U.PORTO

FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2018/2019

Gonçalo Vieira Figueirôa Gomes

Poor outcomes after gastric Endoscopic Submucosal Dissection: a systematic review and meta-analysis on predictive factors

Resultados desfavoráveis após disseção endoscópica da submucosa gástrica: revisão sistemática e meta-análise

março, 2019

Gonçalo Vieira Figueirôa Gomes

Poor outcomes after gastric Endoscopic Submucosal Dissection: a systematic review and meta-analysis on predictive factors

Resultados desfavoráveis após disseção endoscópica da submucosa gástrica: revisão sistemática e meta-análise

Mestrado Integrado em Medicina

Área: Gastrenterologia

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Dr. Diogo Miguel Pereira Libânio Monteiro

E sob a Coorientação de:

Professor Doutor Mário Jorge Dinis Ribeiro

Trabalho organizado de acordo com as normas da revista:

Digestive Endoscopy

março, 2019

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

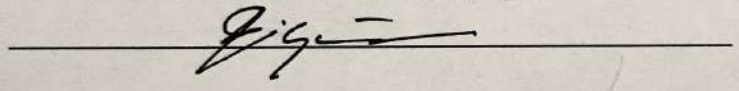
Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Gonçalo Vieira Figueirôa Gomes, abaixo assinado, nº mecanográfico 201304075, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 18/03/2019

Assinatura conforme cartão de identificação:



U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Gonçalo Vieira Figueirôa Gomes

NÚMERO DE ESTUDANTE	E-MAIL
201304075	up201304075@med.up.pt

DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina Clínica

TÍTULO DISSERTAÇÃO

Poor outcomes after gastric Endoscopic Submucosal Dissection: a systematic review and meta-analysis on predictive factors

ORIENTADOR

Diogo Miguel Pereira Libânio Monteiro

COORIENTADOR (se aplicável)

Mário Jorge Dinis Ribeiro

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 18/03/2019

Assinatura conforme cartão de identificação: _____

Poor outcomes after gastric Endoscopic Submucosal Dissection: a systematic review and meta-analysis on predictive factors

Gonçalo Figueirôa[1], Pedro Pimentel-Nunes MD PhD[1,2], Mário Dinis-Ribeiro MD PhD[1,2], Diogo Libânio MD[1,2]

[1] MEDCIDS – Departamento de Medicina da Comunidade, Informação e Decisão em Saúde, Porto, Portugal

[2] Gastroenterology Department, Instituto Português de Oncologia do Porto, Porto, Portugal

Corresponding author:

Gonçalo Figueirôa

Departamento de Medicina da Comunidade, Informação e Decisão em Saúde (MEDCIDS)

Faculdade de Medicina da Universidade do Porto

Rua Doutor Plácido da Costa

4200-450 Porto, Portugal

Phone: +351 969 925 733

E-mail: g.figueiroa8@gmail.com

ABSTRACT

BACKGROUND AND AIMs: Endoscopic submucosal dissection (ESD) is now established as the first option to manage early gastric neoplasms but its efficacy may vary according to diverse factors. We aimed to systematically identify variables predictive of poor outcomes of gastric ESD.

METHODS: Three online databases (MEDLINE, ISI Web of Knowledge and Scopus) were searched (last search on June 2018) for poor outcomes of gastric ESD (deep submucosal invasion, piecemeal/incomplete resection, non-curative resection, local recurrence and metachronous lesions).

RESULTS: One hundred and fourteen studies were included referring to 55.986 ESDs. Undifferentiated histology and upper location (*vs* lower) were found to be associated to submucosal invasion (OR=2.42 [95%CI 1.62-3.61] and OR=3.20 [1.04-9.86], respectively) and deep submucosal invasion (OR=2.98 [2.02-4.39] and OR=2.35 [1.45-3.81], respectively). Lesion size >30mm and ulceration were associated with piecemeal resection (OR=2.78 [1.17-6.60] and OR=2.76 [1.23, 6.20]). Lesion size >30mm, ulceration, upper location and fibrosis were risk factors for incomplete resection (OR=3.83 [2.68-5.49], OR=4.06 [1.62-10.16], OR=3.71 [2.49-5.54] and OR=4.46 [1.66-11.96]), respectively). A non-curative resection was more often observed for lesions with upper location (OR=1.49 [1.24-1.79]), depressed morphology (OR=1.49 [1.04-2.12]) and those outside standard criteria (OR=3.56 [2.31-5.48]). Older age was significantly linked with local recurrence rates (OR=3.08 [1.13-5.02]) and metachronous lesions (OR=3.00 [1.77-4.22]).

CONCLUSIONS: Several risk factors influence poor efficacy outcomes of gastric ESD that may be used to inform both patients and health providers about the expected efficacy.

Key words: Endoscopic submucosal dissection, gastric cancer, outcomes, risk factors.

Introduction

Early gastric neoplasms with null or minimal risk of lymph node metastasis (LNM) can be effectively treated by gastric endoscopic submucosal dissection (ESD). Endoscopic resection (by Endoscopic Mucosal Resection or ESD) is recommended as the standard treatment for differentiated adenocarcinoma <2cm clinically diagnosed as intramucosal (T1a); lesions with low risk of LNM but outside these criteria can also be treated with ESD as an alternative to surgery, although it is still considered as an investigational treatment in Japanese guidelines[1]. Recent European guidelines recommend endoscopic resection as the first line treatment for gastric superficial neoplastic lesions with very low risk of LNM, being ESD recommended as the treatment of choice[2].

Since the introduction of ESD, several studies evaluated its efficacy and safety in the treatment of early gastric neoplasms [3-6]. After efficacy and safety is proven and a technology becomes accepted and widely performed, research should aim to predict and optimize outcomes, in order to improve patient selection for the technique and also to improve patient information about expected outcomes [7-9].

ESD achieves en-bloc/R0 resections in more than 90% of the cases [10]. Lesions suitable for endoscopic treatment are selected based on the endoscopic evaluation with chromoendoscopy (endoscopic ultrasound does not improve prediction of submucosal invasion and therefore is not routinely recommended) [2]. However, ESD is not curative in nearly 20% of the cases because histopathological evaluation shows previously unsuspected submucosal invasion or lymphovascular invasion (among other criteria)[11]. Thus, evaluation of risk factors for submucosal invasion is important in order to improve patient selection for ESD. Since en-bloc resection and R0 resection are requisites for curative resection, it is also important to analyze risk factors for piecemeal and R1 that could possibly help in the selection of procedural modifications or perhaps referral for expert centers [12-14].

ESD is associated with low local recurrence rates (1-3%) but with a high risk of metachronous lesions on long-term follow-up which makes endoscopic surveillance necessary [11, 15, 16]. Several studies also assessed risk factors for these long-term outcomes, although results are often controversial. The identification of risk factors for recurrence and metachronous could therefore influence surveillance schedule.

In summary, several patient- and lesion-specific factors have been found to influence both short- and long-term outcomes, but there is no consensus regarding which factors are actually significant.

The aim of this study was to assess risk factors (clinical or endoscopic variables, available at the pre-resection stage) for poor efficacy outcomes of gastric ESD, both short-term (submucosal invasion, piecemeal and incomplete resection, non-curative resection) and long-term (local recurrence and metachronous lesions).

Methods

a) Study selection

A systematic review of the literature was conducted in three electronic databases (MEDLINE through Pubmed), ISI Web of Knowledge and Scopus from inception until 26th June 2018. The following search query without language restriction was used in Pubmed: ([gastric OR stomach] AND [“endoscopic submucosal dissection” OR “ESD”]) AND (non-curative OR “non curative” OR “submucosal invasion” OR “treatment failure” OR “procedure failure” OR “recurrence”), with the search query for other databases being adapted from this query.

The references of included studies and retrieved articles were uploaded to Covidence online platform (www.covidence.org) that was used for articles selection. Both title and abstract screening (for exclusion of irrelevant articles) and full text screening were made by two independent investigators (GF, DL), being conflicts solved by consensus. The following inclusion

criteria were defined: 1) Study design: case-control or cohort studies (either retrospective or prospective) or clinical trials (including randomized controlled trials [RCTs]); 2) Publication status: full article or abstract; 3) Types of participants and interventions: patients with gastric superficial neoplasms (dysplastic lesions or early gastric cancers) submitted to ESD; 4) Assessed risk factors: clinical or endoscopic variables, available/assessed at the pre-resection stage 5) Assessed outcomes: studies evaluating risk factors for at least one of the following outcomes: a) submucosal invasion; b) deep submucosal invasion; c) piecemeal resection; d) incomplete resection (R1); e) non-curative resection; f) recurrence; g) metachronous lesions. Exclusion criteria were: 1) Fewer than 20 patients included; 2) Feasibility studies of innovative techniques/devices without control group; 3) Comments, reviews, letters, or surveys; 4) Case reports; 5) Animal studies; 6) Patient overlap between studies (in this case, only the study with largest sample / study period was included).

b) Data extraction and quality evaluation

Data extraction was performed by GF and independently checked by DL using a predefined form, which included: 1) title; 2) author; 3) country of origin; 4) local; 5) year; 6) study period; 7) study design; 8) population studied; 9) outcomes assessed. Raw data for each risk factor was collected and registered in the extraction form. Quality evaluation was performed by GF using the Newcastle-Ottawa scale (NOS). In the case of risk factors such as size, age, histology and macroscopic morphology, where often more than two categories were reported, data was regrouped so that comparisons could be made. Concerning morphology, lesions were grouped into lesions either elevated or flat (I, IIa or IIb) or depressed (IIc or III). For size the main cut points were 20 and 30 mm. Finally, regarding histology, lesions classified as ‘Well differentiated’ or ‘Moderately differentiated’ were grouped as differentiated histology, whereas those classified as ‘Poorly differentiated’ or ‘Signet Ring Cell’ were grouped as undifferentiated lesions.

c) Data synthesis and statistical analysis

Odds ratios (OR) along with 95% confidence intervals (95% CI) were calculated for categorical variables, while mean and standard deviation were used for continuous variables. Pooled odds ratio and pooled mean difference were then computed using RevMan 5.3 [17]. Heterogeneity was assessed with Cochran's Q and I^2, with $p<0.05$ and $I^2 > 40\%$ respectively being defined as thresholds for significant heterogeneity. Random effects model was used when significant heterogeneity ($I^2>40\%$) was detected. Although no subgroup analysis was planned in advance, we planned to separately evaluate studies that included only gastroesophageal junction lesions and studies that only included undifferentiated carcinomas. In case of articles with patient/lesions overlap for the same outcome and risk factor, only the study with largest study period/sample size was included in the analysis.

Results

After the removal of duplicates, a total of 928 studies were identified. Of these, 114 studies respected inclusion and exclusion criteria after full text screening, and 71 were included in meta-analysis (Figure 1), corresponding to 55.986 ESDs. All the studies were cohort (n=112) or case control (n=2), and the majority from Asia (n=110). Characteristics of included studies are shown in table 1. The median Newcastle-Ottawa score was 8 (IQR 7-8). Selective reporting was not detected in the included studies. The results of short-term and long-term outcomes are detailed below.

a) Submucosal invasion and Deep Submucosal Invasion

Several studies evaluated risk factors for Submucosal invasion (SI) and Deep Submucosal Invasion (DSI), although few could be pooled in meta-analysis (table 2). Regarding demographic variables, sex was not found to significantly influence the risk of SI (OR_{male} 1.42 [0.96, 2.10]).

Lesion size >20mm showed a trend to higher SI risk, although not reaching statistical significance (OR 1.50 [0.28, 8.14]).

On the other hand, localization was found to have a significant influence on SI and DSI risk. Lesions located in the upper and middle third of the stomach were associated with a significantly higher risk of SI when compared with lower third lesions (OR_{upper} 3.20 [1.04, 9.86] and OR_{middle} 2.11 [1.41, 3.16]), but there were no significant differences between upper and middle third lesions (OR 1.17 [0.36, 3.80]). Early gastric cancers (EGCs) from the upper third also showed higher chances of DSI when compared to middle EGCs (OR 2.11 [1.18, 3.79]) and lower third (OR 3.35 [1.45, 3.81]), but there were no differences in DSI risk in middle and lower lesions (OR 1.12 [0.81, 1.56].

Undifferentiated histology was also significantly associated with a higher risk of SI and DSI (OR 2.42 [1.62, 3.61] and OR 2.98 [2.02, 4.39], respectively). Depressed lesions did not show significantly higher rates SI (OR 1.05 [0.60, 1.84]). Finally, *H. pylori* eradication (OR 1.35 [0.85, 2.16]) and the presence of Ulceration (OR 1.42 [0.98, 2.06]) were not found to be significant risk factors for SI and DSI, respectively.

Some additional risk factors were evaluated in single studies and thus not included in meta-analysis (table 2).

b) Piecemeal resection and Incomplete Resection

Regarding demographic variables, age, the resection of lesions in the remnant stomach or gastric tube and the presence of liver cirrhosis were not perceived as a significant risk factors for both Piecemeal resection (PR) and Incomplete resection (IR) (table 4). Similarly, sex showed no significant influence on IR rates (table 3). On the contrary, a size greater than 20mm (OR 3.20 [2.07, 4.95] for PR and 3.64 [2.24, 5.91] for IR) and 30mm (OR 2.78 [1.17, 6.60] for PR and OR 3.83 [2.68, 5.49] for IR) were identified as significant risk factors (Figure 2).

Concerning location, no significant association was found when comparing PR rates although there was a trend to higher piecemeal rates in lesions from the upper stomach (Upper vs Middle (OR 1.57 [0.51, 4.80]), Upper vs Lower (OR 3.57 [0.31, 41.12]) and Middle vs Lower (OR 2.35 [0.74, 7.43]). On the other hand, lesions from the Upper third of the stomach were significantly associated with higher IR rates, when compared to lesions of the middle and lower parts (OR 1.62 [1.14, 2.31] and 3.71 [2.49, 5.54], respectively). Furthermore, EGCs located on the middle part were also significantly associated to higher IR rates, when compared to lesions of the lower part (OR 2.28 [1.58, 3.28]).

EGCs that met Expanded Indication (EI) also have a higher chance of a piecemeal resection when compared to Absolute Indication (AI) lesions (OR 2.25 [1.44, 3.53]). Beyond-Expanded Indication (BEI) also was associated with a significantly higher risk of PR (OR 4.64 [1.68, 12.82]). Yet, when comparing the EI and BEI groups, no significant relation was found (OR 1.53 [0.53, 4.37]). With relation to IR rates, EGCs that met EI showed a significant association when compared to AI EGCs (OR 3.22 [2.01, 5.18]). On the other hand, morphology does not seem to have a significant impact on IR ($OR_{depressed}$ 0.90 [0.47, 1.75]).

The presence of ulceration proved to have a significant influence on both PR (OR 3.05 [1.92, 4.85]) and IR rates (OR 4.06 [1.62, 10.16]) (Figure 3). Undifferentiated histology was also found to be significantly associated with higher rates of IR (OR 6.67 [3.42, 12.99]), but not PR (OR 1.60 [0.73, 3.53]). Also, the presence of invasion of the submucosa and deep invasion of the submucosa reported significant higher rates of IR rates (OR 27.89 [3.57, 218.01] and OR 14.99 [2.84, 79.25], respectively). Moreover, the presence of fibrosis (degrees F1 or F2) was also identified as a significant risk factor for this last outcome (OR 4.46 [1.66, 11.96]).

Further risk factors were evaluated in single studies (table 3).

c) Non-curative resection

Age over 75 years was significantly associated with higher non-curative resection (NCR) rates (OR 1.28 [1.02, 1.61], I^2=0%), although in studies using 60 and 70 years as cut-off no higher risk was found in older patients (OR 1.09 [0.72, 1.68] and 1.17 [0.81, 1.69], respectively). In two studies that analyzed age as continuous variable, the mean age difference between groups was similar (mean difference 1.00 [-0.27, 2.27]). Other demographic variables such as Body Mass Index (BMI) or sex were not significantly associated with NCR (table 4).

Greater lesion size was found to be a significant risk factor for NCR: mean lesion size was significantly higher in NCR (mean difference 6.14mm, [95% CI 4.82, 7.47]), and the risk of NCR paralleled lesion size (OR_{NCR} for lesions >20mm 3.66 [3.10, 4.31]; OR_{NCR} for lesions >30mm 5.01 [2.83, 8.87]). Likewise, location in the upper third of the stomach had significant higher risk of NCR when compared with localization in the middle or lower (OR 1.49 [1.24, 1.79] and 2.08 [1.72, 2.50], respectively) (Figure 4). Comparing middle and lower location, middle lesions were also associated with higher NCR (OR 1.33 [1.13, 1.56]). On the other hand, location on the horizontal axis (anterior vs posterior; greater vs lesser curvature) was not found to significantly influence NCR.

Concerning macroscopic appearance, depressed EGCs showed significant higher NCR rates when compared to elevated/flat ones (OR 1.49 [1.04, 2.12]), while polypoid EGCs were not significantly associated with NCR when compared with flat lesions despite a trend to higher NCR ($OR_{polypoid}$ 2.15 [0.60, 7.77]]). The presence of ulceration and piecemeal resection were also significantly associated with NCR (OR 2.69 [1.38, 5.27] and 4.02 [1.49, 10.87], respectively).

Concerning the indication for endoscopic resection, lesions meeting EI were identified to have significant higher chances of NCR when compared with AI lesions (OR 3.56 [2.31, 5.48] as well as lesions classified as BEI ($OR_{vs\ EI}$ 187.33 [23.93, 1466.76]).

Two studies included EGCs from the esophagogastric junction (EGJ). Analysis of these studies revealed that Macroscopic Appearance and Endoscopic Criteria were not significant risk

factors for NCR in this population ($OR_{depressed}$ 0.73 [0.19, 2.85] and OR_{EI} 2.07 [0.81, 5.32], respectively).

Single studies reported other risk factors potentially related to NCR, such as Helicobacter pylori infection [18], carcinoma detected in biopsies before resection [19] and submucosal invasion [20] (table 4).

d) Local Recurrence and Metachronous Lesions

Meta-analysis evaluating risk factors for local recurrence (LR) found that undifferentiated histology was a risk factor for this outcome (OR 5.72 [1.73, 18.89]). Localization on the upper or middle third also presented a higher risk of LR when compared with lower third lesions (OR 2.54 [1.20, 5.38] and OR 1.66 [1.04, 2.64], respectively). Mean age was significantly higher in patients with LR (mean difference 3.1 years [1.1, 5.0]), although in age >75 years was not found to significantly influence LR rates (OR 1.75 [0.47, 6.56]). Beyond expanded criteria (BEC) were also found to be associated with higher recurrence rate (OR 7.12 [1.24, 40.85]), when compared to Absolute/Standard Criteria (AC). However, when comparing Expanded Criteria (EC) and AC or BEC, no significant association was found.

On the other hand, clinico-demographic risk factors such as sex and current smoking had no influence on LR in meta-analysis (table 5). Lesion size and the presence of ulceration was also not found to significantly influence LR, just as depth of invasion (table 5).

We only found two significant risk factors for the emergence of metachronous lesions (ML), namely older age (mean difference 3.00 [1.77, 4.22]) and the presence of multiple lesions at diagnosis (OR 2.02 [1.46, 2.81]). Among others, risk factors such location, size, morphology, undifferentiated histology or the infection of Helicobacter pylori at the time of resection did not prove to be statistically significant (table 5).

Single studies reported some factors not included in the Meta-Analysis (MA) (table 5).

Discussion

This systematic review and meta-analysis is, to our knowledge, the first that evaluated pre-resection risk factors for poor outcomes of gastric ESD (deep submucosal invasion, non-curative resection, piecemeal/incomplete resection, local recurrence and metachronous lesions). ESD is gaining worldwide acceptance as the first line treatment for gastric superficial neoplasms, although it is unsuccessful in nearly 20% of the cases [11]. Identification of pre-resection risk factors for poorer efficacy outcomes of gastric ESD is thus important in order to refine patient selection for this technique and also to better inform patients about the success probability of endoscopic treatment, given that surgical resection can also be considered when the risk of poor outcomes is significant. We previously evaluated risk factors which potentially influenced safety of resection, but data was controversial regarding the predictors of poor effectiveness of gastric ESD [7] [8] [3] [4].

We found that an undifferentiated histology is a significant risk factor for submucosal invasion and deep submucosal invasion, which is probably explained by the predominantly infiltrative growth pattern of undifferentiated lesions [21]. Concerning location, proximal lesions seem to have a higher propensity of harboring submucosal invasion. While the biological explanation remains unknown, possibly upper lesions are more prone to be missed at endoscopy and are detected later.

Greater lesion size and ulceration were associated with incomplete/piecemeal resection, likely given to technical procedural difficulties. Furthermore, an upper location also increases the risk of IR which is probably related with the more challenging dissection in retroflexed position. A higher degree of fibrosis was also identified as being associated with higher IR rates, and can also difficult resection given that the identification of the resection field may be impaired. Expanded Endoscopic Indication was found to be associated with PR/IR, which is in line with a previous meta-analysis[22]. Finally, an undifferentiated histology was associated with IR, which

is probably related with difficulties in identifying lesion margins even using chromoendoscopy and also with deeper infiltration which may difficult achieving a free vertical margin.

Lesions characteristics, namely greater size, upper location, depressed morphology and ulceration were significantly associated with non-curative resection. Furthermore, EGCs outside standard criteria were also found to be associated with NCR, which supports the importance of this classification. An age over 75 years, contrasting with other cut-offs also evaluated, was identified as a significant risk factor, which is probably related to the preference of minimally invasive treatment like ESD in older patients even when the probability of NCR is higher.

Age is consistently reported as a risk factor for LR and ML and was found to be a significant risk factor in our study. This finding can have implications in surveillance schedule, given that according to this data it is difficult to define an age cut-off when resection is no longer of benefit (contrasting with colorectal cancer and post-polypectomy surveillance). Other significant risk factors, such as an upper location, an undifferentiated histology and BEC lesions were linked to the occurrence of LR. We acknowledge that incomplete resection is also the most important risk factor for LR; however, the aim of this systematic review was to identify pre-resection variables associated with this outcome, and so the significance of incomplete resection on LR was not evaluated in this study although it was evaluated in a previous meta-analysis by our group [23]. On the other hand, ML was significantly associated with the presence of multiple lesions, most likely due to the presence of a field defect and microsatellite instability [24].

In summary, a proximal location is a risk factor for SI, DSI, IR, LR and NCR. Undifferentiated histology is a risk factor for SI, DSI, IR, and LR, ulceration for PR, IR and NCR, Expanded Endoscopic Indication for PR and IR and Expanded Endoscopic Criteria for NCR and LR. Finally, age is a risk factor for NCR, LR and ML and greater lesion size for PR, IR and NCR.

The primary limitation that we acknowledge in our study is the occasional scarcity of studies for some risk factors. As such, some of the conclusions here drawn may be underpowered, given that it hinders the detection of possible interactions and confounding between risk factors.

Nevertheless, we consider that our results are valuable and are a step forward in enabling endoscopists in better selecting patients that should be submitted ESD.

In conclusion, this study identifies a set of pre-resection risk factors which significantly influence several poor efficacy outcomes, both short- and long-term, related to the resection of gastric EGCs using ESD. We believe that the conclusions here drawn can be useful in guiding gastroenterologists when selecting patients that should undergo ESD and better defining the prognosis of such resection.

Figure 1 – Flowchart of included studies.

Figure 2 – Forrest plot of Piecemeal resection rate according to the presence/absence of ulceration.

Figure 3 – Forrest plot of Incomplete resection rate according to size (20mm as cut-off).

Figure 4 – Forrest plot of Non-curative resection rate according to localization (upper vs lower).

Tables

Table 1 – General characteristics of included studies.

	Period	n_1 (n_2)	Outcome(s) evaluated	Risk factors evaluated	Quality	MA
Prospective studies						
Japan						
Hirata K, 2013 [25]	2008-2010	65 (65)	ML	Multiple	8	Yes
Semba S, 2008 [26]	-	73 (-)	ML	Single (Claudin expression)	8	No
Hasuo T, 2007 [27]	2000-2004	110 (110)	ML	Single (Microsatellite Instability Status)	7	No
Yagi K, 2014 [28]	2010-2013	- (197)	SI	Multiple	7	Yes
Takenaka R, 2008 [29]	2001-2005	275 (306)	PR, IR, LR	Multiple	7	Yes
China						
Shi H, 2017 [30]	2013-2014	32 (32)	LR	Single (MicroRNA-499 rs3746444 A/G polymorphism)	7	No
Yu K, 2017 [31]	2013-2014	45 (45)	LR	Single (miR-34b rs4938723 Polymorphism)	8	No
Li H, 2012 [32]	2009-2011	146 (164)	DSI	Single (ME-NBI image type)	7	No
Xue H, 2016 [33]	2013-2015	230 (-)	LR	Single (CD44 expression)	6	No
Fu QY, 2016 [34]	2009-2015	242 (242)	SI, DSI	Single (Lateral Margin Positivity)	8	No
Korea						
Ok KS, 2016 [35]	2012-2014	160 (160)	SI	Multiple	7	No
Choi IJ, 2016 [18]	2010-2011	712 (737)	SI, NCR	Multiple	9	Yes
Europe						
Probst A, 2017 [36]	2005-2016	179 (191)	SI, DSI, PR, IR, NCR	Single (Endocopic Criteria)	9	No
Retrospective studies						
Japan						
Nagami Y, 2014 [37]	2007-2011	43 (43)	SI, PR, IR, NCR	Single (Histology)	8	No
Omae, 2013 [38]	2004-2010	44 (44)	SI, NCR	Multiple	7	Yes
Nishide N, 2012 [39]	2002-2009	59 (62)	PR, IR	Multiple	7	Yes
Yonezawa J, 2006 [40]	2004-2005	60 (60)	PR, NCR, LR	Single (R-scope ESD)	8	No
Ojima T, 2016 [41]	2002-2013	85 (85)	LR	Multiple	7	No
Oka S, 2014 [42]	2002-2011	97 (97)	SI, DSI, IR, NCR	Single (Histology)	8	No
Kanemistu T, 2014 [43]	2006-2011	- (105)	SI	Multiple	8	No
Komori K, 2016 [44]	2002-2012	107 (124)	PR, IR	Single (Age)	9	Yes
Hirasaki S, 2007 [45]	2002-2006	112 (112)	SI, PR, IR	Single (Size)	8	Yes
Nakata B, 2016 [46]	2007-2016	123 (140)	PR, NCR	Single (Endocopic Indication)	8	Yes

Yamada T, 2014 [47]	2007-2012	132 (143)	SI	Single (Submucosal and lymphovascular invasions)	8	No
Sugimoto T, 2015 [48]	2000-2009	155 (-)	ML	Multiple	8	Yes
Horiguchi N, 2016 [49]	2007-2015	164 (182)	SI, DSI	Single (Helicobacter pylori Eradication)	8	Yes
Kakushima N, 2007 [50]	2000-2004	165 (184)	IR	Single (Age)	7	Yes
Sanomura Y, 2012 [51]	1994-2009	173 (173)	DSI, PR, IR	Multiple	8	No
Nakamoto S, 2009 [52]	1999-2007	177 (202)	PR, IR	Single (Size)	7	No
Oka S, 2006 [53]	2002-2004	185 (195)	PR, IR, LR	Multiple	7	Yes
Imagawa A, 2006 [54]	2002-2005	185 (196)	PR, IR	Multiple	7	Yes
Katsube T, 2015 [55]	2003-2013	231 (-)	SI, DSI, PR, NCR	Multiple	8	Yes
Goto O, 2009 [56]	2000-2007	231 (276)	SI, PR, IR	Single (Submucosal Invasion)	8	Yes
Horiuchi Y, 2018 [57]	2005-2017	264 (268)	NCR	Multiple	8	Yes
Takenaka R, 2006 [58]	2001-2005	269 (-)	LR	Multiple	6	No
Oda I, 2006 [59]	2001	- (303)	PR, NCR	Multiple	7	Yes
Yoshida M, 2016 [60]	2009-2014	307 (334)	PR, IR	Single (Learning Curve Phases)	6	No
Boda T, 2014 [61]	2002-2010	357 (357)	ML	Multiple	8	No
Ohara Y, 2016 [62]	2008-2012	363 (398)	NCR	Multiple	8	Yes
Sugimoto T, 2012 [63]	2006-2010	418 (485)	PR	Multiple	9	Yes
Kosaka T, 2014 [64]	2002-2007	438 (-)	PR, NCR, LR, ML	Multiple	8	Yes
Ohnita K, 2009 [65]	2003-2008	468 (495)	SI, PR, NCR	Multiple	8	Yes
Toyokawa T, 2011 [66]	2003-2009	514 (586)	PR, NCR	Sinlge (Age)	9	Yes
Ojima T, 2016 [67]	2002-2013	532 (583)	SI, PR, IR	Single (Remnant)	8	Yes
Goto, 2013 [68]	2006-2011	533 (605)	SI, DSI, IR, NCR	Multiple	8	Yes
Isomoto H, 2009 [69]	2001-2007	551 (589)	SI, PR, NCR, LR, ML	Multiple	8	Yes
Yamaguchi N, 2009 [70]	2001-2007	551 (589)	SI, DSI, PR, IR, NCR	Single (Endoscopic Criteria)	8	No
Isomoto H, 2010 [71]	2001-2007	661 (713)	SI, DSI, PR, IR, NCR	Single (Age)	8	Yes
Nagahama T, 2017 [72]	2006-2012	704 (863)	DSI	Multiple	7	Yes
Hirasawa K, 2011 [73]	2000-2010	784 (961)	PR, IR, NCR	Multiple	8	No
Hoteya S, 2011 [74]	2003-2009	818 (977)	SI, DSI, IR, NCR	Multiple	7	Yes
Numata N, 2015 [75]	2005-2011	890 (1053)	IR	Multiple	7	Yes
Higashimaya M, 2013 [76]	2005-2011	891 (1027)	IR	Multiple	8	Yes
Oda I, 2005 [77]	2000-2003	945 (1033)	PR, IR, NCR	Multiple	7	Yes
Toyokawa T, 2012 [20]	2003-2010	967 (1123)	SI, NCR	Multiple	9	Yes
Maehata Y, 2017 [78]	2003-2014	1053 (-)	SI, ML	Single (Helicobacter pylori Eradication)	8	Yes
Nakamura K, 2015 [79]	2002-2011	1161 (1332)	SI, PR, IR	Single (Endocopic Criteria)	8	No
Hoteya S, 2013 [80]	2005-2010	1224 (1463)	IR, NCR	Single (Location)	8	No
Abe S, 2015 [81]	1999-2006	1526 (-)	ML	Multiple	9	Yes

Kakushima N, 2011 [82]	2002-2008	- (1578)	SI	Single (Lateral Margin Positivity)	7	No
Suzuki H, 2016 [83]	1999-2008	2268 (2268)	IR	Single (Lateral Margin Positivity)	8	No
Horiuchi Y, 2018 [84]	2005-2016	2551 (2585)	NCR	Multiple	8	Yes
China						
Chen ZS, 2017 [85]	2014-2015	80 (90)	SI	Single (Multiple Lesions)	8	No
Li SJ, 2015 [86]	2011-2013	116 (116)	SI, DSI, NCR	Multiple	8	Yes
Yan Zhang MM, 2014 [87]	2010-2013	171 (187)	SI, PR, NCR, LR	Single (Age)	8	Yes
Wen J, 2014 [88]	2006-2013	316 (319)	SI, DSI, IR	Multiple	8	Yes
Korea						
Lee JY, 2010 [89]	2004-2008	43 (43)	PR, IR, NCR	Single (Location)	7	No
Park JC, 2011 [90]	2002-2010	47 (47)	SI, PR, IR, NCR	Single (Location)	8	No
Kim TK, 2015 [91]	2005-2012	55 (55)	LR	Single (Lateral Margin Positivity)	7	No
Jeon HK, 2018 [92]	2005-2014	66 (66)	SI, PR, IR, NCR	Multiple	7	Yes
Kim YY, 2013 [93]	2003-2010	74 (74)	PR, IR, NCR, LR	Single (Endoscopic Criteria)	8	No
Choi MH, 2013 [94]	2002-2012	81 (82)	SI, PR, IR, NCR, LR, ML	Single (Histology)	8	No
Gong EJ, 2016 [95]	2004-2011	88 (88)	PR, IR, NCR	Single (Location)	7	Yes
Choe WH, 2018 [96]	2006-2013	90 (-)	SI, DSI, PR, IR, LR, ML	Single (Liver Cirrhosis)	9	Yes
Choi JH, 2012 [97]	2004-2010	92 (-)	SI, DSI, PR, IR	Single (Liver Cirrhosis)	8	Yes
Bae JH, 2015 [98]	2007-2013	110 (110)	PR, IR, LR	Single (Location)	7	No
Myung YS, 2017 [99]	2005-2014	136 (-)	SI, PR, IR	Single (Proton Pump Inhibitor)	8	No
Jang J, 2014 [100]	2010-2012	141 (141)	LR	Single (Endoscopic Healing Type)	7	No
Kim DY, 2014 [101]	2004-2007	142 (-)	LR, ML	Single (Endocopic Criteria)	8	Yes
Han JP, 2016 [102]	2001-2012	152 (152)	LR	Multiple	8	No
Jeong JY, 2012 [103]	2006-2011	167 (161)	SI, PR	Single (Submucosal Fibrosis)	7	No
Kim H, 2017 [104]	-	176 (-)	ML	Single (Helicobacter pylori Infection)	8	Yes
Chung CS, 2017 [105]	2008-2013	185 (-)	SI, ML	Multiple	8	Yes
Jang JS, 2009 [106]	2004-2007	198 (198)	PR, IR	Single (Size)	7	Yes
Goh PG, 2011 [107]	2005-2009	210 (210)	SI, DSI, PR, IR, LR	Multiple	8	Yes
Kang MS, 2015 [108]	2002-2008	280 (309)	PR, IR, LR	Single (Endocopic Criteria)	7	Yes
Kwon YH, 2014 [109]	2007-2010	283 (-)	ML	Multiple	8	Yes
Han JP, 2013 [110]	2001-2008	304 (335)	PR, IR, NCR	Multiple	7	No
Kim BJ, 2010 [111]	2003-2006	337 (337)	SI, PR, IR, LR, ML	Single (Charlson Comorbidity Scale)	7	No
Han JP, 2015 [112]	2002-2009	395 (430)	PR, IR, LR, ML	Single (Histology)	7	Yes
Lee JY, 2016 [113]	2003-2010	401 (415)	LR	Multiple	7	Yes
Kang HY, 2010 [114]	2005-2008	- (456)	SI, IR	Single (Histology)	8	Yes
Choi MK, 2013 [115]	2006-2010	515 (522)	SI, PR, NCR, LR, ML	Single (Endocopic Indication)	8	Yes
Ryu DG, 2017 [116]	2009-2015	532 (557)	PR, IR	Single (Histology)	8	Yes

Sohn SH, 2017 [117]	2005-2014	599 (611)	DSI, PR, IR	Single (Endocopic Indication)	8	Yes
Kim JM, 2016 [118]	2010-2011	712 (737)	SI, DSI	Multiple	8	Yes
Kim JS, 2017 [119]	2009-2015	729 (-)	PR, NCR, LR	Multiple	8	Yes
Kim YI, 2016 [120]	2004-2011	756 (765)	PR, IR, NCR	Single (Endocopic Indication)	9	Yes
Lee H, 2011 [121]	2003-2010	780 (806)	PR, IR, LR, ML	Single (Endoscopic Criteria)	8	Yes
Ahn JY, 2011 [122]	2005-2009	- (833)	PR, IR, LR, ML	Single (Endoscopic Criteria)	8	Yes
Park CH, 2013 [123]	2005-2011	916 (931)	PR, IR, NCR, LR, ML	Multiple	8	Yes
Jung S, 2015 [124]	2007-2011	1041 (-)	SI, PR, ML	Multiple	9	Yes
Shin KY, 2015 [125]	2003-2010	1105 (1105)	SI, DSI, PR, IR, NCR	Single (Endoscopic Criteria)	8	No
Yang HJ, 2017 [126]	2005-2014	1115 (-)	ML	Single (H pylori eradication)	8	No
Kang D, 2017 [127]	2010-2016	1181 (-)	SI, PR, IR, NCR	Single (BMI)	7	Yes
Yang HJ, 2018 [128]	2005-2014	1237 (-)	LR, ML	Single (Age)	8	Yes
Hahn KY, 2016 [129]	2007-2014	1347 (-)	LR	Multiple	9	Yes
Min BH, 2015 [130]	2003-2011	1497 (1539)	SI, ML	Multiple	8	Yes
Kim EH, 2016 [131]	2007-2013	1639 (-)	NCR	Multiple	9	Yes
Joh DH, 2015 [132]	2008-2011	1823 (1929)	PR, IR, NCR	Single (Multiple Lesions)	9	No
Taiwan						
Hsieh Y, 2015 [133]	2004-2009	65 (69)	NCR, LR, ML	Multiple	7	No
Europe						
Seara Costa R, 2018 [134]	2012-2017	105 (114)	SI, PR, IR, NCR, LR, ML	Single (Endoscopic Criteria)	8	Yes
Libânio D, 2016 [19]	2005-2014	164 (194)	NCR	Multiple	8	Yes
Libânio D, 2017 [9]	2005-2015	- (245)	NCR	Multiple	9	Yes

n_1 – number of patients included in the study; n_2 – number of lesions included in the study; MA – Included in the meta-analysis (studies that reported risk factors not evaluated in other studies or that not provided data allowing calculation of odds ratio were not included in meta-analysis); ME-NBI – Narrow Band Imaging Magnification Endoscopy.

Table 2 – Submucosal Invasion and Deep Submucosal Invasion related factors.

Outcome	Risk factors			
Submucosal Invasion	**Significantly associated**	**Studies (n)**	**Effect Estimate**	**I^2**
	Location Vertical (MxL)	3	2.11 [1.41, 3.16]	0%
	Location Vertical (UxL)	3	3.20 [1.04, 9.86]	64%
	Histology	4	2.42 [1.62, 3.61]	0%
	Single factors significantly associated			
	VEC pattern [43], submucosal fibrosis [103], destructive micro surface pattern [35], ulceration [74] and metachronous lesions [34].			
	Not significantly associated	**Studies (n)**	**Effect Estimate**	**I^2**
	Lesion size (20mm)	2	1.50 [0.28, 8.14]	71%
	Location Vertical (UxM)	3	1.17 [0.36, 3.80]	76%
	Morphology	3	1.05 [0.60, 1.84]	50%
	HP erradication	2	1.35 [0.85, 2.16]	0%
	Single factors not significantly associated			
	Gastrectomy [67], PPIs administration [99], cirrhosis [97], charlson comorbidity scale (at least one risk factor) [111], BMI [127] and multiple lesions [85].			
Deep Submucosal Invasion	**Significantly associated**	**Studies (n)**	**Effect Estimate**	**I^2**
	Location Vertical (UxM)	3	2.11 [1.18, 3.79]	52%
	Location Vertical (UxL)	3	2.35 [1.45,3.81]	42%
	Histology	3	2.98 [2.02, 4.39]	0%
	Single factors significantly associated			
	Size over 30mm [118], metachronous lesions [34] and pattern C with ME-NBI (no surface pattern and sparse microvessels markedly distorted, isolated, heterogeneous or with avascular areas) [32].			
	Not significantly associated	**Studies (n)**	**Effect Estimate**	**I^2**
	Location Vertical (MxL)	3	1.12 [0.81, 1.56]	0%
	Ulceration	3	1.42 [0.98, 2.06]	31%
	Single factors not significantly associated			
	Age [69], sex [74], size over 20mm [72], location [118], morphology [118] and HP eradication [49].			

n – number of studies; I^2 – heterogeneity; M – middle third; L – lower third; U – upper third; VEC Pattern – Vessels within epithelial circle pattern; HP eradication – Helicobacter pylori eradication; PPIs – Proton-pump inhibitors; BMI – Body Mass Index; ME-NBI – Magnification Endoscopy (Narrow Band Imaging).

Table 3 – Piecemeal Resection and Incomplete Resection related factors.

Outcome	Risk factors			
Piecemeal Resection	**Significantly associated**	**Studies (n)**	**Effect Estimate**	**I^2**
	Lesion size >20mm	5	3.20 [2.07, 4.95]	24%
	Lesion size >30mm	2	2.78 [1.17, 6.60]	0%
	Endoscopic Indication (AI x EI)	7	2.25 [1.44, 3.53]	0%
	Endoscopic Indication (AI x BEI)	2	4.64 [1.68, 12.82]	0%
	Ulceration	6	2.76 [1.23, 6.20]	44%
	Single factors significantly associated			
	Degree of fibrosis [103]			
	Not significantly associated	**Studies (n)**	**Effect Estimate**	**I^2**
	Age	3	1.37 [0.49, 3.79]	69%
	Location Vertical (UxM)	3	1.57 [0.51, 4.80]	57%
	Location Vertical (UxL)	3	3.57 [0.31, 41.12]	82%
	Location Vertical (MxL)	3	2.35 [0.74, 7.43]	59%
	Endoscopic Indication (EI x BEI)	2	1.53 [0.53, 4.37]	0%
	Histology	2	1.60 [0.73, 3.53]	0%
	Gastrectomy	2	2.04 [0.01, 411.2]	91%
	Cirrhosis	2	2.58 [0.70, 9.56]	0%
	Single factors not significantly associated			
	Morphology [59], age over 70 years [63], age over 80 years [44], sex [63], multiple lesions [132], metachronous lesions [132], PPIs administration [99], Charlson comorbidity scale >=1[111], R-scope ESD [40], learning curve [60] and BMI [127]**.**			
Incomplete Resection	**Significantly associated**	**Studies (n)**	**Effect Estimate**	**I^2**
	Lesion size >20mm	7	3.64 [2.24, 5.91]	63%
	Lesion size >30mm	4	3.83 [2.68, 5.49]	0%
	Location Vertical (UxM)	5	1.62 [1.14, 2.31]	0%
	Location Vertical (UxL)	5	3.71 [2.49, 5.54]	0%
	Location Vertical (MxL)	5	2.28 [1.58, 3.28]	0%
	Endoscopic Indication (AI x EI)	3	3.86 [1.23, 12.08]	77%
	Ulceration	6	4.06 [1.62, 10.16]	83%
	Depth of Invasion (MxSM)	3	27.89 [3.57, 218.0]	91%

	Depth of Invasion (M/SM1xSM2)	2	14.99 [2.84, 79.25]	56%
	Histology	5	6.67 [3.42, 12.99]	66%
	Degree of Fibrosis	2	4.46 [1.66, 11.96]	69%
	Single factors significantly associated			
	Size [58], tumor location [58], Endoscopic Indication [117] and age (mean) [88]**.**			
	Not significantly associated	**Studies (n)**	**Effect Estimate**	**I^2**
	Age	4	1.04 [0.54, 1.98]	55%
	Sex	2	0.96 [0.55, 1.68]	34%
	Morphology	2	0.90 [0.47, 1.75]	0%
	Gastrectomy	2	0.37 [0.07, 2.15]	87%
	Cirrhosis	2	3.66 [0.64, 20.74]	0%
	Single factors not significantly associated			
	Sex [83], age >65 years [83], age >80 years [44], size [88], location (short axis) [68], location EGJ [80], PPI administration [99], Charlson comorbidity scale >=1 [111], learning curve phase [60], BMI [127], multiple lesions [132] and local recurrence [29].			

n – number of studies; I^2 – heterogeneity; AI – Absolute Indication; EI – Expanded Indication; BEI – Beyond-Expanded Indication; U – upper third; M – middle third; L – lower third; PPIs – Proton-pump inhibitors; ESD – Endoscopic Submucosal Dissection; BMI – Body Mass Index; M – Mucosa; SM – submucosa; SM1 – lesions invading less than 500 μm from the submucosa in depth; SM2 – lesions invading 500 μm or more from the submucosa in depth; EGJ –Esophagogastric junction.

Table 4 – Non-Curative Resection related factors.

Outcome	Risk factors			
Noncurative Resection	**Significantly associated**	**Studies (n)**	**Effect Estimate**	**I^2**
	Age (75)	4	1.28 [1.02, 1.61]	0%
	Endoscopic Indication (AI vs EI)	6	3.56 [2.31, 5.48]	58%
	Endoscopic Indication (EI vs BEI)	2	187.33 [23.93, 1466.76]	0%
	Lesion Size (mean)*	3	6.14 [4.82, 7.47]	0%
	Lesion size (20mm)	7	3.66 [3.10, 4.31]	38%
	Lesion size (30mm)	4	5.01 [2.83, 8.87]	76%
	Location Vertical (UxM)	10	1.49 [1.24, 1.79]	26%
	Location Vertical (MxL)	10	1.33 [1.13, 1.56]	16%
	Location Vertical (UxL)	10	2.08 [1.72, 2.50]	0%
	Ulceration	8	2.69 [1.38, 5.27]	72%
	Piecemeal Resection	2	4.02 [1.49, 10.87]	43%
	Morphology	8	1.49 [1.04, 2.12]	51%
	Single factors significantly associated			
	Age >70 years [73], size >30mm [73], distal location [73, 133], BEI [64], ulceration [133], depth of invasion (EGJ) [38], *H. pylori* infection [18], carcinoma in pre-resection biopsies [19], submucosal invasion [20], fusion of fold [131], interruption [131] or smooth tapering of fold [131], whitish scar [131], nodularity [131] and spontaneous bleeding [131].			
	Not significantly associated	**Studies (n)**	**Effect Estimate**	**I^2**
	Age (mean)*	2	1.00 [-0.27, 2.27]	0%
	Age (60)	2	1.09 [0.72, 1.68]	0%
	Age (70)	2	1.17 [0.81, 1.69]	0%
	Sex	11	1.11 [0.96, 1.29]	28%
	BMI	2	0.84 [0.57, 1.26]	0%
	Location Horizontal (A vs P)	4	0.93 [0.71, 1.23]	0%
	Location Horizontal (GC vs LC)	4	1.08 [0.81, 1.44]	0%
	EGJ: Morphology	2	0.73 [0.19, 2.85]	55%
	EGJ: Endoscopic Criteria	2	2.07 [0.81, 5.32]	0%
	Polypoid Appearance	3	2.15 [0.60, 7.77]	50%
	Single factors not significantly associated			
	Sex [73], size >20 mm [133], ulceration [73], EGJ: size (mean) [38], EGJ: size >20mm [95], gastrectomy [89], EGJ: location [80] [38], location (Anastomosis) [20], R-Scope ESD [40], multiple lesions [132], hybrid-ESD[18],			

	alcohol consumption [18], smoking [18] [131], cancer family history [18], hypertension [20], Diabetes Mellitus [20], hyperlipidemia [20], heart disease [20], cerebrovascular disease [20], chronic renal failure [20], ASA status [19], antiplatelet agent [20], anticoagulant agent [20], elevated margin [131], exudate [131] and atrophy [131].

* Mean Difference (IV)

n – number of studies; I^2 – heterogeneity; AI – Absolute Indication; EI – Expanded Indication; BEI – Beyond-Expanded Indication; U – upper third; M – middle third; L – lower third; EGJ – Esophagogastric junction; BMI – Body Mass Index; A – anterior surface; P – posterior surface; GC – great curvature; LC – lesser curvature; ESD – Endoscopic Submucosal Dissection; ASA status – American Society of Anesthesiologists physical status classification system.

Table 5 – Local Recurrence and Metachronous Lesions related factors.

Outcome	Risk factors			
Local Recurrence	**Significantly associated**	**Studies (n)**	**Effect Estimate**	**I^2**
	Age (mean)*	3	3.08 [1.13, 5.02]	0%
	Location Vertical (MxL)	4	1.66 [1.04, 2.64]	0%
	Location Vertical (UxL)	4	2.54 [1.20, 5.38]	15%
	Histology	4	5.72 [1.73, 18.89]	56%
	Endocopic Criteria (AC vs BEC)	2	7.12 [1.24, 40.85]	0%
	Single factors significantly associated			
	Nodular lesion healing [100], ill-defined margin [113], lateral margin <1mm [113] and incomplete resection [29].			
	Not significantly associated	**Studies (n)**	**Effect Estimate**	**I^2**
	Age	2	1.75 [0.47, 6.56]	0%
	Sex	3	0.81 [0.50, 1.31]	0%
	Lesion size (20mm)	3	0.56 [0.26, 1.20]	50%
	Lesion size (30mm)	2	0.47 [0.09, 2.59]	42%
	Location Vertical (UxM)	4	1.36 [0.62, 2.96]	0%
	Ulceration	3	0.66 [0.15, 2.85]	0%
	Smoking	2	1.14 [0.63, 2.06]	0%
	Depth of Invasion (M vs SM)	2	4.57 [0.38, 54.63]	75%
	Endocopic Criteria (AC vs EC)	8	1.61 [0.99, 2.64]	12%
	Endocopic Criteria (EC vs BEC)	2	5.07 [0.47, 54.48]	44%
	Single factors not significantly associated			
	Size (mean)[29], size >20mm[41], location[29], circumference[41], Endocopic Curative Criteria (EC vs BEC)[41], ulceration[29, 41], undifferentiated histology [41], submucosal invasion[41], size >40mm[113], intestinal metaplasia [129], hypertrophic polypoid healing [100], scar healing [100], Charlson comorbidity >=1 [111], hypertension [129], diabetes[129], smoking [129], alcohol use consumption [40], R-scope ESD [40], macroscopic appearance [41, 58], scar[41], incomplete/piecemeal resection[41]			
Metachronous Lesions	**Significantly associated**	**Studies (n)**	**Effect Estimate**	**I^2**
	Age (mean)*	5	3.00 [1.77, 4.22]	19%
	Multiple Lesions	4	2.02 [1.46, 2.81]	0%
	Single factors significantly associated			

	Male sex [61], age >60years [109], corpus neutrophil infiltration[48] or with intestinal metaplasia[104], anticoagulation [124], I-CLDN(+) phenotype [26], microsatellite instability [27], synchronous neoplasm [128], Polymorphism Rs4938723 [31] and Rs3746444 A/G[30].			
	Not significantly associated	**Studies (n)**	**Effect Estimate**	**I^2**
	Age	2	1.16 [0.32, 4.17]	87%
	Sex	7	0.67 [0.31, 1.43]	82%
	Lesion Size (mean)*	2	-0.76 [-2.85, 1.32]	0%
	Endoscopic Criteria (AC vs EC)	7	1.24 [0.83, 1.84]	0%
	Histology	2	0.67 [0.31, 1.48]	0%
	Location Vertical (UxM)	5	0.96 [0.45, 2.04]	37%
	Location Vertical (MxL)	5	1.23 [0.78, 1.94]	0%
	Location Vertical (UxL)	5	1.38 [0.63, 2.99]	0%
	Morphology	4	1.01 [0.78, 1.31]	0%
	Helicobacter Pylori Status	7	1.60 [0.96, 2.66]	61%
	Ulceration	2	1.67 [0.73, 3.80]	0%
	Smoking	3	0.68 [0.40, 1.15]	0%
	Depth of Invasion (M vs SM)	3	1.18 [0.52, 2.67]	22%
	Atrophy	3	1.28 [0.45, 3.63]	69%
	Single factors not significantly associated			
	Age (mean) [61], age over 75 years [109], size (mean), size over 20mm [81], maximum size [105], location [61], morphology [61], histology [61], submucosal invasion [61], BMI [25], intestinal metaplasia [48, 124], synchronous lesions [61], alcohol consumption [124], Diabetes Mellitus [124], hypertension [124], cirrhosis [61], aspirin exposure [124], anti-platlet agent use [124], cancer family history [124], charlson comorbidity scale (at least one risk factor) [111], neutrophil infiltration in the antrum [48], pepsinogen levels and gastrin levels [48, 61].			

* Mean Difference (IV)

n – number of studies; I^2 – heterogeneity; M – middle third; L – lower third; U – upper third; AC – Absolute/Standard criteria; BEC – Beyond-Expanded criteria; M – Mucosa; SM – Submucosa; EC – Expanded criteria; BMI – Body Mass Index.

Figures

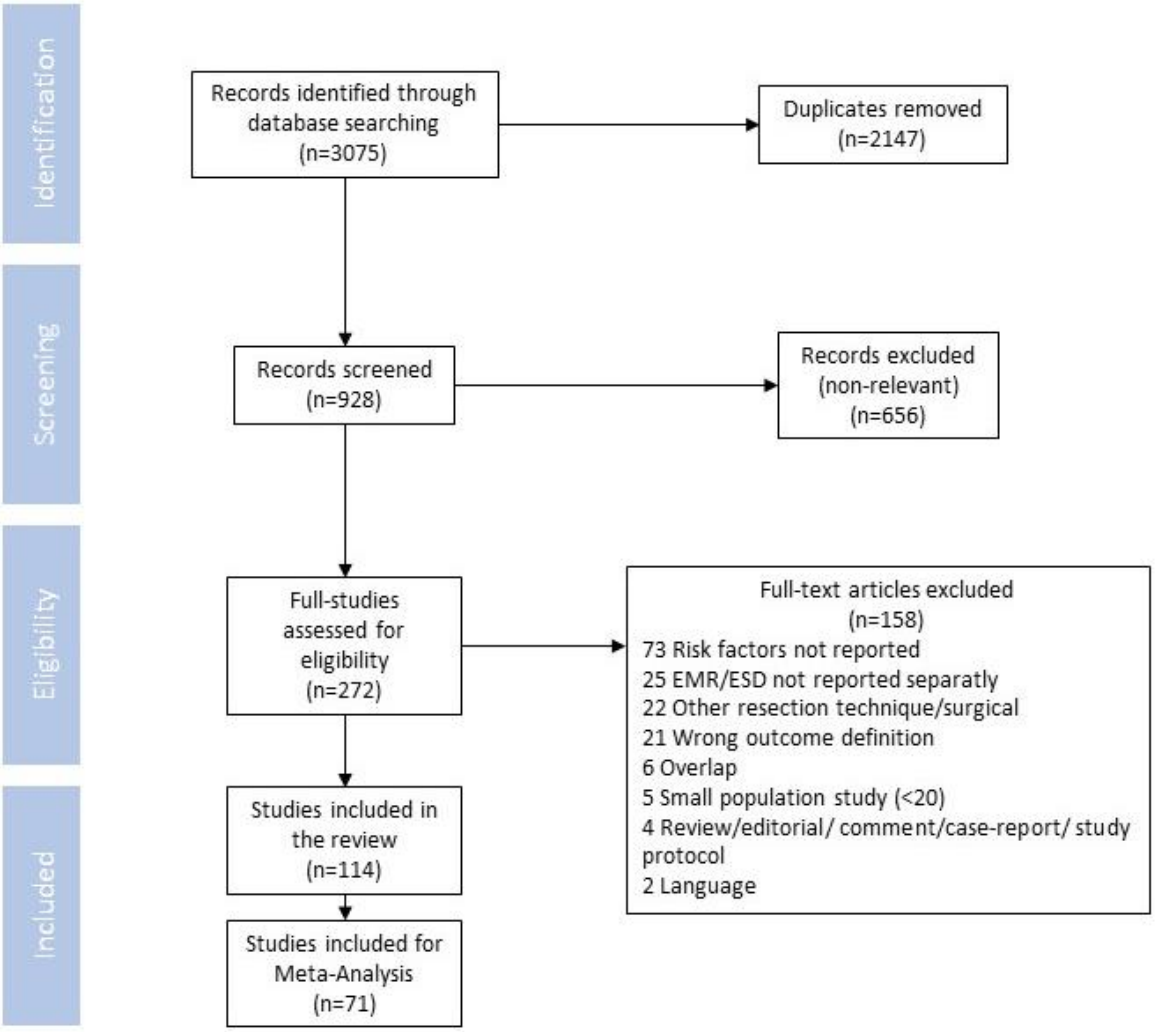


Figure 1 – Flowchart of included studies.

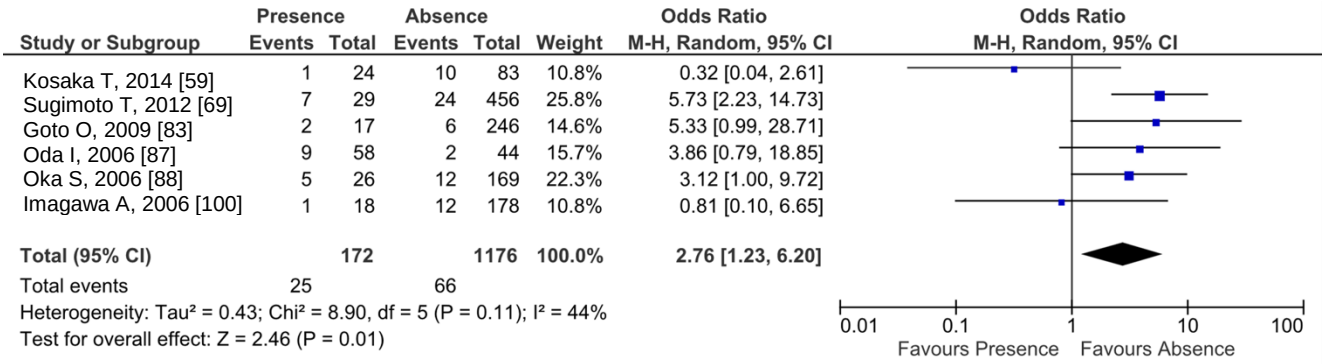


Figure 2 – Forrest plot of Piecemeal resection rate according to the presence/absence of ulceration.

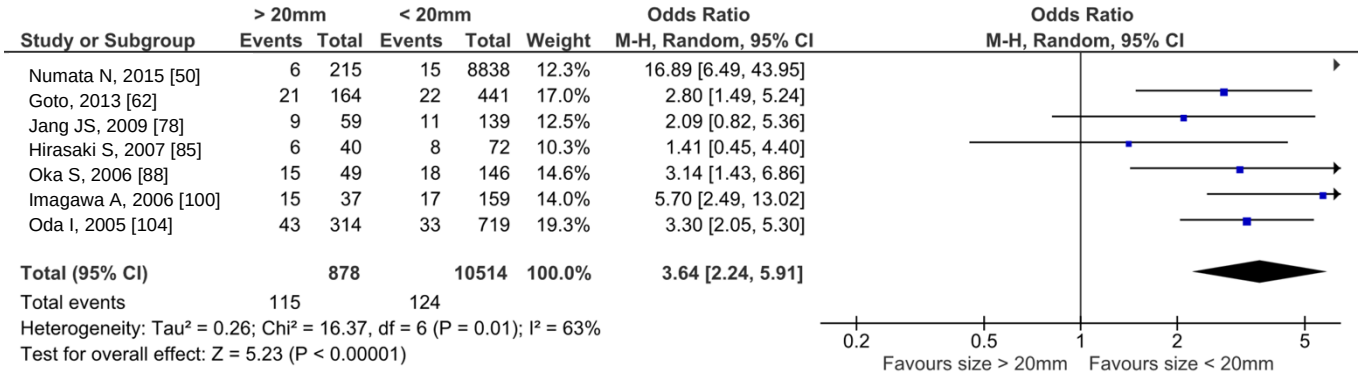


Figure 3 – Forrest plot of Incomplete resection rate according to size (20mm as cut-off).

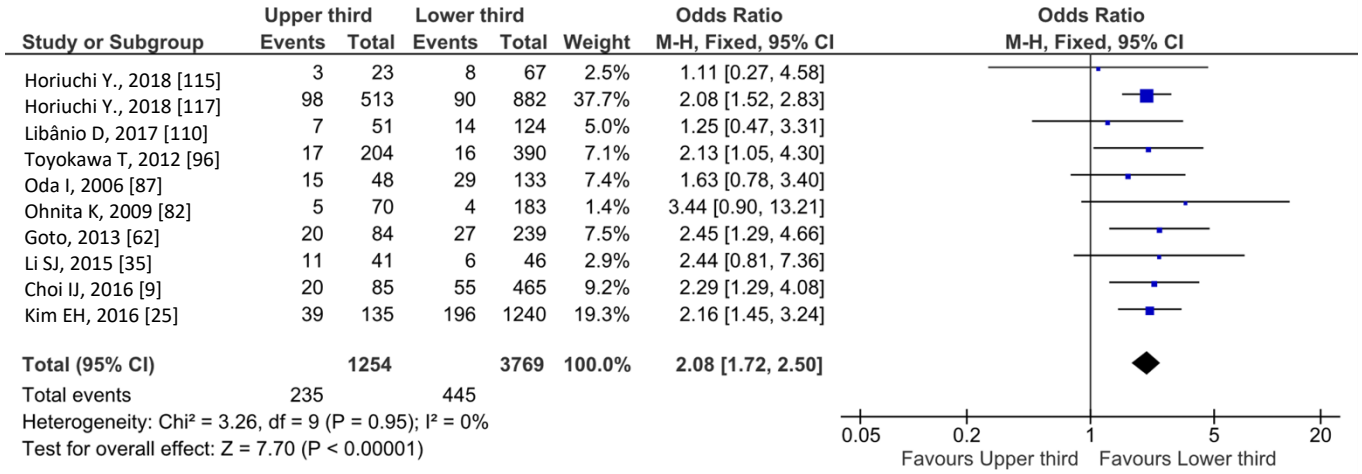


Figure 4 – Forrest plot of Non-curative resection rate according to localization (upper vs lower).

References

1. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Dig Endosc. 2016;28(1):3-15.

2. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European society of gastrointestinal endoscopy (ESGE) guideline. Endoscopy. 2015;47(09):829-54.

3. Libânio D, Costa MN, Pimentel-Nunes P, et al. Risk factors for bleeding after gastric endoscopic submucosal dissection: a systematic review and meta-analysis. Gastrointest Endosc. 2016;84(4):572-86.

4. Libânio D, Pimentel-Nunes P, Dinis-Ribeiro M. Complications of endoscopic resection techniques for upper GI tract lesions. Best Pract Res Clin Gastroenterol. 2016;30(5):735-48.

5. Pimentel-Nunes P, Libânio D, Dinis-Ribeiro M. Evaluation and management of gastric superficial neoplastic lesions. GE Port J Gastroenterol. 2017;24(1):8-21.

6. Libânio D, Braga V, Ferraz S, et al. Prospective comparative study of endoscopic submucosal dissection and gastrectomy for early neoplastic lesions including patients' perspectives. Endoscopy. 2019;51(01):30-9.

7. Ribeiro-Mourão F, Pimentel-Nunes P, Dinis-Ribeiro M. Endoscopic submucosal dissection for gastric lesions: results of an European inquiry. Endoscopy. 2010;42(10):814-9.

8. Ribeiro-Mourão F, Veloso N, Dinis-Ribeiro M, et al. Endoscopic submucosal dissection of gastric superficial lesions: predictors for time of procedure in a Portuguese Center. GE Port J Gastroenterol. 2015;22(2):52-60.

9. Libânio D, Dinis-Ribeiro M, Pimentel-Nunes P, et al. Predicting outcomes of gastric endoscopic submucosal dissection using a Bayesian approach: a step for individualized risk assessment. Endosc Int Open. 2017;5(7):E563-E72.

10. Dinis-Ribeiro M, Pimentel-Nunes P, Afonso M, et al. A European case series of endoscopic submucosal dissection for gastric superficial lesions. Gastrointest Endosc. 2009;69(2):350-5.

11. Park Y-M, Cho E, Kang H-Y, et al. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. Surg Endosc. 2011;25(8):2666-77.

12. Pimentel-Nunes P, Mourão F, Veloso N, et al. Long-term follow-up after endoscopic resection of gastric superficial neoplastic lesions in Portugal. Endoscopy. 2014;46(11):933-40.

13. Pimentel-Nunes P, Dinis-Ribeiro M. Endoscopic Submucosal Dissection in the Treatment of Gastrointestinal Superficial Lesions: Follow the Guidelines! GE Port J Gastroenterol. 2015;22(5):184.

14. Libânio D, Pimentel-Nunes P, Afonso L, et al. Long-term outcomes of gastric endoscopic submucosal dissection: focus on metachronous and non-curative resection management. GE Port J Gastroenterol. 2017;24(1):31-9.

15. Facciorusso A, Antonino M, Di Maso M, et al. Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: A meta-analysis. World J Gastrointest Endosc. 2014;6(11):555.

16. Lian J, Chen S, Zhang Y, et al. A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer. Gastrointest Endosc. 2012;76(4):763-70.

17. Collaboration NCCTC. Review manager (RevMan)[computer program] Version 53. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2014.

18. Choi IJ, Lee NR, Kim SG, et al. Short-Term Outcomes of Endoscopic Submucosal Dissection in Patients with Early Gastric Cancer: A Prospective Multicenter Cohort Study. Gut Liver. 2016;10(5):739-48.

19. Libânio D, Pimentel-Nunes P, Afonso LP, et al. Long-Term Outcomes of Gastric Endoscopic Submucosal Dissection: Focus on Metachronous and Non-Curative Resection Management. GE Port J Gastroenterol. 2016.

20. Toyokawa T, Inaba T, Izumikawa K, et al. Risk Factors of Non-Curative Resection of Early Gastric Neoplasms Performed Endoscopic Submucosal Dissection: Analysis of 1123 Lesions. Gastrointest Endosc. 2012;75(4):135-.

21. Kim H, Kim J-H, Lee YC, et al. Growth patterns of signet ring cell carcinoma of the stomach for endoscopic resection. Gut Liver. 2015;9(6):720.

22. Peng LJ, Tian SN, Lu L, et al. Outcome of endoscopic submucosal dissection for early gastric cancer of conventional and expanded indications: Systematic review and meta-analysis. J Dig Dis. 2015;16(2):67-74.

23. Figueiredo PC, Pimentel-Nunes P, Libânio D, et al. A systematic review and meta-analysis on outcomes after Rx or R1 endoscopic resection of superficial gastric cancer. Eur J Gastroenterol Hepatol. 2015;27(11):1249-58.

24. Miyoshi E, Haruma K, Hiyama T, et al. Microsatellite instability is a genetic marker for the development of multiple gastric cancers. Int J Cancer. 2001;95(6):350-3.

25. Hirata K, Suzuki H, Imaeda H, et al. CD44 variant 9 expression in primary early gastric cancer as a predictive marker for recurrence. Br J Cancer. 2013;109(2):379-86.

26. Semba S, Hasuo T, Satake S, et al. Prognostic significance of intestinal claudins in high-risk synchronous and metachronous multiple gastric epithelial neoplasias after initial endoscopic submucosal dissection. Pathol Int. 2008;58(6):371-7.

27. Hasuo T, Semba S, Li D, et al. Assessment of microsatellite instability status for the prediction of metachronous recurrence after initial endoscopic submucosal dissection for early gastric cancer. Br J Cancer. 2007;96(1):89-94.

28. Yagi K, Saka A, Nozawa Y, et al. Prediction of submucosal gastric cancer by narrow-band imaging magnifying endoscopy. Dig Liver Dis. 2014;46(2):187-90.

29. Takenaka R, Kawahara Y, Okada H, et al. Risk factors associated with local recurrence of early gastric cancers after endoscopic submucosal dissection. Gastrointest Endosc. 2008;68(5):887-94.

30. Shi H, Yang X, Zhen Y, et al. MicroRNA-499 rs3746444 A/G polymorphism functions as a biomarker to predict recurrence following endoscopic submucosal dissection in primary early gastric cancer. Mol Med Rep. 2017;15(5):3245-51.

31. Yu K. The Rs4938723 Polymorphism Reduces Expression of MicroRNA-34b and Increases the Risk of Recurrence after Endoscopic Dissection in Early Gastric Cancer. Cell Physiol Biochem. 2017;43(3):1235-46.

32. Li HY, Dai J, Xue HB, et al. Application of magnifying endoscopy with narrow-band imaging in diagnosing gastric lesions: A prospective study. Gastrointest Endosc. 2012;76(6):1124-32.

33. Xue HG, Yang AH, Sun XG, et al. Expression of microRNA-328 Functions as a Biomarker for Recurrence of Early Gastric Cancer (EGC) After Endoscopic Submucosal Dissection (ESD) by Modulating CD44. Med Sci Monit. 2016;22:4779-85.

34. Fu QY, Cui Y, Li XB, et al. Relevant risk factors for positive lateral margin after en bloc endoscopic submucosal dissection for early gastric adenocarcinoma. J Dig Dis. 2016;17(4):244-51.

35. Ok KS, Kim GH, Park DY, et al. Magnifying endoscopy with narrow band imaging of early gastric cancer: Correlation with histopathology and mucin phenotype. Gut Liver. 2016;10(4):532-41.

36. Probst A, Schneider A, Schaller T, et al. Endoscopic submucosal dissection for early gastric cancer: are expanded resection criteria safe for Western patients? Endoscopy. 2017;49(9):855-65.

37. Nagami Y, Machida H, Shiba M, et al. Clinical Efficacy of Endoscopic Submucosal Dissection for Adenocarcinomas of the Esophagogastric Junction.

Endosc Int Open. 2014;2(1):E15-20.

38. Omae M, Fujisaki J, Horiuchi Y, et al. Safety, efficacy, and long-term outcomes for endoscopic submucosal dissection of early esophagogastric junction cancer. Gastric Cancer. 2013;16(2):147-54.

39. Nishide N, Ono H, Kakushima N, et al. Clinical outcomes of endoscopic submucosal dissection for early gastric cancer in remnant stomach or gastric tube. Endoscopy. 2012;44(6):577-83.

40. Yonezawa J, Kaise M, Sumiyama K, et al. A novel double-channel therapeutic endoscope ("R-scope") facilitates endoscopic submucosal dissection of superficial gastric neoplasms. Endoscopy. 2006;38(10):1011-5.

41. Ojima T, Takifuji K, Nakamura M, et al. Feasibility of Endoscopic Submucosal Dissection for Submucosal-invasive Gastric Cancer and the Predictors of Residual or Recurrent Cancer. Surg Laparosc Endosc Percutan Tech. 2016;26(5):401-5.

42. Oka S, Tanaka S, Higashiyama M, et al. Clinical validity of the expanded criteria for endoscopic resection of undifferentiated-type early gastric cancer based on long-term outcomes. Surg Endosc. 2014;28(2):639-47.

43. Kanemitsu T, Yao K, Nagahama T, et al. The vessels within epithelial circle (VEC) pattern as visualized by magnifying endoscopy with narrow-band imaging (ME-NBI) is a useful marker for the diagnosis of papillary adenocarcinoma: a case-controlled study. Gastric cancer. 2014;17(3):469-77.

44. Komori K, Nakamura K, Ihara E, et al. Endoscopic Submucosal Dissection is Feasible for Very Elderly Patients with Early Gastric Cancer : Comparison of Short-Term and Long-Term Outcomes in Very Elderly and Non-Elderly Patients. Fukuoka igaku zasshi. 2016;107(4):72-81.

45. Hirasaki S, Kanzaki H, Matsubara M, et al. Treatment of over 20 mm gastric cancer by endoscopic submucosal dissection using an insulation-tipped diathermic knife. World J Gastroenterol. 2007;13(29):3981-4.

46. Nakata B, Tendo M, Okuyama M, et al. Additional surgical resection after endoscopic mucosal dissection for early gastric cancer: A medium-sized hospital's experience. Int J Surg. 2016;36(Pt A):335-41.

47. Yamada T, Sugiyama H, Ochi D, et al. Risk factors for submucosal and lymphovascular invasion in gastric cancer looking indicative for endoscopic submucosal dissection. Gastric Cancer. 2014;17(4):692-6.

48. Sugimoto T, Yamaji Y, Sakitani K, et al. Neutrophil infiltration and the distribution of intestinal metaplasia is associated with metachronous gastric cancer following endoscopic submucosal dissection. Can J Gastroenterol Hepatol. 2015;29(6):321-5.

49. Horiguchi N, Tahara T, Kawamura T, et al. Distinct Clinic-Pathological Features of Early Differentiated-Type Gastric Cancers after Helicobacter pylori Eradication. Gastroenterol Res Pract. 2016;2016:8230815.

50. Kakushima N, Fujishiro M, Kodashima S, et al. Technical feasibility of endoscopic submucosal dissection for gastric neoplasms in the elderly Japanese population. J Gastroenterol Hepatol. 2007;22(3):311-4.

51. Sanomura Y, Oka S, Tanaka S, et al. Clinical validity of endoscopic submucosal dissection for submucosal invasive gastric cancer: a single-center study. Gastric cancer. 2012;15(1):97-105.

52. Nakamoto S, Sakai Y, Kasanuki J, et al. Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: a comparative study with endoscopic submucosal dissection. Endoscopy. 2009;41(9):746-50.

53. Oka S, Tanaka S, Kaneko I, et al. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. Gastrointes Endosc. 2006;64(6):877-83.

54. Imagawa A, Okada H, Kawahara Y, et al. Endoscopic submucosal dissection for early gastric cancer: Results and degrees of technical difficulty as well as sucsess. Endoscopy. 2006;38(10):987-90.

55. Katsube T, Murayama M, Yamaguchi K, et al. Additional Surgery After Non-curative Resection of ESD for Early Gastric Cancer. Anticancer Res. 2015;35(5):2969-74.

56. Goto O, Fujishiro M, Kodashima S, et al. Outcomes of endoscopic submucosal dissection for early gastric cancer with special reference to validation for curability criteria. Endoscopy. 2009;41(2):118-22.

57. Horiuchi Y, Fujisaki J, Yamamoto N, et al. Mixed poorly differentiated adenocarcinoma in undifferentiated-type early gastric cancer predicts endoscopic noncurative resection. Gastric Cancer. 2018;21(4):689-95.

58. Takenaka R, Kawahara Y, Okada H, et al. Factors Associated with Local Recurrence and Incomplete Resection in Endoscopic Submucosal Dissection for the Treatment of Early Gastric Cancers. Gastrointest Endosc. 2006;63(5):AB182-AB.

59. Oda I, Saito D, Tada M, et al. A multicenter retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer. 2006;9(4):262-70.

60. Yoshida M, Kakushima N, Mori K, et al. Learning curve and clinical outcome of gastric endoscopic submucosal dissection performed by trainee operators. Surg Endosc. 2016.

61. Boda T, Ito M, Oka S, et al. Characteristics of metachronous gastric tumors after endoscopic submucosal dissection for gastric intraepithelial neoplasms. Gastroenterol Res Pract. 2014;2014:863595.

62. Ohara Y, Toshikuni N, Matsueda K, et al. The superficial elevated and depressed lesion type is an independent factor associated with non-curative endoscopic submucosal dissection for early gastric cancer. Surg Endosc. 2016;30(11):4880-8.

63. Sugimoto T, Okamoto M, Mitsuno Y, et al. Endoscopic submucosal dissection is an effective and safe therapy for early gastric neoplasms: a multicenter feasible study. J Clin Gastroenterol. 2012;46(2):124-9.

64. Kosaka T, Endo M, Toya Y, et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a single-center retrospective study. Dig Endosc. 2014;26(2):183-91.

65. Ohnita K, Isomoto H, Yamaguchi N, et al. Factors related to the curability of early gastric cancer with endoscopic submucosal dissection. Surg Endosc. 2009;23(12):2713-9.

66. Toyokawa T, Fujita I, Morikawa T, et al. Clinical outcomes of ESD for early gastric neoplasms in elderly patients. Eur J Clin Invest. 2011;41(5):474-8.

67. Ojima T, Takifuji K, Nakamura M, et al. Long-term Survival of Patients With Endoscopic Submucosal Dissection for Remnant Gastric Cancers. Surg Laparosc Endosc Percutan Tech. 2016;26(1):78-81.

68. Goto A, Nishikawa J, Okamoto T, et al. Outcomes of endoscopic submucosal dissection for early gastric cancer and factors associated with incomplete resection. Hepatogastroenterology. 2013;60(121):46-53.

69. Isomoto H, Shikuwa S, Yamaguchi N, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut. 2009;58(3):331-6.

70. Yamaguchi N, Isomoto H, Fukuda E, et al. Clinical Outcomes of Endoscopic Submucosal Dissection for Early Gastric Cancer by Indication Criteria. Digestion. 2009;80(3):173-81.

71. Isomoto H, Ohnita K, Yamaguchi N, et al. Clinical outcomes of endoscopic submucosal dissection in elderly patients with early gastric cancer. Eur J Gastroenterol Hepatol. 2010;22(3):311-7.

72. Nagahama T, Yao K, Imamura K, et al. Diagnostic performance of conventional endoscopy in the identification of submucosal invasion by early gastric cancer: the "non-extension sign" as a simple diagnostic marker. Gastric Cancer. 2017;20(2):304-13.

73. Hirasawa K, Kokawa A, Oka H, et al. Risk assessment chart for curability of early gastric cancer with endoscopic submucosal dissection. Gastrointest Endosc. 2011;74(6):1268-75.

74. Hoteya S, Yamashita S, Kikuchi D, et al. Endoscopic submucosal dissection for submucosal invasive gastric cancer and curability criteria. Dig Endosc. 2011;23(1):30-6.

75. Numata N, Oka S, Tanaka S, et al. Risk factors and management of positive horizontal margin in early gastric cancer resected by en bloc endoscopic submucosal dissection. Gastric Cancer. 2015;18(2):332-8.

76. Higashimaya M, Oka S, Tanaka S, et al. Outcome of endoscopic submucosal dissection for gastric neoplasm in relationship to endoscopic classification of submucosal fibrosis. Gastric Cancer. 2013;16(3):404-10.

77. Oda I, Gotoda T, Hamanaka H, et al. Endoscopic submucosal dissection for early gastric cancer: Technical feasibility, operation time and complications from a large consecutive series. Dig Endosc. 2005;17(1):54-8.

78. Maehata Y, Nakamura S, Esaki M, et al. Characteristics of Primary and Metachronous Gastric Cancers Discovered after Helicobacter pylori Eradication: A Multicenter Propensity Score-Matched Study. Gut Liver. 2017;11(5):628-34.

79. Nakamura K, Honda K, Akahoshi K, et al. Suitability of the expanded indication criteria for the treatment of early gastric cancer by endoscopic submucosal dissection: Japanese multicenter large-scale retrospective analysis of short- and long-term outcomes. Scand J Gastroenterol. 2015;50(4):413-22.

80. Hoteya S, Matsui A, Iizuka T, et al. Comparison of the clinicopathological characteristics and results of endoscopic submucosal dissection for esophagogastric junction and non-junctional cancers. Digestion. 2013;87(1):29-33.

81. Abe S, Oda I, Suzuki H, et al. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy. 2015;47(12):1113-8.

82. Kakushima N, Ono H, Tanaka M, et al. Factors related to lateral margin positivity for cancer in gastric specimens of endoscopic submucosal dissection. Dig Endosc. 2011;23(3):227-32.

83. Suzuki H, Oda I, Sekiguchi M, et al. Factors associated with incomplete gastric endoscopic submucosal dissection due to misdiagnosis. Endosc Int Open. 2016;4(7):E788-93.

84. Horiuchi Y, Fujisaki J, Yamamoto N, et al. Undifferentiated-type component mixed with differentiated-type early gastric cancer is a significant risk factor for endoscopic non-curative resection. Dig Endosc. 2018.

85. Chen ZS, Jin XF, Wu HL, et al. Simultaneous endoscopic submucosal dissection for multiple early gastric cancers in a low volume center. Medicine (Baltimore). 2017;96(36):e7745.

86. Li SJ, Wang J, Li ZY, et al. [Application of endoscopic submucosal dissection in treatment of early gastric cancer]. Beijing Da Xue Xue Bao Yi Xue Ban. 2015;47(6):945-51.

87. Zhang Y, Huang L, Li L, et al. Endoscopic submucosal dissection for early gastric neoplasms in elderly patients. J Laparoendosc Adv Surg Tech A. 2014;24(6):391-8.

88. Wen J, Linghu EQ, Yang YS, et al. Associated risk factor analysis for positive resection margins after endoscopic submucosal dissection in early-stage gastric cancer. J BUON. 2014;20(2):421-7.

89. Lee JY, Choi IJ, Cho SJ, et al. Endoscopic submucosal dissection for metachronous tumor in the remnant stomach after distal gastrectomy. Surg Endosc. 2010;24(6):1360-6.

90. Park JC, Kim JH, Youn YH, et al. How to manage pyloric tumours that are difficult to resect completely with endoscopic resection: comparison of the retroflexion vs. forward view technique. Dig Liver Dis. 2011;43(12):958-64.

91. Kim TK, Kim GH, Park DY, et al. Risk factors for local recurrence in patients with positive lateral resection margins after endoscopic submucosal dissection for early gastric cancer. Surg Endosc. 2015;29(10):2891-8.

92. Jeon HK, Lee SJ, Kim GH, et al. Endoscopic submucosal dissection for undifferentiated-type early gastric cancer: short- and long-term outcomes. Surg Endosc. 2018;32(4):1963-70.
93. Kim YY, Jeon SW, Kim J, et al. Endoscopic submucosal dissection for early gastric cancer with undifferentiated histology: Could we extend the criteria beyond? Surg Endosc. 2013;27(12):4656-62.
94. Choi MH, Hong SJ, Han JP, et al. Therapeutic outcomes of endoscopic submucosal dissection in undifferentiated-type early gastric cancer. Korean J Gastroenterol. 2013;61(4):196-202.
95. Gong EJ, Kim do H, So H, et al. Clinical Outcomes of Endoscopic Submucosal Dissection for Adenocarcinoma of the Esophagogastric Junction. Dig Dis Sci. 2016;61(9):2666-73.
96. Choe WH, Kim JH, Park JH, et al. Endoscopic Submucosal Dissection of Early Gastric Cancer in Patients with Liver Cirrhosis. Dig Dis Sci. 2018;63(2):466-73.
97. Choi JH, Kim ER, Min BH, et al. The feasibility and safety of the endoscopic submucosal dissection of superficial gastric neoplastic lesions in patients with compensated liver cirrhosis: a retrospective study. Gut Liver. 2012;6(1):58-63.
98. Bae JH, Kim GH, Lee BE, et al. Factors associated with the outcomes of endoscopic submucosal dissection in pyloric neoplasms. Gastrointest Endosc. 2015;81(2):303-11.
99. Myung YS, Hong SJ, Han JP, et al. Effects of administration of a proton pump inhibitor before endoscopic submucosal dissection for differentiated early gastric cancer with ulcer. Gastric Cancer. 2017;20(1):200-6.
100. Jang J, Han S, Kang S, et al. Correlation of healing type of lesion and recurrence in gastric neoplastic lesions after endoscopic submucosal dissection. Helicobacter. 2014;19:164-.
101. Kim DY, Hong SJ, Cho GS, et al. Long-term efficacy of endoscopic submucosal dissection compared with surgery for early gastric cancer: a retrospective cohort study. Gut Liver. 2014;8(5):519-25.

102. Han JP, Hong SJ, Kim HK, et al. Risk stratification and management of non-curative resection after endoscopic submucosal dissection for early gastric cancer. Surg Endosc. 2016;30(1):184-9.

103. Jeong JY, Oh YH, Yu YH, et al. Does submucosal fibrosis affect the results of endoscopic submucosal dissection of early gastric tumors? Gastrointest Endosc. 2012;76(1):59-66.

104. Kim H, Shin J, Bang B, et al. Risk factor of metachronous recurrence after endoscopic submucosal dissection for gastric epithelial neoplasm. Helicobacter. 2017;22.

105. Chung CS, Woo HS, Chung JW, et al. Risk Factors for Metachronous Recurrence after Endoscopic Submucosal Dissection of Early Gastric Cancer. J Korean Med Sci. 2017;32(3):421-6.

106. Jang JS, Choi SR, Qureshi W, et al. Long-term outcomes of endoscopic submucosal dissection in gastric neoplastic lesions at a single institution in South Korea. Scand J Gastroenterol. 2009;44(11):1315-22.

107. Goh PG, Jeong HY, Kim MJ, et al. Clinical outcomes of endoscopic submucosal dissection for undifferentiated or submucosal invasive early gastric cancer. Clin Endosc. 2011;44(2):116-22.

108. Kang MS, Hong SJ, Kim DY, et al. Long-term outcome after endoscopic submucosal dissection for early gastric cancer: focusing on a group beyond the expanded indication. J Dig Dis. 2015;16(1):7-13.

109. Kwon YH, Heo J, Lee HS, et al. Failure of Helicobacter pylori eradication and age are independent risk factors for recurrent neoplasia after endoscopic resection of early gastric cancer in 283 patients. Aliment Pharmacol Ther. 2014;39(6):609-18.

110. Han JP, Hong SJ, Choi MH, et al. Clinical outcomes of early gastric cancer with lateral margin positivity after endoscopic submucosal dissection. Gastrointest Endosc. 2013;78(6):956-61.

111. Kim BJ, Chang TH, Kim JJ, et al. Efficacy and safety of endoscopic submucosal dissection for early gastric cancer in patients with comorbid diseases. Gut Liver. 2010;4(2):186-91.

112. Han JP, Hong SJ, Kim HK. Long-term outcomes of early gastric cancer diagnosed as mixed adenocarcinoma after endoscopic submucosal dissection. J Gastroenterol Hepatol. 2015;30(2):316-20.

113. Lee JY, Cho KB, Kim ES, et al. Risk factors for local recurrence after en bloc endoscopic submucosal dissection for early gastric cancer. World J Gastrointest Endosc. 2016;8(7):330-7.

114. Kang HY, Kim SG, Kim JS, et al. Clinical outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. Surg Endosc. 2010;24(3):509-16.

115. Choi MK, Kim GH, Park DY, et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a single-center experience. Surg Endosc. 2013;27(11):4250-8.

116. Ryu DG, Choi CW, Kang DH, et al. Predictive factors to diagnosis undifferentiated early gastric cancer after endoscopic submucosal dissection. Medicine (Baltimore). 2017;96(36).

117. Sohn SH, Lee SH, Kim KO, et al. Therapeutic outcomes of endoscopic submucosal dissection for early gastric cancer: single-center study. Eur J Gastroenterol Hepatol. 2017;29(1):61-7.

118. Kim JM, Sohn JH, Cho MY, et al. Pre- and post-ESD discrepancies in clinicopathologic criteria in early gastric cancer: the NECA-Korea ESD for Early Gastric Cancer Prospective Study (N-Keep). Gastric Cancer. 2016;19(4):1104-13.

119. Kim JS, Kang SH, Moon HS, et al. Clinical outcome after endoscopic submucosal dissection for early gastric cancer of absolute and expanded indication. Medicine (Baltimore). 2017;96(17):e6710.

120. Kim YI, Kim HS, Kook MC, et al. Discrepancy between Clinical and Final Pathological Evaluation Findings in Early Gastric Cancer Patients Treated with Endoscopic Submucosal Dissection. J Gastric Cancer. 2016;16(1):34-42.

121. Lee H, Yun WK, Min BH, et al. A feasibility study on the expanded indication for endoscopic submucosal dissection of early gastric cancer. Surg Endosc. 2011;25(6):1985-93.

122. Ahn JY, Jung HY, Choi KD, et al. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications. Gastrointest Endosc. 2011;74(3):485-93.

123. Park CH, Shin S, Park JC, et al. Long-term outcome of early gastric cancer after endoscopic submucosal dissection: expanded indication is comparable to absolute indication. Dig Liver Dis. 2013;45(8):651-6.

124. Jung S, Park CH, Kim EH, et al. Preventing metachronous gastric lesions after endoscopic submucosal dissection through Helicobacter pylori eradication. J Gastroenterol Hepatol. 2015;30(1):75-81.

125. Shin KY, Jeon SW, Cho KB, et al. Clinical Outcomes of the Endoscopic Submucosal Dissection of Early Gastric Cancer Are Comparable between Absolute and New Expanded Criteria. Gut Liver. 2015;9(2):181-7.

126. Yang HJ, Kim SG, Lim JH, et al. Novel risk stratification for metachronous recurrence after curative endoscopic submucosal dissection for early gastric cancer. Gastrointest Endosc. 2017.

127. Kang D, Ha SE, Park JM, et al. Body Mass Index and Clinical Outcomes from Endoscopic Submucosal Dissection of Gastric Neoplasia. Dig Dis Sci. 2017;62(6):1657-65.

128. Yang HJ, Kim SG, Lim JH, et al. Surveillance strategy according to age after endoscopic resection of early gastric cancer. Surg Endosc. 2018;32(2):846-54.

129. Hahn KY, Park JC, Kim EH, et al. Incidence and impact of scheduled endoscopic surveillance on recurrence after curative endoscopic resection for early gastric cancer. Gastrointest Endosc. 2016;84(4):628-38.e1.

130. Min BH, Kim ER, Kim KM, et al. Surveillance strategy based on the incidence and patterns of recurrence after curative endoscopic submucosal dissection for early gastric cancer. Endoscopy. 2015;47(9):784-93.

131. Kim EH, Park JC, Song IJ, et al. Prediction model for non-curative resection of endoscopic submucosal dissection in patients with early gastric cancer. Gastrointest Endosc. 2016.

132. Joh DH, Park CH, Jung S, et al. Safety and feasibility of simultaneous endoscopic submucosal dissection for multiple gastric neoplasias. Surgic Endosc. 2015;29(12):3690-7.

133. Hsieh YY, Lee IL, Wei KL, et al. Outcomes of endoscopic submucosal dissection for early gastric cancer and precancer lesion: Experience from a center in Southern Taiwan. AIDM. 2015;2(3):95-101.

134. Costa RS, Ferreira A, Leal T, et al. Endoscopic Submucosal Dissection for the Treatment of Superficial Epithelial Gastric Neoplasia in a Portuguese Centre. GE Port J Gastroenterol. 2018.

Anexos

AUTHOR GUIDELINES

LATEST INFORMATION

Video Articles: DEN now accepts video focused article with brief explanation about a video which has basic and clinical importance. The new manuscript category's name is "DEN Video Articles". Please read the Author Guidelines and submit articles to this category.

Case Reports: Only cases of exceptional interest and novelty are considered. For manuscripts that do not qualify, Editors may ask authors to shorten manuscripts and rewrite as Letters.

Guidelines, Consensus Reports: DEN welcomes submission of Guidelines and Consensus Reports. Please contact Editorial Office at **digestive_endoscopy@jges.or.jp** / **fukuda@jges.or.jp** for further information.

1. MANUSCRIPT SUBMISSION

Thank you for your interest in *Digestive Endoscopy*. Please read the complete Author Guidelines carefully prior to submission, including the section on copyright. To ensure fast peer review and publication, manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium. Once you have prepared your submission in accordance with the Guidelines, manuscripts should be submitted online at **http://mc.manuscriptcentral.com/den/**

For assistance, please contact the Editorial Office of Digestive Endoscopy (email: **digestive_endoscopy@jges.or.jp** / **fukuda@jges.or.jp** ; phone: 81-3- 3525-4670; fax: 81-3-3525-4677).

We look forward to your submission.

2. ABOUT THE JOURNAL

Scope: *Digestive Endoscopy* (DEN) is the official journal of the Japan Gastroenterological Endoscopy Society, the Asian Pacific Society for Digestive Endoscopy and the World Endoscopy Organization. *Digestive Endoscopy* serves as a medium for presenting original articles that offer significant contributions to knowledge in the broad field of endoscopy. The Journal also includes Reviews, Original Articles, How I Do It, Case Reports (only of exceptional interest and novelty are accepted), Letters, Techniques and Images, abstracts and news items that may be of interest to endoscopists.

Editor: Takayuki Matsumoto
Frequency: Bi-Monthly
ISSN: 0915-5635 (print), 1443-1661 (online).
Impact Factor 2017: 3.375
Journal Abbreviation: Dig Endosc
Publisher: John Wiley & Sons Australia, Ltd

3. EDITORIAL REVIEW AND ACCEPTANCE

The acceptance criteria for all papers are the quality and originality of the research and its significance to our readership. Except where otherwise stated, manuscripts are peer reviewed by two anonymous reviewers and the Editor. All manuscripts will be reviewed by using the online submission system, and all relevant data should be submitted online. Final acceptance or rejection rests with the Editorial Board.

All manuscripts should be written so that they are intelligible to the professional reader who is not a specialist in the particular field. They should be written in a clear, concise, direct style. Where contributions are judged as acceptable for publication on the basis of content, the Editor and the Publisher reserve the right to modify manuscripts to eliminate ambiguity and repetition and improve communication between author and reader.

Authorship should be finalized during the submission process. Please ensure that all authors are listed and in the correct order, because changes are not permissible once the accepted manuscript goes into production.

4. AUTHORSHIP

Digestive Endoscopy follows the recommendations formulated by the International Committee of Medical Journal Editors regarding criteria for authorship (**http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html**). Accordingly, each person listed as an author or coauthor for a submitted manuscript must meet all four criteria. An author or coauthor shall have:

1) Substantial contributions to the conception or design of the work, or acquisition, analysis or interpretation of data for the work;
2) Drafting the work or revising it critically for important intellectual content;
3) Final approval of the version to be published;
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Meeting these criteria should provide each author with sufficient knowledge of and participation in the work that he or she can accept public responsibility for the report.

Person who does not meet the above 4 criteria should be mentioned in the acknowledgment section.

The corresponding author must submit an Authorship confirmation form (with COI statement from all authors) and must guarantee that all authors listed in the manuscript meet these criteria and that all authors are aware of the submission and about the authorship. If there is a serious breach of authorship, the matter will be investigated according to the **COPE guideline** and reprimand and punishment will be considered according to the seriousness of the matter. Please use **this form** to confirm the authorship of all authors.

5. DISCLOSURE

Conflict of Interests: All authors should declare, according to the standard of each country, any employment, leadership role or advisory role with a company, stockownership and option, patent royalties and licensing fees, honoraria, received fees for promotional materials, financial support and grants, devices donated from the industry and other potential relationships that may pose conflict of interests as “Interests” between the Acknowledgments and References sections. The corresponding author should collect all authors COI disclosure and must complete a conflict of interests disclosure form as part of the initial manuscript submission process. The corresponding author is responsible for obtaining all the relevant information from all authors of the manuscript. Please visit **here** to consult the details of the latest disclosure guidelines according to the standards of the International Committee of Medical Journal Editors (ICMJE).If a failure of accurate report about COI disclosure is suspected, the matter will be resolved following the procedure detailed in **COPE guidelines**.

Please disclose all Conflict of Interests for all authors using **this format**.

6. ETHICAL CONSIDERATIONS

Authors must state that the protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013), available at: **https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/**. In general, submission of a case report should be accompanied by the written consent of the subject (or parent/guardian) before publication; this is particularly important where photographs are to be used or in cases

where the unique nature of the incident reported makes it possible for the patient to be identified. While the Editors recognize that it might not always be possible or appropriate to seek such consent, the onus will be on the authors to demonstrate that this exception applies in their case. Any experiments involving animals must be demonstrated to be ethically acceptable and where relevant conform to national guidelines for animal usage in research. *Digestive Endoscopy* retains the right to reject any manuscript on the basis of unethical conduct of either human or animal studies.

Data Sharing and Data Accessibility

The journal encourages authors to share the data and other artefacts supporting the results in the paper by archiving it in an appropriate public repository. Authors should include a data accessibility statement, including a link to the repository they have used, in order that this statement can be published alongside their paper.

7. REGISTRY OF RESEARCH STUDIES INVOLVING HUMAN SUBJECTS

As shown in the Declaration of Helsinki (Fortaleza, Brazil, October 2013), every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject. Thus any research project that assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome must be registered. The above policy applies to every research study which began with enrollment of patients after November 1st 2013 (If authors are considering submitting a non-registered prospectively designed research study, please explain the reason why it has not been registered. Registration of retrospective studies is not required, but must have official approval from an appropriate ethical committee at submission of the study).

Research studies mentioned above should be registered in one of the registries approved by ICMJE. Registries that currently meet all necessary criteria include: (1) the registry sponsored by the United States National Library of Medicine (**http://www.clinicaltrials.gov**); (2) the International Standard Randomized Controlled Trial Number Registry (**http://www.controlled-trials.com/**); (3) the Australian New Zealand Clinical Trials Registry (**http://www.anzctr.org.au/**); (4) the Chinese Clinical Trials Registry (**http://www.chictr.org/**); and (5) the Clinical Trials Registry – India (**http://www.ctri.nic.in/**); (6) University Hospital Medical Information Network (UMIN) (**http://www.umin.ac.jp/ctr/**).

8. RANDOMIZED CONTROLLED TRIALS

Randomized controlled trials should follow the guidelines of the CONSORT Statement. The CONSORT Statement will also be used as the criteria of peer review for randomized controlled trial papers: **http://www.consort-statement.org/**.
Please upload the **Consort 2010 Checklist** with your main text when you submit RCT manuscripts.

9. MANUSCRIPT CATEGORIES AND REQUIREMENTS

(i) ORIGINAL ARTICLES

Word Limit: 3000 words including abstract but excluding references, tables and figures.
Authors: Maximum of 29 authors. In case you have 30 authors or more, please contact Editorial Office at **digestive_endoscopy@jges.or.jp** / **fukuda@jges.or.jp** prior to submission.
Abstract: 250 words maximum, structured (subheaders): Objectives, Methods, Results, Conclusions.
References: No limit.
Figures/Tables: No limit.
Supporting Information: Video, additional data, tables and audio are acceptable as supporting information.
Description: Full-length reports of current research in either basic or clinical science. Arrange text as follows: Introduction, Methods, Results, Discussion, Acknowledgment, Conflict of Interests, References, and when relevant, Supplementary Material.

(ii) REVIEW ARTICLES

Word Limit: 3500 words including abstract but excluding references, tables and figures.

Authors: Maximum of 29 authors. In case you have 30 authors or more, please contact Editorial Office at **digestive_endoscopy@jges.or.jp** / **fukuda@jges.or.jp** prior to submission.
Abstract: 250 words maximum, structured or unstructured.
References: No limit.
Figures/Tables: No limit.
Supporting Information: Video, additional data, tables and audio are acceptable as supporting information.
Description: Reviews are comprehensive analyses of specific topics with an inclusive reference list, or they may be systematic reviews. Although narrative review articles are accepted, systematic reviews would be preferable for publication. Some of them will be submitted upon invitation by the Editor. Both solicited and unsolicited review articles will undergo peer review prior to acceptance.

(iii) CASE REPORTS
Only cases of exceptional interest and novelty are considered. For manuscripts that do not qualify, Editors may ask authors to shorten manuscripts and rewrite as Letters, Techniques and Images.
Word Limit: 1500 words including abstract but excluding references, tables and figures.
Abstract: Short, unstructured (no use of subheaders). Maximum of 250 words.
References: Up to 10 in total.
Figures/Tables: Up to four in total.
Supporting Information: Video, additional data, tables and audio are acceptable as supporting information.
Description: New observations of diseases, clinical findings or novel/unique treatment outcomes relevant to practitioners in Endoscopy. Arrange text as follows: Abstract; Introduction; Case Report; Discussion; Acknowledgment; Conflict of Interests; References.

(iv) HOW I DO IT
Word Limit: 3000 words including abstract but excluding references, tables and figures.
Abstract: 250 words, unstructured (no use of subheaders).
References: Up to 20 in total.
Figures/Tables: Up to five in total.
Supporting Information: Video, additional data, tables and audio are acceptable as supporting information.
Description: How I Do It contains useful clinical improvements for diagnosis and treatment. It must be based on empirical observation and it should include discussions about methods and results with references. Arrange text as follows: Abstract; Introduction; Procedure or Technique; Discussion.

(v) LETTERS, TECHNIQUES AND IMAGES
Word Limit: 300 words.
Authors: Maximum of three authors.
Abstract: No abstract.
References: Up to five.
Figures/Tables/Images: Up to two. Size of one figure should not exceed 80 mm horizontal x 80 mm vertical. Composite photos can be accepted within this size regulation when necessary.
Supporting Information: Additional data, figures and tables are acceptable as supporting information. Videos should be submitted to the category “DEN VIDEO ARTICLES.”
Description: Letters may be submitted to the Editor on any topic of discussion; clinical observations, as well as letters commenting on papers published in recent issues. Manuscripts formerly published as New Instruments and Techniques, Endoscopic Images of Interest, and Clinical Trial Notes are now published under this manuscript category.

(vi)DEN VIDEO ARTICLES
[ONLINE ONLY]
Brief Explanation (not structured, in one paragraph): Up to 300 words.
Authors: Maximum of three authors.
Abstract: No abstract.

References: Up to five.
Figures/Tables/Images: Up to two (set of photographs will be counted as one figure)
Videos: Each Video clip will be online free to access. The total length of the video should not be longer than 10 minutes, and the length of one video stream should be limited to 5 minutes. All video formats are accepted, but authors should bear in mind that m4v or mp4 are sometimes not compatible to play/ download in Internet Explorer or Chrome and only compatible for Firefox. All narration and/ or subtitles should be in English. The video should be edited that the reader can understand and accompanied by a structured narration and/ or subtitle. All videos submitted must be of the highest quality possible. You may be advised to revise your video if its quality is below our standards. The materials are published as they are supplied and are not checked or copyedited in any way. Use the **Video Article Template** to prepare the video. A video file should be named starting with at least the first 20 characters of the manuscript title.
If you have problem in uploading your video because the size of the video is too big, please contact **fukuda@jges.or.jp** / **digestive_endoscopy@jges.or.jp** about submission of the video.
Description: DEN Video Articles are articles with a video and a brief explanation accompanying the submitted video. The video must show innovative techniques or clinically important use of endoscopy with brief and concise explanation of the techniques/ clinical important points in the text.
A publication charge: 300 USD per one article is charged to authors commencing from submissions received after 1 May 2018. An author will be requested to send the completed **page charge form**within 3 days when a manuscript is accepted for publication.

(vii) EDITORIALS
[BY INVITATION OF EDITORS]
Word Limit: 1600 words.
Abstract: No abstract.
References: Up to 10 in total.
Description: Proposals for Editorials may be submitted; however, in this case, authors should only send an outline of the proposed paper for initial consideration.

10. PREPARATION OF THE MANUSCRIPT

Author Services

Prior to submission, we encourage you to browse the 'Author Resources' section of the Wiley 'Author Services' website: **http://authorservices.wiley.com/bauthor/default.asp**. This site includes useful information covering such topics as copyright matters, ethics and electronic artwork guidelines.

Pre-acceptance English-language editing

Authors for whom English is a second language may choose to have their manuscript professionally edited before submission to improve the English. **Visit our site** to learn about the options. All services are paid for and arranged by the author. Please note using the Wiley English Language Editing Service does not guarantee that your paper will be accepted by this journal.

Optimizing Your Article for Search Engines

Many students and researchers looking for information online will use search engines such as Google, Yahoo or similar. By optimizing your article for search engines, you will increase the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in another work. We have compiled **these guidelines** to enable you to maximize the web-friendliness of the most public part of your article.

Style

Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications' as presented at: **http://www.ICMJE.org/**.

Spelling: The journal uses US spelling and authors should therefore follow the latest edition of the *Merriam–Webster's Collegiate Dictionary*.

Units: All measurements must be given in SI or SI-derived units. Statistics and measurements should always be given in numerals; that is, 10 mm. Confusing mathematical notation, and particularly subscripts and superscripts, should be avoided. For more information about SI units, please go to the Bureau International des Poids et Mesures (BIPM) website at: **http://www.bipm.fr/**.

Abbreviations and Acronyms: Standard abbreviations may be used and should be defined in the abstract and on first mention in the text. In general, however, abbreviations should be used sparingly and only where they ease the reader's task by reducing repetition of long, technical terms. Initially use the word in full, followed by the abbreviation in parentheses. Thereafter, use the abbreviation.

Trade Names: Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name, and the name and location of the manufacturer, in parentheses.

11. STRUCTURE OF MANUSCRIPTS

The length of manuscripts must adhere to the specifications under the section Manuscript Categories.

Manuscripts should be presented in the following order: (i) title page; (ii) abstract and key words; (iii) text; (iv) acknowledgments; (v) conflicts of interest; (vi) references; (vii) supporting information; (viii) figure legends; (ix) tables (each table complete with title and footnotes); and (x) figures. Footnotes to the text are not allowed and any such material should be incorporated into the text as parenthetical matter.

TITLE PAGE

The title page should contain: (i) the title of the paper; (ii) the full names of the authors; and (iii) the addresses of the institutions at which the work was carried out together with (iv) the name, the full postal and email address, plus facsimile and telephone numbers, of the author to whom correspondence about the manuscript should be sent.

The present address of any author, if different from that where the work was carried out, should be supplied in a footnote. In keeping with the latest guidelines of the International Committee of Medical Journal Editors, each author's contribution to the paper is to be quantified. The title should be short, informative and contain the major key words. A short running title (less than 40 characters including spaces) should also be provided. The running title is the short title in the upper right-hand corner of the article to help facilitate article search.

ABSTRACT AND KEYWORDS

The length of abstracts must adhere to the specifications under the section Manuscript Categories. Please note that the requirements differ between manuscript types. The abstract should not contain abbreviations or references.

Five key words, for the purposes of indexing, should be supplied below the abstract, in alphabetical order, and should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) Browser list at: **http://www.nlm.nih.gov/mesh/meshhome.html**.

TEXT

Please note that the requirements differ between manuscript types. Please refer to the section Manuscript Categories for individual requirements.

ACKNOWLEDGMENTS

The contribution of colleagues or institutions should be acknowledged. Thanks to anonymous reviewers are not appropriate.

CONFLICT OF INTERESTS

Authors are required to disclose any conflict of interests. The statement should be the same as on the Author Submission Requirement Form. The absence of any interest to disclose must also be stated.

REFERENCES

The Vancouver system of referencing should be used. In the text, references should be cited using superscript Arabic numerals in the order in which they appear. If cited only in

tables or figure legends, number them according to the first identification of the table or figure in the text.

In the references list, the references should be numbered and listed in order of appearance in the text. Cite the names of all authors when there are six or fewer; when seven or more authors, list the first three followed by *et al*. Reference to unpublished data and personal communications should not appear in the references list but should be cited in the text only (e.g. Smith A, 2000, unpubl. data). All citations mentioned in the text, tables or figures must be listed in the references list.

Names of journals should be abbreviated in the style used in Index Medicus.

Authors are responsible for the accuracy of all references.

Standard Journal Article:
1 Oda I, Gotoda T, Hamanaka H et al. Endoscopic submucosal dissection for early gastric cancer: Technical feasibility, operation time and complications from a large consecutive series. *Dig. Endosc.*2004; 17: 54–8.

Standard Journal Article using DOI: articles published online in advance without volume, issue, or page number. The DOI will remain valid and allow an article to be tracked even after its allocation to an issue. (More information about DOIs: http://www.doi.org/faq.html):
2 Noda Y, Fujita N, Kobayashi G et al. Prospective randomized controlled study comparing cell block method and conventional smear method for pancreatic juice cytology. *Dig. Endosc*. Published online: 13 Jul 2011; DOI:10.1111/j.1443-1661.2011.01180.x

Book: 3 Yamada T. *Principles of Clinical Gastroenterology*. Blackwell Publishing, Boston, 2008.

Chapter in an Edited Book: 4 Ginsberg GG. Endoscopic equipment. In: Cotton PB (ed). *Advanced Digestive Endoscopy: Practice and Safety*. Blackwell Publishing, Boston, 2008; 43–76.

Citation to a web page: 5 AMA. *helping doctors help patients [Internet]*. Chicago: American Medical Association; c1995-2007 [cited 2007 Feb 22]. Available from: http://www.ama-assn.org/.

Citation to a web page with authors: 6 D'Alessandro DM, D'Alessandro MP. *Virtual Pediatric Hospital™: a digital library of pediatric information [Internet]*. [Iowa City (IA)]: Donna M. D'Alessandro; c1992-2007 [revised 2006 Jul 20; cited 2007 Feb 20]. Available from: http://www.virtualpediatrichospital.org/.

TABLES
Tables should be self-contained and complement, but not duplicate, information contained in the text. Number tables consecutively in the text in Arabic numerals. Type tables on a separate page with the legend above. Legends should be concise but comprehensive – the table, legend and footnotes must be understandable without reference to the text. Vertical lines should not be used to separate columns. Column headings should be brief, with units of measurement in parentheses; all abbreviations must be defined in footnotes. Footnote symbols: **†**, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings. If tables have been reproduced from another source, a letter from the copyright holder (usually the Publisher) stating authorization to reproduce the material must be attached to the covering letter.

FIGURES
All illustrations (line drawings and photographs) are classified as figures. Figures should be cited in consecutive order in the text. Figures should be sized to fit within the column (80.5 mm), intermediate (112 mm) or the full text width (168 mm). Magnifications should be indicated using a scale bar on the illustration. Line figures should be sharp, black and white graphs or diagrams, drawn professionally or with a computer graphics package. Lettering must be included and should be sized to be no larger than the journal text. Magnifications should be indicated using a scale bar on the illustration.

If figures have been reproduced from another source, a letter from the copyright holder (usually the Publisher) stating authorization to reproduce the material must be attached to the Author Submission Requirement Form and also explicitly explained on the covering letter.

Line Figures: Must be sharp, black and white graphs or diagrams, drawn professionally or with a computer graphics package.

Text Sizing in Figures: Lettering must be included and should be sized to be no larger than the journal text or 8 points (should be readable after reduction – avoid large type or thick lines.)

Line Width: Between 0.5 and 1 point.

Figure Legends Type figure legends on a separate page. Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement. More help on preparation of illustrations can be found at: **http://authorservices.wiley.com/bauthor/illustration.asp**

EQUATIONS

Equations should be numbered sequentially with Arabic numerals; these should be ranged right in parentheses. All variables should appear in italics. Use the simplest possible form for all mathematical symbols.

dx/dt = c(x − x3/3 y z) (1)
DY/DT = −(X BY − A)/C (2)

12. SUPPORTING INFORMATION

Supporting Information is provided by the authors to support the content of an article but it is not integral to that article. Supporting Information is hosted via a link on Wiley Online Library, but does not appear in the print version of the article. Supporting Information must be submitted together with the article for peer review; it should not be added at a later stage. It can be in the form of tables, figures, appendices, audio and video footage. Reference to Supporting Information in the main body of the article is allowed. However, it should be noted that excessive reference to a piece of Supporting Information may indicate that it would be better suited as a proper reference or a fully included figure/table. The materials are published as they are supplied and are not checked or typeset in any way. All Supporting Information files should come with a legend, listed at the end of the main article. Each figure and table file should not be larger than 5 MB, although video files may be larger. If you have problem in uploading your video because the size of the video is too big, please contact **fukuda@jges.or.jp** / **digestive_endoscopy@jges.or.jp** about submission of the video. All videos submitted must be of the highest quality possible. Prior to submission, please check the guidelines at: **http://authorservices.wiley.com/bauthor/suppmat.asp**.

13. SUBMISSION REQUIREMENTS

Manuscripts must be submitted online at: **http://mc.manuscriptcentral.com/den/**.

Authors must supply an email address as all correspondence will be by email. Two files should be supplied: the covering letter and the manuscript (in Word or rich text format (.rtf)). The covering letter should be uploaded as a file not for review.

COVERING LETTER

Papers are accepted for publication in the journal on the understanding that the content has not been published or submitted for publication elsewhere. This must be stated in the covering letter. The covering letter must contain an acknowledgment that all the authors have contributed significantly, and that all authors are in agreement with the content of the manuscript. In keeping with the latest guidelines of the International Committee of Medical Journal Editors, each author's contribution to the paper is to be quantified. If tables or figures have been reproduced from another source, a letter from the copyright holder (usually the Publisher stating authorization to reproduce the material) must be attached to the covering letter.

14. NO PUBLICATION FEES

Up to four color illustrations, if judged relevant and of good quality, will be published free of charge. A charge of A$550/US$265/¥32,000 of the fifth and subsequent color figures will be charged to the author. Composite color photographs made up of smaller pictures will not be accepted.

For DEN Video Articles, a publication charge of 300 USD is charged to authors commencing from submissions received after 1 May 2018. A form requesting payment will be available for download with your PDF proof.

15. PUBLICATION PROCESS AFTER ACCEPTANCE

Accepted papers will be passed to Wiley's production team for publication. The author identified as the formal corresponding author for the paper will receive an email prompting them to login into Wiley's Author Services, where via the Wiley Author Licensing Service (WALS) they will be asked to complete an electronic license agreement on behalf of all authors on the paper. More details on the copyright and licensing options for the journal appear below.

Wiley's Author Services

Author Services enables authors to track their article through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production. The corresponding author will receive a unique link that enables them to register and have their article automatically added to the system. Please ensure that a complete e-mail address is provided when submitting the manuscript. Visit **http://www.authorservices.wiley.com/** for more details on online production tracking and for a wealth of resources including FAQs and tips on article preparation, submission and more.

Accepted Articles

The journal offers Wiley's Accepted Articles service for all manuscripts. This service ensures that accepted 'in press' manuscripts are published online very soon after acceptance, prior to copy-editing or typesetting. Accepted Articles are published online a few days after final acceptance, appear in PDF format only, are given a Digital Object Identifier (DOI), which allows them to be cited and tracked, and are indexed by PubMed. After print publication, the DOI remains valid and can continue to be used to cite and access the article. The Accepted Articles service has been designed to ensure the earliest possible circulation of research papers after acceptance. Given that copyright licensing is a condition of publication, authors are required to complete a copyright license before manuscripts can be processed as an Accepted Article.

Accepted articles will be indexed by PubMed; therefore the submitting author must carefully check the names and affiliations of all authors provided in the cover page of the manuscript, as it will not be possible to alter these once a paper is made available online in Accepted Article format. Subsequently the final copyedited and proofed articles will appear in an issue on Wiley Online Library; the link to the article in PubMed will automatically be updated.

Proofs

Once the paper has been typeset the corresponding author will receive an e-mail alert containing instructions on how to provide proof corrections to the article. It is therefore essential that a working e-mail address is provided for the corresponding author. Proofs should be corrected carefully; responsibility for detecting errors lies with the author.

Early View

The journal offers rapid speed to publication via Wiley's Early View service. Early View articles are complete full-text articles published online in advance of their publication in a printed issue. Early View articles are complete and final. They have been fully reviewed, revised and edited for publication, and the authors' final corrections have been incorporated. Because they are in final form, no changes can be made after online publication. Early View articles are given a Digital Object Identifier (DOI), which allows the article to be cited and tracked before allocation to an issue. After print publication, the DOI

remains valid and can continue to be used to cite and access the article. More information about DOIs can be found at **http://www.doi.org/faq.html**.

Offprints

A PDF reprint of the article will be supplied free of charge to the corresponding author. Additional printed offprints may be ordered online for a fee. Please click on the following link and fill in the necessary details and ensure that you type information in all of the required fields: **http://www.sheridan.com/wiley/eoc**.

Author Marketing Toolkit

The **Wiley Author Marketing Toolkit** provides authors with support on how to use social media, publicity, conferences, multimedia, email and the web to promote their article.

16. COPYRIGHT, LICENSING AND ONLINE OPEN

Accepted papers will be passed to Wiley's production team for publication. The author identified as the formal corresponding author for the paper will receive an email prompting them to login into Wiley's Author Services, where via the Wiley Author Licensing Service (WALS) they will be asked to complete an electronic license agreement on behalf of all authors on the paper.

Authors may choose to publish under the terms of the journal's standard copyright transfer agreement (CTA), or under open access terms made available via Wiley OnlineOpen.

Standard Copyright Transfer Agreement: FAQs about the terms and conditions of the standard CTA in place for the journal, including standard terms regarding archiving of the accepted version of the paper, are available at: **Copyright Terms and Conditions FAQs.**

Note that in signing the journal's license agreement authors agree that consent to reproduce figures from another source has been obtained.

OnlineOpen – Wiley's Open Access Option: OnlineOpen is available to authors of articles who wish to make their article freely available to all on Wiley Online Library under a Creative Commons license. With OnlineOpen, the author, the author's funding agency, or the author's institution pays a fee to ensure that the article is made open access. Authors of OnlineOpen articles are permitted to post the final, published PDF of their article on their personal website, and in an institutional repository or other free public server immediately after publication. All OnlineOpen articles are treated in the same way as any other article. They go through the journal's standard peer-review process and will be accepted or rejected based on their own merit.

OnlineOpen licenses. Authors choosing OnlineOpen retain copyright in their article and have a choice of publishing under the following Creative Commons License terms: Creative Commons Attribution License (CC BY); Creative Commons Attribution Non-Commercial License (CC BY NC); Creative Commons Attribution Non-Commercial-NoDerivs License (CC BY NC ND). To preview the terms and conditions of these open access agreements please visit the **Copyright Terms and Conditions FAQs.**

Funder Open Access and Self-Archiving Compliance: Please **click here** for more information on Wiley's compliance with specific Funder Open Access and Self Archiving Policies, and **click here** for more detailed information specifically about Self-Archiving definitions and policies.

17. EDITORIAL OFFICE ADDRESS

Editorial Office
Digestive Endoscopy
Shin-ochanomizu Urban Trinity Bldg. 4F,
3-2-1 Kandasurugadai, Chiyoda-ku,
Tokyo 101-0062, Japan
Email: **digestive_endoscopy@jges.or.jp**, **fukuda@jges.or.jp**
Tel: 81-3-3525-4670
Fax: 81-3-3525-4677

Author Guidelines updated 28 February 2019

Agradecimentos

Em primeiro lugar, um especial agradecimento ao Doutor Diogo Libânio pela orientação e apoio incondicional, pelo exemplo de rigor científico e pela total disponibilidade e a quem agradeço, ainda, a confiança depositada em mim e nas minhas capacidades.

Ao Professor Doutor Mário Dinis Ribeiro por me ter dado a oportunidade de realizar este projeto com a sua equipa e ainda pela inestimável ajuda na conceptualização e revisão do trabalho.

Ao Professor Doutor Pedro Pimentel Nunes o contributo indispensável à concretização e finalização desta tese.

Finalmente, um especial agradecimento à minha família, amigos e colegas que acompanharam esta jornada e cujo apoio me foi imprescindível.