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Prognostic factors for ESD of early gastric cancers: a systematic review and meta-analysis

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ABSTRACT

Background and study aims Gastric neoplasms are one of the leading types of cancer in the world and early detection is essential to improve prognosis. Endoscopy is the gold-standard diagnostic procedure and allows adequate treatment in selected cases. Endoscopic submucosal dissection (ESD) has been reported to safely address most early gastric cancers (EGCs), with high curability rates. However, data on prognostic factors related to ESDs of EGCs are conflicting. Therefore, we aimed to systematically review the available literature and to perform a meta-analysis to identify the relevant prognostic factors in this context.

Methods We performed this study according to PRISMA guidelines. Comparative studies assessing the relationship between curative resection or long-term curability rates and relevant prognostic factors were selected. Prognostic factors were demographic data, lesion features (location, morphology of the lesion, size, and depth of invasion), histological findings, *Helycobacter pylori* (HP) infection, presence of gastric a atrophy and body mass index (BMI). Finally, we also evaluated risk factors related to metachronous gastric neoplasm.

Results The initial search retrieved 2829 records among which 46 studies were included for systematic review and meta-analysis. The total sample comprised 28366 patients and 29282 lesions. Regarding curative resection, pooled data showed no significant influence of sex [odds ratio (OR): 1.15 (0,97, 1.36) $P=0.10$ $I^2=47\%$] , age [OR: 1.00 (0.61, 1.64) $P=1.00$ $I^2=58\%$], posterior vs non-posterior location [OR: 1.35 (0.81, 2.27) $P=0.25$ $I^2=84\%$], depressed vs von-depressed macroscopic type[OR: 1.21 (0.99, 1.49) $P=0.07$ $I^2=0\%$], non-upper vs upper location [OR: 1.41 (0.93, 2.14) $P=0.10$ $I^2=77\%$] and BMI [OR: 0.84 (0.57; 1.26) $P=0.41$ $I^2=0\%$]. Differentiated neoplasms presented greater chance of cure compare to undifferentiated [OR: 0.10 (0.07, 0.15) $P<0.00001$ $I^2=0\%$]. Ulcerated lesions had lower curative rates compared to non-ulcerated [OR: 3.92 (2.81, 5.47) $P<0.00001$ $I^2=44\%$]. Lesions smaller than 20 mm had greater chance of curative resection [OR: 3.94 (3.25, 4.78) $P<0.00001$ $I^2=38\%$]. Bleeding during procedure had lower curative rates compared to non-bleeding [OR: 2.13 (1.56, 2.93) $P<0.0001$ $I^2=0\%$]. Concerning long-term cure, female gender [OR 1.62 (1.33, 1.97) $P<0.00001$ $I^2=0\%$] and the mucosal over SM1 cancers were protective factors [OR: 0.08 (0.02, 0.39) $P=0.002$ $I^2=86\%$]. Gastric atrophy [OR: 0.60 (0.45, 0.81) $P=0.0006$ $I^2=42\%$] and the pepsinogen I/pepsinogen II ratio [OR 2.29 (1.47, 3.57) $P=0.0002$ $I^2=0\%$] were risk factors to metachronous gastric neoplasm.

Conclusions Ulcerated lesions, histology, bleeding and size > 20 mm are prognostic factors concerning curative resection. Regarding long-term cure, female gender and mucosal over SM1 cancer are predictive factors. Gastric atrophy and the pepsinogen ratio are risk factors for metachronous gastric neoplasm.

Introduction

Gastric cancer is a major worldwide health problem. It is the fourth most common cancer and the second leading cause of cancer death worldwide. More than 950,000 new diagnoses occur annually. It is estimated that 720,000 patients died of gastric cancer in 2012 [1].

Early diagnosis of gastric cancer is of economic significance because expenses related to advanced cancer treatment are usually high. Cancer treatment accounts for 4 % to 10 % of total health costs worldwide, with the ever-increasing costs widely seen as unsustainable from a public health perspective [2].

Upper endoscopy is the method by which detection is possible, allowing for adequate treatment. Endoscopic submucosal dissection (ESD) is considered the gold standard for cure of early gastric cancer [3–6]. Kondo et al. [7] established that in a meta-analysis that compared endoscopic and surgical treatment for early gastric cancer. Results revealed that in regards to survival, surgery and endoscopy have similar outcomes. However, endoscopy has lower risk of adverse events (AEs), as well as less morbidity, preserves gastric anatomy and promotes better long-term quality of life. Therefore, endoscopic treatment is considered the first choice for treatment of early gastric cancer [8–12]. A gastric tumor that does not extend beyond the submucosal layer is defined as early gastric cancer, regardless of presence or absence of lymph node metastasis [6, 7, 13].

Limited data are available in the literature on evaluation of prognostic factors related to endoscopic treatment of early gastric cancer. Some researchers have postulated that the topography of certain tumors prevents resection and curability, as there is doubt regarding performance of such procedures in elderly patients or tumors of undifferentiated histology. Minimally invasive treatment is part of current practice. Knowledge of prognostic factors associated with it is as important as diagnostics for proper selection of therapy and individualized management.

We sought to identify the main prognostic factors related to ESD for treatment of early gastric cancer through a systematic review and meta-analysis of currently available literature. As a secondary objective, we aimed to evaluate factors associated with incidence of metachronous tumor during follow-up, after curative resection of the primary tumor.

Methods

Database search

A systematic and structured search was carried out through the PICO system up to June 2019 [14]. MEDLINE, Embase, Web of Science, OVID, Cochrane, Scopus, LILACS/Bireme, Ageline/CINAHL/EBSCo and CAPES were used, as well as the grey literature (hand-searching and scanning reference lists). Two independent reviewers using predefined inclusion and exclusion criteria performed an eligibility assessment and selection of studies identified in the primary search. If reviewers disagreed about inclusion or exclusion of a given study, eligibility was decided in a consensus meeting. Cohort observational studies and case series were included.

Search strategy in MEDLINE: *(gastric OR stomach) AND (tumor OR tumors OR tumour OR tumours OR tumoral OR cancer OR cancers OR cancerous OR neoplasm* OR adenoma*) OR (Neoplasm, Stomach OR Stomach Neoplasm OR Neoplasms, Stomach OR Gastric Neoplasms OR Gastric Neoplasm OR Neoplasm, Gastric OR Cancer of Stomach OR Stomach Cancers OR Gastric Cancer OR Cancers, Gastric OR Stomach Cancer OR Cancers, Stomach OR Cancer of the Stomach) AND ((endoscopic mucosal resections OR mucosal resection, endoscopic OR mucosal resections, endoscopic OR strip biopsy OR biopsies, strip OR endoscopic mucous membrane reaction OR endoscopic submucosal dissection OR dissections, endoscopic submucosal OR endoscopic submucosal dissection OR EMR OR ESD).*

Search strategy in EMBASE: *'stomach cancer' AND 'endoscopic submucosal dissection' AND [embase]/lim NOT [medline]/lim.*

In the remaining databases, search strategies were derived from those aforementioned with simplifications due to intrinsic limitations of the search tools.

This study was recorded in *The International Prospective Register of Systematic Reviews–University of York-* PROSPERO: CRD42018115754) and approved by our institution's ethics committee.

Inclusion criteria:

1. Adults over 18 years
2. Patients who underwent ESD for resection of early gastric cancer
3. Studies that assessed prognostic factors associated with curability and clinical outcomes.

Exclusion criteria:

1. Reviews, editorials, letters and conference summaries
2. Animal studies
3. Studies without full text in English
4. Studies in which data could not be extracted
5. Studies that evaluated cure without reporting follow-up.

Quality verification of studies:

Study quality was evaluated according to NewCastle-Ottawa [15]. The items analyzed by this scale include: (1) Selection criteria: representativeness of the included cohort, selection of the unexposed cohort, the ascertainment of the exposure, demonstration that the expected result was not present at the

beginning of the study; (2) Comparability criteria: comparability of the cohort based on the analysis. (3) Outcome criteria: Analysis of results and adequate follow-up.

Statistical analysis:
Absolute numbers were extracted and differences in risk or odds ratio from dichotomous variables for each outcome were analyzed using Review Manager Software Version 5.3 (Copenhagen, the Nordic Cochrane Center, The Cochrane Collaboration, 2014). Both fixed and random effects models were used depending on the findings of heterogeneity between studies. The Mantel-Haenszel test was used for categorical variables and inverse variance was used for continuous variables. Meta-analysis results were expressed in forest plot graphs. Funnel plot graphics were used to identify publication bias, as explained below.

Additional analysis:
The cut-off value of 30 % heterogeneity was considered adequate for this meta-analysis. Thus, sensitivity analysis was performed when the heterogeneity measured by the Higgins test (I^2) was higher than 30 %. A subsequent analysis was performed, which excluded possible outliers. When outliers were not detected, true heterogeneity was presumed with exclusion of publication bias and random analysis model was assumed.

Definitions

Indications for ESD

According to the Japanese Endoscopy Society [16], ESD is indicated as follows:

Absolute criterion: differentiated intramucosal carcinoma of less than 2 cm, independent of macroscopy, preferably without ulcer (UL–).

Expanded criteria: (1) differentiated intramucosal carcinoma greater than 2 cm; (2) differentiated carcinoma less than 3 cm, which may be ulcerated (UL+); (3) Undifferentiated carcinoma of less than 2 cm and without ulcer (UL–).

Curative resection

Studies that matched the inclusion criteria defined curative resection as one in which indications for ESD were associated with absence of venous, neural or lymphatic invasion and free margins after histological evaluation.

Cure

Similar to the above, studies that met inclusion criteria defined cure as curative resection with no evidence of local or metastatic recurrence during follow up.

Metachronous tumor

Metachronous tumor was defined as a new early gastric tumor 1 year after treatment of the primary site, in a different location, and that was diagnosed during follow-up.

Histological, macroscopic, and topographic classification

The current classifications are in accordance with the third edition of the Japanese classification of gastric carcinoma [3]. For histological type, this classification subdivides tumors into more than 20 subtypes, listed in the supplementary material (**Supplementary Table 1**). In this study, we evaluated the histological types mentioned in the included studies, which are differentiated adenocarcinoma, undifferentiated adenocarcinoma, and undifferentiated tumor with signet ring cells. The Japanese classification divides early neoplasms, called superficial tumors (Type 0), into: (1) Polypoid (Type 0–I), (2) Flat-slightly elevated (Type 0–IIa), (3) Superficial flat (Type 0–IIb), (4) Superficial depressed (Type 0–IIc), (5) Tumors with deep depression, excavated or ulcerated (Type 0–III). Concerning topography, this classification divides tumor location according to the longitudinal and transverse axis of the stomach, with the divisions of the longitudinal axis: upper, middle and lower third; and those of the transverse axis: anterior wall, posterior wall, small curvature and greater curvature. Schematic figure is found in the supplementary material (**Supplementary Fig. 1**).

Definition of Obese

Used as referred by the Consensus Statement for Diagnosis Of Obesity In Asian populations [17]: (1) normal: BMI $<23\,kg/m^2$, (2) overweight: $23\,kg/m^2 \leq$ BMI $<25\,kg/m^2$, (3) obese: BMI $\geq 25\,kg/m^2$.

Results

The initial search retrieved 4050 records, of which, after evaluation of titles and abstracts, 146 articles were selected. After reading the full text individually, 46 studies were selected to be included in the systematic review and meta-analysis. The total sample comprised 28 366 patients and 29 282 lesions (▶ **Fig. 1**). All included studies achieved excellent quality (score > 6).

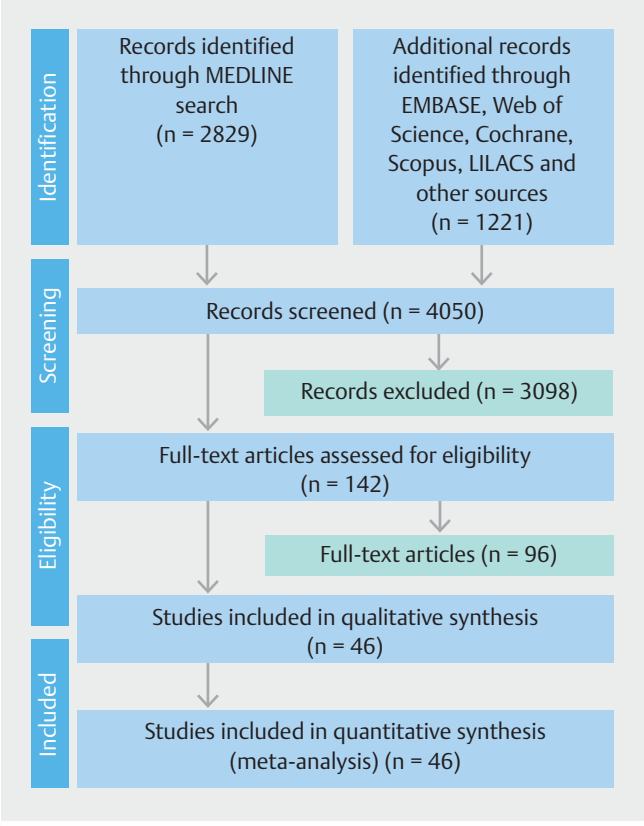
The articles were divided into two groups: those that evaluated curative resection associated with prognostic factors and without follow-up; and those that included long-term follow-up, allowing for characterization of cure.

Curative resection

Data were extracted from 19 articles including 13704 patients and 14468 lesions (▶ **Table 1**), correlating curative resection with prognostic outcomes. Tables with the correlations of all prognostic outcomes are included (**Supplementary Table 2, Supplementary Table 3**).

Gender – There was no significant difference in relation to curative resection between genders [Odds Ratio (OR): 1.15 (0,97, 1.36) $P = 0.10$ $I^2 = 47\,\%$] (**Supplementary Fig. 2**).

Age – There was no significant difference in relation to curative resection between elderly and non-elderly patients. Sensitivity analysis did not show any outlier, with heterogeneity being considered as true and considered a random effect [OR: 1.00 (0.61, 1.64) $P = 1.00$ $I^2 = 58\,\%$]. Two articles in this review (Iwai N et al and Katsube T et al) considered elderly people as those over 80 years old and one (Kato M et al) considered over



▶ **Fig. 1** PRISMA Chart.

75 years. This article, when excluded from the analysis, did not affect the results, which showed no statistical significance (▶ **Fig. 2**).

BMI – There was no difference in the curative resection when comparing obese and non-obese individuals [OR: 0.84 (0.57; 1.26) $P = 0.41$ $I^2 = 0\%$] (**Supplementary Fig. 3**).

Helicobacter pylori infection–There was a significant statistical difference in the curative resection of patients with *H. pylori* infection [OR: 0.63 (0.49, 0.80) $P = 0.0002$ $I^2 = 48\%$] (**Supplementary Fig. 4**).

Histological type – Differentiated neoplasms have a greater chance of curative resection in relation to undifferentiated ones, with statistical significance. The sensitivity assessment identified an outlier, which was eliminated for the final analysis [OR: 0.10 (0.07, 0.15) $P < 0.00001$ $I^2 = 0\%$] (**Supplementary Fig. 5**).

Location – In relation to the longitudinal axis, the analysis showed a statistical significance for curative resection of cancers located in the middle and distal third (not superior), however, with high heterogeneity [OR: 1.62 (1.36, 1.93) $P < 0.00001$ $I^2 = 77\%$)]. The sensitivity analysis revealed an outlier, with a high heterogeneity even after its elimination [OR: 1.34 (1.06, 1.68) $P = 0.01$ $I^2 = 76\%$)]. Therefore, heterogeneity was considered as true and another analysis was performed with random effect. After equalization, despite favoring tumors not located in the upper third, statistical significance was lost [OR: 1.41 (0.93, 2.14) $P = 0.10$ $I^2 = 77\%$]. (**Supplementary Fig. 6**).

In relation to the transverse axis, there was no statistical difference between the curative resection of tumors located in the posterior and non-posterior walls [OR: 1.35 (0.81, 2.27) $P = 0.25$ $I^2 = 84\%$]. The initial analysis revealed high heterogeneity, however, there was no outlier, and the random effect was used in the final analysis. (**Supplementary Fig. 7**).

Macroscopic type – There was no statistical difference between depressed and non-depressed macroscopic types [OR: 1.21 (0.99, 1.49) $P = 0.07$ $I^2 = 0\%$] (**Supplementary Fig. 8**).

Ulcerative lesions – Non-ulcerated tumors have a greater chance of curative resection compared to ulcerated tumors, with statistical significance [OR: 3.92 (2.81, 5.47) $P < 0.00001$ $I^2 = 44\%$] (**Supplementary Fig. 9**).

Size – Lesions smaller than 20 mm had a greater chance of curative resection [OR: 4.16 (3.44, 5.03) $P < 0.00001$ $I^2 = 67\%$]. The sensitivity assessment identified an outlier, which was eliminated for the final analysis [OR: 3.94 (3.25, 4.78) $P < 0.00001$ $I^2 = 38\%$] (**Supplementary Fig. 10**).

Depth – Lesions limited to the submucosa or superficial mucosa (SM1) had a greater chance of curative resection. Sensitivity analysis did not identify any outlier [OR: 0.02 (0.00, 0.69) $P = 0.03$ $I^2 = 95\%$] (**Supplementary Fig. 11**).

Bleeding – Gastric cancers that do not present with bleeding during endoscopic resection have a greater chance of curative resection [OR: 2.13 (1.56, 2.93) $P < 0.0001$ $I^2 = 0\%$] (▶ **Fig. 3**).

Long-term results

Data were extracted from 27 articles (▶ **Table 2**) with analysis of 14,662 patients and 14,814 lesions. Cure was correlated with prognostic outcomes presented in each study. Tables with all prognostic factors are found in the supplementary material. We also extracted data on incidence of metachronous tumor during follow-up, correlating its presence with Helicobacter pylori infection, degree of gastric atrophy and pepsinogen ratio I and II. Mean follow-up time was 44.85 months (**Supplementary Table 5, Supplementary Table 6**)

Gender – Women had a greater chance of long-term cure compared to men [OR 1.62 (1.33, 1.97) $P < 0.00001$ $I^2 = 0\%$] (**Supplementary Fig. 12**).

Age – Regarding long-term cure, there was no difference between the elderly and the non-elderly. One of the articles (NAM HS et al) defined the elderly as being older than 65 years. Others defined elderly as being over 75 years old. Analysis of sensitivity did not affect heterogeneity, which is why the random effect was considered for final analysis [OR: 1.49 (0.69, 3.23) $P = 0.31$ $I^2 = 63\%$] (**Supplementary Fig. 13**).

Histology – There was no difference in long-term cure of differentiated and undifferentiated tumors [OR: 0.71 (0.20, 2.51) $P = 0.60$ $I^2 = 89\%$]. Sensitivity analysis was performed, with high heterogeneity remaining after elimination of the outlier, and, therefore, the random effect was used in the analysis **(Supplementary Fig. 14**).

There was also no difference in long-term cure between undifferentiated tumors: undifferentiated adenocarcinoma (PDA) and carcinoma with signet ring cells (SRC). Due to the high heterogeneity, a random effect was used for OR analysis: [OR: 2.24 (0.44, 11.35) $P = 0.33$ $I^2 = 87\%$] (**Supplementary Fig. 15**).

▶ **Table 1** Curative resection with prognostic outcomes.

	Country	Patients	Lesions	Male	Female
Horiuchi Y 2017	Japan	268	268	25/152	14/116
Horiuchi Y 2018	Japan	2551	2585	288/2008	66/577
Choi JM 2016	South Korea	1615	1641		
Iwai N 2018	Japan	585	708		
Horiuchi Y, Fujisaki J 2018	Japan	81	81		
Yoon JY 2014	South Korea	1319	1443		
Numata N 2013	Japan	63	79		
Kim EH 2017	Korea	1639	1670	193/1211	79/428
Libânio D 2017	Portugal	164	194	21/104	009/90
Kato M 2016	Japan	892	1062		
Choi IJ 2016	Korea	712	737	77/584	20/173
Katsube T 2015	Japan	231	231	40/178	14/53
Toyokawa T 2015	Japan	967	1123	49/723	010/277
Sanomura Y 2014	Japan	78	94		
Shindo Y 2016	Japan	250	262		
Choi YK 2018	Korea	316	316		
Nakanishi H 2016	Japan	760	760		
Tanaka S 2014	Japan	32	33		
Kang D 2017	Korea	1181	1181		

Macroscopic type – There was also no significant difference when comparing depressed and non-depressed macroscopic types [OR: 1.12 (0.72, 1.74) $P=0.60$ $I^2=66\%$], as the presence of ulcer was not statistically significant associated with cure [OR: 0.91 (0.21, 3.95) $P=0.09$ $I^2=0\%$] (**Supplementary Fig. 16**).

Location – Although favoring inferior localization, location was not significant when comparing tumors from upper and lower two thirds [OR: 1.25 (0.97, 1.63) $P=0.09$ $I^2=0\%$) (**Supplementary Fig. 17**).

Size – Tumors larger or smaller than 20 mm [OR: 1.20 (0.93, 1.55) $P=0.16$ $I^2=74\%$) or 30 mm [OR: 1.63 (0.89, 2.97) $P=0.11$ $I^2=77\%$] did not show any statistical significance regarding long-term cure (**Supplementary Fig. 18**)

Depth – Tumors that invade less than 500 microns of submucosa (SM1) have a greater chance cure rate than those that go more deeply [OR: 0.08 (0.02, 0.39) $P=0.002$ $I^2=86\%$]. The sensitivity analysis did not change significantly the heterogeneity, so the random effect was used in the final analysis. (**Supplementary Fig. 19**).

Metachronous tumor

Gender – The analysis showed that the female gender is a protective factor [OR: 1.64 (1.32, 2.03) $P<0.00001$ $I^2=0\%$] (**Supplementary Fig. 20**).

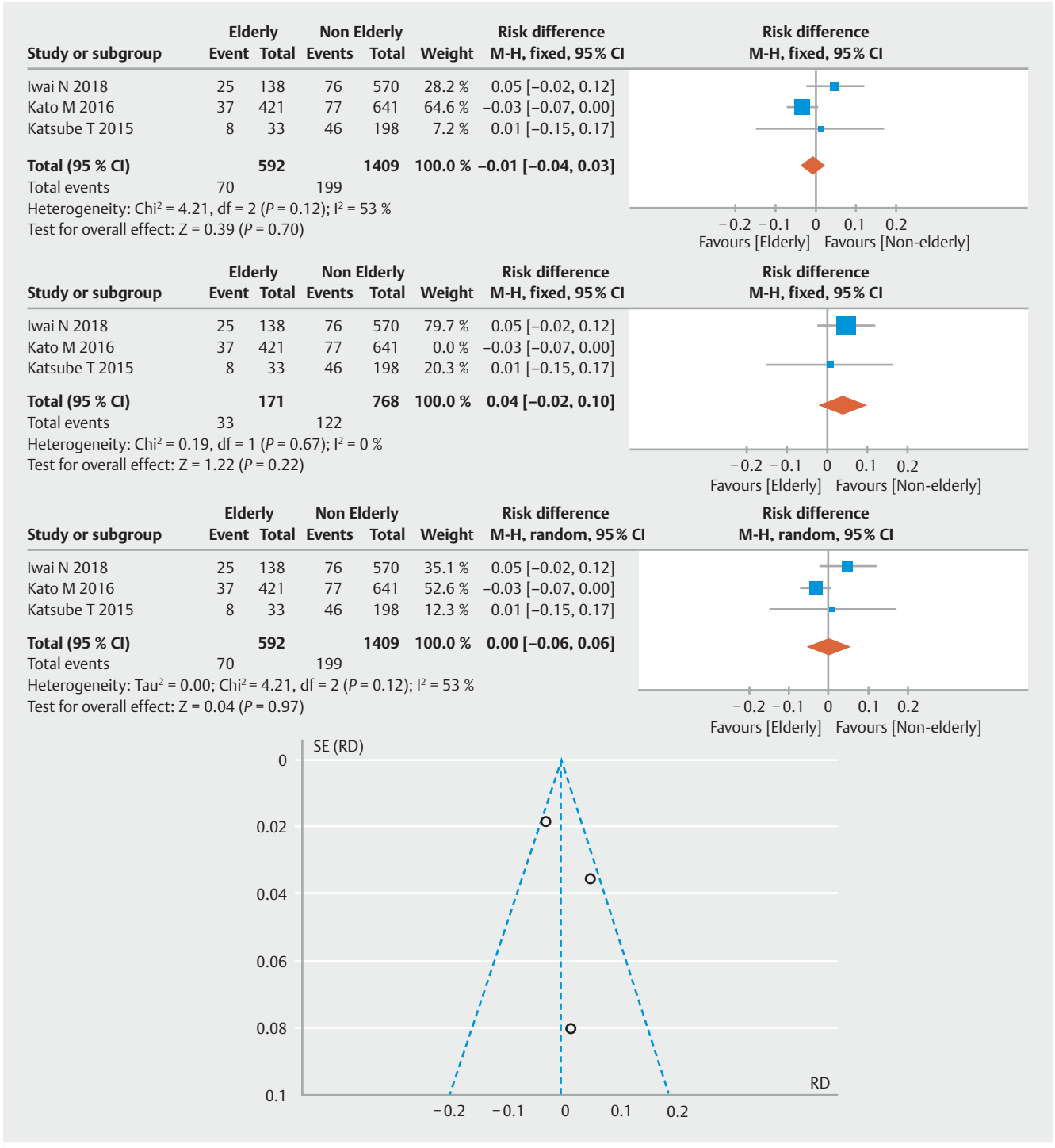
H. pylori-infection status was not relevant *per se* at onset of metachronous tumor. We analyzed patients with eradicated and persistent *H. pylori* [OR: 1.37 (0.95, 1.97) $P=0.09$ $I^2=0\%$] and found no statistical significant difference between them (**Supplementary Fig. 21**).

The analysis of persistent and negative *H. pylori* infection had high heterogeneity, with no evidence of any outlier. We assumed the heterogeneity to be true and used the random effect in the analysis, which did not have statistical difference [OR: 1.61 (0.90, 2.89) $P=0.11$ $I^2=69\%$] (**Supplementary Fig. 22**).

There was also no significance between incidence of metachronous tumor between the group that was always *H. pylori* negative and the group that became negative after eradication. Sensitivity analysis did not allow for removal of outliers, so a random effect was used. [OR 0.88 (0.21, 3.61) $P=0.85$ $I^2=82\%$] (**Supplementary Fig. 23**).

Gastric atrophy – Degree of atrophy was related to the incidence of metachronous tumor, with a lower risk of progression being associated with less severe atrophy. [OR: 0.60 (0.45, 0.81) $P=0.0006$ $I^2=42\%$] (▶ **Fig. 4**).

Pepsinogen – The ratio between pepsinogen I and II greater than 3 is a protective factor when considering incidence of a new cancer [OR 2.29 (1.47, 3.57) $P=0.0002$ $I^2=0\%$) (**Supplementary Fig. 24**), ▶ **Table 3** summa the results of this study.



▶ **Fig. 2** Graphs analyzing age in curative resection. There is no significant difference.

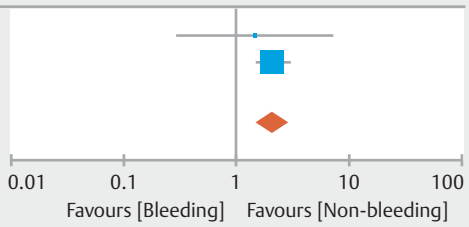
Discussion

This is the first systematic review in the literature that simultaneously evaluates several groups of prognostic factors in endoscopic treatment of early gastric cancer. This effort has great clinical relevance because identification of unfavorable factors allows for a more precise discussion of the indication for endoscopic resection and also allows for individualization of follow-up based on real risk of relapse.

Male gender and advanced age are risk factors for gastric cancer [1]. There was no statistical difference between genders when the analysis considered only curative resection, but female gender was considered a protective variable for long-term results and for risk for metachronous tumor. Also, there

Study or subgroup	Bleeding Events	Bleeding Total	Non-bleeding Events	Non-bleeding Total	Weight	Odds ratio M-H, fixed, 95% CI
Horiuchi Y 2017	2	10	37	258	4.9%	1.49 [0.31, 7.31]
Kim EH 2017	64	234	208	1405	95.1%	2.17 [1.57, 2.99]
Total (95% CI)		**244**		**1663**	**100.0%**	**2.13 [1.56, 2.93]**
Total events	66		245			

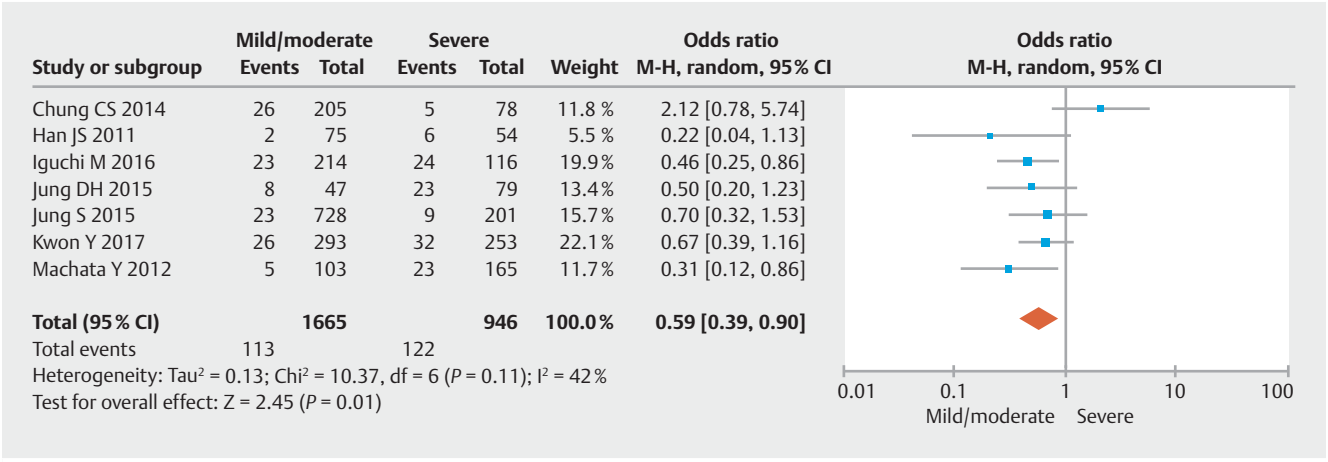
Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 4.70 (P < 0.00001)



▶ **Fig. 3** Forest plot analyzing bleeding in curative resection.

▶ **Table 2** Cure: Prognostic outcomes presented in each study.

	Country	N Patients	N Lesion	Follow-up median (mo)	Male	Female
Jeon HK 2018	Korea	66	66	40		
Bang CS 2017	Korea	275	275	47		
Zhang Y 2014	China	171	187	27.5		
Sumiyoshi T 2017	Japan	177	209	79	27/118	005/59
NAM HS 2018	Korea	639	639	36.2	13/502	002/137
Isomoto H 2010	Japan	661	713	30		
Goto A 2017	Japan	423	423	61	007/343	002/80
Toyokawa T 2011	Japan	514	586	26.7		
Lee JY 2016	Korea	401	415	19.7	25/291	11/124
Goh PG 2011	Korea	210	210	19.3		
Han SJ 2018	Korea	565	565	60	46/440	004/125
Yang HJ 2018	Korea	1115	1115	50		
Yang HJ, Kim SG 2018	Korea	1237	1237	50.2		
Kwon Y 2017	Korea	590	590	54.4	47/398	017/192
Kim SB 2016	Korea	433	433	35.6	015/325	000/108
Machata Y 2012	Japan	268	268	62.4	022/194	006/74
Iguchi M 2016	Japan	330	330	50.4	039/240	008/90
Park CH 2016	Korea	1447	1478	22.5		
Moribata K 2015	Japan	122	122	46.8	017/091	005/31
Abe S 2015	Japan	1526	1526	82.2	201/1180	037/346
Jung DH 2015	Korea	136	136	30.1	026/104	008/32
Min BH 2015	Korea	1306	1306	61	40/1044	007/302
Sugimoto T 2015	Japan	155	155	50.7	20/119	003/36
Chung CS 2014	Korea	283	183	44	23/190	008/93
Jung S 2015	Korea	1041	1041	42.6	23/773	009/268
Han JS 2011	Korea	176	176	34.6		
Han JP 2014	Korea	395	430	47.3		



▶ **Fig. 4** Graphs analyzing gastric atrophy in the incidence of metachronous tumors.

is evidence that gender may influence grade of cellular differentiation in gastric neoplasms [18].

There was no difference in relation to curative resection and cure between the elderly and the non-elderly. The precise definition of the elderly depends on the life expectancy of each geographic region. According to the Japanese Census of 2015 [19], life expectancy in Japan was 80 years for men and 86 years for women. This definition is the reason why two articles [20, 21] considered the elderly to be 80 years old. Five articles that we analyzed [22–26] used over 75 years as a definition of the elderly and one used over 65 years old [27]. There was no impact on results when we analyzed articles that evaluated subjects within the same age range, or even after exclusion of an article that defined elderly as 65 years old and above. Therefore, included all articles in the final analysis. Lin et al. published a meta-analysis that demonstrated efficacy and safety of gastric ESD in elderly patients, despite the high chance of pneumonia as a complication after the procedure [28]. Despite this frequent complication, technological advances in minimally invasive medical therapies such as ESD have contributed to increased life expectancy in the elderly population worldwide [23, 29]. Interestingly, patient age does not impact prognosis of cancer. Thus, this factor should not be a criterion used routinely to contraindicate ESD in an elderly patient.

In regards to histological type, we were able to compare curative resection and cure of differentiated and undifferentiated tumors. Differentiation is a good prognostic factor when evaluating curative resection rate, but there was no statistical difference when evaluating long-term cure rate. High heterogeneity among studies, proven to be true after outlier removal, may have contributed to the absence of difference in long-term cure.

In 2000, Gotoda et al. [30–33] suggested the expanded ESD criteria after demonstrating that risk of lymph node metastasis was very low. This allowed for resection of undifferentiated non-ulcerated tumors smaller than 2 cm. In the current study, we analyzed two articles that evaluated cure between two types of undifferentiated tumors: undifferentiated adenocarcinoma and signet ring neoplasia. There was no difference between these two tumor types in relation to cure in our analysis. In the retrospective study by Jeon et al. [34] there was also no recurrence or metastasis in tumors resected, according to the expanded criteria. However, submucosa extension and size larger than 2 cm were the main predictors of incomplete resection, with similar results to the meta-analysis performed by Zhao et al. [35].

Some studies [36–38] evaluated undifferentiated early gastric cancer that had a mixed component (signet ring associated with areas of undifferentiated adenocarcinoma or foci of undifferentiated neoplasm in differentiated tumors) and concluded that these mixed neoplasms have a higher risk of non-curative endoscopic treatment, independent of other factors. However, absence of studies that met our inclusion criteria did not allow for this meta-analysis to evaluate this prognostic factor (mixed tumors).

A meta-analysis performed by Bang et al. [39] evaluated overall safety of ESD for early gastric cancer with undifferentiated histology, based on the expanded criteria, according to AEs that occurred during the procedure (gastric hemorrhage and perforation). Rates of gastric hemorrhage and perforation from the procedure were estimated to be 6.7 % (95 % CI: 4.1 %–10.8 %, $P<0.1$) and 4.8 % (95 % CI: 2.6 %–8.6 %, $P<0.1$), respectively. However, our study evaluated bleeding potential as a predictor of poor prognosis in gastric ESD. We found that bleeding decreases rate of curative resection. Such results are possibly related to hindered visualization that may prevent more precise assessment of lesion boundaries, increasing chance of residual lesion or compromised margins.

Tumor location is one of the most important factors associated with absence of complications and resection success [40–42]. However, few studies and no meta-analyses have evaluated ESD curability outcomes according to location in the longitudinal and transverse planes, as mentioned in the Japanese classification of gastric cancer [3]. Regarding curative resection, it is more likely to be successful in tumors located in the middle and distal portions of the stomach. Regarding the division in the transverse axis, the posterior wall is described as being the most technically difficult [40]. However, in the cur-

▶ **Table 3** Results of the current study.

	Odds ratio	*P*	Favors
Curative resection			
Patient prognostic factors			
▪ Female vs male	1.20 (0,93, 1.57)	*P* = 0.17	Female
▪ Elderly vs non-elderly	1.00 (0.61, 1.64)	*P* = 1.00	
▪ BMI ≥ 25 vs < 25	0.84 (0.57; 1.26)	*P* = 0.41	BMI ≥ 25
▪ HP positive vs HP negative	0.59 (0.36, 0.97)	*P* = 0.04	HP positive
Lesion prognostic factors			
▪ Non-upper vs upper	1.41 (0.93, 2.14)	*P* = 0.10	Non-upper
▪ Differentiated vs undifferentiated	0.10 (0.07, 0.15)	*P* < 0.00001	Differentiated
▪ Non-posterior vs posterior	1.35 (0.81, 2.27)	*P* = 0.25	Non-posterior
▪ Non-depressed vs depressed	1.21 (0.99, 1.49)	*P* = 0.07	Non-depressed
▪ Non-ulcer vs ulcer	3.91 (2.31, 6.60)	*P* < 0.00001	Non-ulcer
▪ Size < 20 mm vs > 20 mm	3.61 (2.67, 4.88)	*P* < 0.00001	< 20 mm
▪ Mucosa/SM1 vs submucosa, m	0.02 (0.00, 0.69)	*P* = 0.03	Mucosa/SM1
Procedure prognostic factors			
▪ Non-bleeding vs bleeding	2.13 (1.56, 2.93)	*P* < 0.00001	Non-bleeding
Cure			
Patient prognostic factors			
▪ Female vs male	1.62 (1.33, 1.97)	*P* < 0.00001	Female
▪ Non-elderly vs elderly	1.49 (0.69, 3.23)	*P* = 0.31	Non-elderly
Lesion prognostic factors			
▪ Differentiated vs undifferentiated	0.71 (0.20, 2.51)	*P* = 0.60	
▪ SRC vs PDR	2.24 (0.44, 11.35)	*P* = 0.33	SRC
▪ Depressed vs non-depressed	1.12 (0.72, 1.74)	*P* = 0.60	
▪ Non-ulcer vs ulcer	0.91 (0.21, 3.95)	*P* = 0.90	
▪ Upper vs non-upper	1.25 (0.97, 1.63)	*P* = 0.90	Non-upper
▪ Size < 20 mm vs > 20 mm	1.68 (0.82, 3.45)	*P* = 0.16	< 20 mm
▪ Size < 30 mm vs > 30 mm	2.22 (0.56, 8.81)	*P* = 0.326	< 30 mm
▪ Mucosa/SM1 vs SM2	0.08 (0.02, 0.39)	*P* = 0.002	Mucosa/SM1
Metachronous tumor			
▪ Female vs male	1.64 (1.32, 2.03)	*P* < 0.00001	Female
▪ HP eradicated vs HP persistent	1.37 (0.95, 1.97	*P* = 0.09	HP eradicated
▪ HP negative vs HP persistent	1.61 (0.90, 2.89)	*P* = 0.11	HP negative
▪ HP negative vs eradicated	0.88 (0.21, 3.61	*P* = 0.85	
▪ Gastric atrophy–mild vs severe	0.60 (0.45, 0.81)	*P* = 0.006	Mild gastric atrophy
▪ Pepsinogen ratio	2.29 (1.47, 3.57)	*P* = 0.0002	PGI: PG II > 3

BMI, body mass index; HP, *Helicobacter pylori*; SRC, signet ring cells; PDR, poorly differentiated adenocarcinoma.

rent study, we did not see any difference in success of curative resection. Experienced ESD endoscopists for whom difficult locations are no longer challenging were involved in most of the published studies. This may possibly explain the absence of difference in the success of curative resection.

Regarding macroscopic type, there was no difference in success of curative resection in depressed vs. non-depressed lesions. However, ulcer presence is a strong predictor of nonresectability, according to our study, corroborating the expanded criteria [30]. Ulcer presence may prevent adequate margin delimitation due to the inflammatory process, as well as hindering adequate depth assessment. However, once curative resection is obtained, ulcer presence does not interfere with long-term cure [42].

Lesions smaller than 20 mm have a higher chance of curative resection than those larger than 20 mm. On the other hand, size was not statistically significant when evaluating long-term cure. Therefore, if a tumor was removed with curative resection criteria, size itself was not relevant for follow-up and should not be used alone to contraindicate endoscopic resection.

Resection is more likely to be curative and over the long term in tumors restricted to the mucosal layer and superficial submucosa, corroborating previous studies [30].

Interestingly, *H. pylori* infection status affected the success of curative resection. One hypothesis to justify this observation could be that inflammation caused by this pathogen around the neoplastic and dysplastic tissue could help in its delimitation, which is different than the hypothesis proposed by Horiuchi et al. [43], who postulated that inflammation could impair resection of some tumors, especially undifferentiated ones. However, only two studies could be used in the analysis after outlier withdrawal, which may limit generalization of this result. It was not possible to analyze the impact of *H. pylori* o long-term cure due to absence of adequate articles to include in the analysis.

Two articles in our study analyzed BMI of patients who underwent ESD for early gastric cancer [18, 44]. The rationale for this analysis is that obesity is associated with several intraoperative and postoperative complications [44], and it is postulated that it may also influence endoscopic resections. Adipose tissue is often found in gastric submucosa during ESD. Excessive adipose tissue may prevent recognition of vessels in the submucosa, a fact that precludes preventative coagulation and may increase bleeding, thereby making it difficult to perform the procedure [44]. In our study, there was no difference in curative resection between obese and non-obese patients. However, the small number of articles and use of the Asian classification for obesity [17] substantially limit generalization of these data.

Although *H. pylori* is considered a carcinogen because it induces chronic inflammation and leads to development of pre-neoplastic lesions, many studies attempt to correlate *H. pylori* infection with a higher incidence of metachronous tumor. There is substantial discussion and divergence in the literature [45–54] on this topic. Whether eradication of *H. pylori* can actually facilitate regression of precancerous lesions, such as atrophy and metaplasia, is unknown [49, 50]. In a prospective study, eradication of *H. pylori* reduced incidence of gastric cancer only when there were no pre-neoplastic lesions [51]. Within this framework, we sought to identify whether infectious status would imply worse prognosis in relation to incidence of metachronous tumors. There was no difference in incidence of metachronous tumors when comparing patients who were infected, treated, and cured of *H. pylori*. The difference was significant only in relation to degree of atrophy; increased atrophy was associated with greater probability of a metachronous tumor [52, 53]. In a meta-analysis performed by Xiao [54], it was found that eradication of the pathogen only prevented metachronous tumor occurrence in early stages of carcinogenesis. In other words, chronic inflammation was not enough to cause a severe degree of atrophy. This notion is supported by our evidence that there is a higher chance of metachronous tumor with significant gastric atrophy when compared to mild gastric atrophy.

The gastric mucosa is known to produce two types of pepsinogen (PGI and PGII). In the presence of atrophic gastritis, PGI production by oxyntic cells is lower, while PGII production remains relatively constant. Reduced serum levels of pepsinogen I (< 70 mg/L) and a PGI/PGII ratio of less than three are useful in identifying patients with atrophic gastritis. Because significant atrophy is a significant risk factor for incidence of metachronous tumor, the ratio of pepsinogen I and II also directly reflects risk for metachronous tumor. Two studies included in this meta-analysis evaluated incidence of metachronous tumor with these ratios [55, 56]. The rate between pepsinogen I and II less than three is a risk factor for tumor recurrence, making it crucial to closely follow these patients.

One limitation of this review is that none of the selected studies was a randomized trial, because there are no randomized trials in the literature that evaluate the studied prognostic factors. The selected studies were retrospective cohorts, and therefore, susceptible to selection biases, which may have been mitigated by inclusion of only high-quality work by the NewCastle Score. The included studies vary considerably in relation to number of patients and lesions, as well as high variability in follow-up time, which could explain the high heterogeneity observed in some analyses. However, the heterogeneity limit of 30 % with calculation of sensitivity analysis from this point made it possible to reduce the impact of this variation in our analysis. Most studies (45 from 46) are from Asian countries, which makes it impossible to accurately generalize the results to the Western population. Due to the high incidence of this cancer, some Asian countries, such as Korea and Japan, have an efficient screening program, which provides useful data for future studies. Regarding the histological analysis, Choi and colleagues [18] emphasize that pathological diagnosis may differ significantly between observers, a fact that corroborates the necessity of careful analysis. Western and Korean countries use the World Health Organization classification [57], which differ from some histological subdivisions of Japanese classification [3]. The divergence between western and eastern pathologists was partially resolved with use of the Vienna classification [58], however, there is still heterogeneity among pathologists. Thus, authors should carefully consider different histologies in the efforts for classification of prognostic factors.

Despite the aforementioned limitations, this meta-analysis is meaningful given the robust correlation of several prognostic factors in a cancer with significant morbidity and mortality. Awareness of prognostic factors of gastric cancer in the early stages will enable clinicians to predict the utility of endoscopic treatment. Also, such prognostic factors allow for patient counseling on the probabilities of an expected outcome based on evidence, according to that individual's unique cancer metrics. We hope this study will lead to new avenues of research and updated guidelines for the scientific community.

Conclusion

Lesions presenting differentiated histology, without ulceration, smaller than 20 mm, and with invasion over SM1 are associated with a higher rate of curative resection. Absence of bleeding during endoscopic resection and presence of *H. pylori* infection are also factors suggestive of good prognosis related to curative resection. In relation to long-term cure, female sex and invasion of just SM1 increases curative rates. Female gender is a protective factor for developing a metachronous tumor. Severe gastric atrophy and PG I: PGII less than three are risk factors for incidence of metachronous tumor. Awareness of prognostic factors associated to ESD will aid in selection of patients with a higher probability to benefiting from treatment and allow follow-up of these individuals to be customized.

Competing interests

The authors declare that they have no conflict of interest.

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