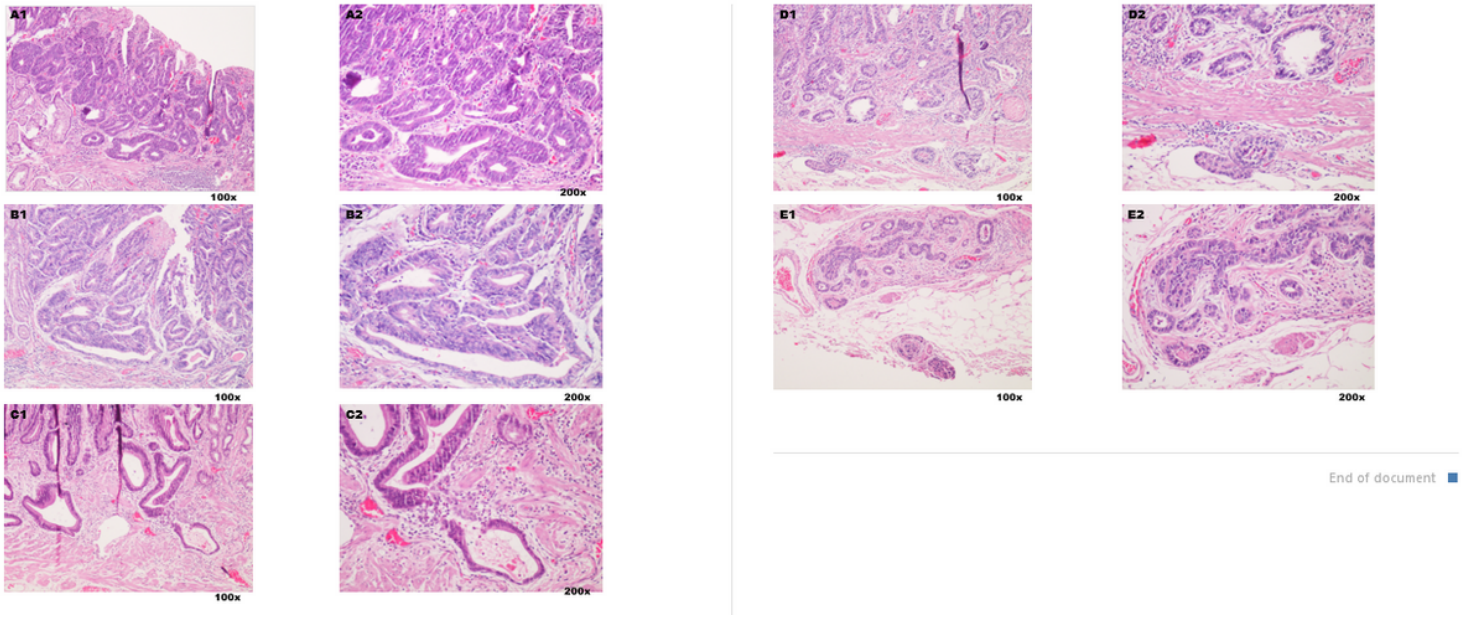

Figure 3

Different stages of early gastric neoplasia according to the depth of invasion and their respective total magnification under microscope (100x & 200x, respectively). Hematoxylin and Eosin staining. (A1/A2) Gastric high grade dysplasia displaying complex glandular structure, significant cellular atypia, nuclear

pseudo-stratification, hyperchromasia and poor nuclear polarization. (B1/B2) Cancer invading lamina propria. (C1/C2) Invasion involving the muscularis mucosae layer. (D1/D2) Gastric cancer that infiltrates in to the submucosal layer but less than 500 μm depth from the muscularis mucosae, there is also associated lymphatic invasion. (E1/E2) Submucosal invasion greater than 500 μm from the muscularis mucosae with positive vertical margin.