

Risk Factors for Technical Difficulty of Endoscopic Submucosal Dissection in Colorectal Tumors: A Case Series and Meta-Analysis

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Abstract

Background and Aims: Endoscopic submucosal dissection has become widely accepted as an efficient and well-established option for colorectal neoplastic lesions (CRNs). However, there are still some barriers for endoscopists that hinder the successful ESD. The current study was to evaluate risk factors for the failure of en-bloc resection in the colorectal endoscopic submucosal dissection (ESD).

Methods: A retrospective chart review was performed from patients who underwent ESD for colorectal neoplasms (CRNs) between January 2015 and April 2017. The demographics and colonoscopic reports were analyzed. A meta-analysis was conducted for the risk factors for the failure of en-bloc or R0 resection.

Results: 253 ESD cases were completed in en-bloc resection. Ulcerative colitis, previous abdominal surgeries, lesions on the Bauhin's valve/ dentate line, non-lifting sign and submucosal fibrosis were associated with the failure of en-bloc resection ($P < 0.05$). Meta-analysis showed that laterally spreading tumors, tumor larger than 40mm, Bauhin's valve/dentate line, flexure, non-lifting sign, and submucosal fibrosis were the factors for the failure of en bloc or R0 resection. The rates of perforation were obviously higher in N-EBR groups compared to EBR groups. No significant results can be observed on the local recurrence based on these studies.

Conclusions: Preoperative factors such as laterally spreading tumors, tumor larger than 40mm, Bauhin's valve/dentate line, flexure and intraoperative factors such as non-lifting sign, submucosal fibrosis should be put more focus to reach better outcomes in CRNs patients.

Introduction

Endoscopic submucosal dissection (ESD) has become widely accepted as an efficient and well-established option for colorectal neoplastic lesions (CRNs). However, it still confers technical challenge to achieve a high rate of en bloc resection [1, 2, 3]. Unmet need is posed to investigate how to get through such barrier to achieve en bloc resection.

Several studies focusing on risk factors for technical difficulties of colorectal ESD have been published since the year 2008 [5-8]. Most papers were reported in Japan, as ESD has played a critical role in the treatment algorithm of most colorectal neoplasms once permitted under Japanese Medical Insurance [9]. However, as colorectal ESD has not yet been standardized in all referral centers, the definitions and risk factors for "difficult ESD" have yielded conflicting results among individual center [10, 11]. Furthermore, in the West, colorectal ESD can only be performed proficiently in few centers. Only sporadic studies reported the difficulty of colorectal ESD and the rescued measure if ESD failed [11, 12]. The experience drawn from the East (Japan, Korea, China) can not necessarily correspond to the situation in western centers. Discordant data mixed with different definitions and factors would confuse endoscopists which factor should be considered to achieve a successful ESD procedure.

This study is to evaluate preoperative and intraoperative factors for the failure of en bloc resection in the setting of colorectal ESD within retrospective, single-center cohort. Furthermore, a meta-analysis was conducted to analyze risk factors for the failure of en-bloc or R0 resection.

Methods

Study population, data collection and study outcomes in one tertiary setting

The data from patients who underwent ESD for colorectal neoplasms (CRNs) in a tertiary referral center between January 2015 and April 2017 were retrieved and analyzed. Patients were excluded in terms of the following criteria: 1) Postoperative histopathology evaluation showed the submucosal penetration was deeper than 1000 μm from the muscularis mucosa. 2) Not suggestive of precancerous lesions or adenocarcinomas (neuroendocrine tumor, lipoma, gastrointestinal stroma tumors, et al) based on histopathology. 3) Locally residual or recurrence colorectal lesions on site after endoscopic treatment.

Data related to demographics of patients, lesions, procedures, and adverse events were collected. All ESD cases were categorized as en bloc or non-en bloc resection group. The ESD procedure was classified as technically difficult in the case of the non-en bloc resection.

Meta-Analysis

A systematic review was conducted using meta-analytical approaches outlined in the *Cochrane Handbook for Systematic Reviewers* and reported according to the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) criteria.

Literature search strategy and selection criteria

A comprehensive literature search was performed through database such as Pubmed, EMBASE, Cochrane library and large bibliographic database in China such as Wanfang MedOnline, China National Knowledge Infrastructure (CNKI) and China Biology Medicine disc (CBMdisc) through 1 June 2019. The subject terms were used: "Endoscopic submucosal dissection," "ESD," "Difficult ESD", "difficult endoscopic submucosal dissection" and "colorectal neoplasm." An additional search was performed among references of included studies to find potentially eligible studies.

Inclusion criteria were as follows: 1) no limitations on study design, including prospective or retrospective observational cohorts, case-control studies, and randomized controlled trials (RCTs), and 2) studies reporting the therapeutic outcomes of ESD for colorectal neoplasm lesions, such as en bloc resection rate, R0 resection rate, and follow-up results, including follow-up period, recurrence rate, and rescued surgery, etc.

Exclusion criteria were as follows: 1) case reports, 2) literature on ESD for other diseases, such as esophageal, gastric lesions. 3) experiments on animals, 4) reviews, comments, or letters, 5) studies published in other languages besides English and Chinese, 6) studies with unavailable full text. W.J. and Y.G. evaluated the quality of the included studies using the Newcastle-Ottawa scale.

Data extraction

Data collection objectives included the following items. 1) Study design, duration, country, setting, Authors, year of publication; 2) Preoperative factors: patient demographics (such as age, gender distribution, previous abdominal surgeries, diagnosis of ulcerative colitis), location (colon vs rectum), morphology and tumor size, flexure, special anatomic regions such as Bauhin's valve/dentate line and the experience of endoscopists; 3) Intraoperative factors: submucosal fibrosis, non-lifting sign. For comparison with data in our center, we only retrieved these two intraoperative factors. 4) The prognostic outcomes were also involved as data collection objectives. The factors reported in more than three literatures would be recruited to meta-analysis. As some factors (the cutoff of age and tumor size, morphology, location) may be classified differently among references, for the convenience of pooling

these estimates, we included the values as follows. That is, we categorized tumor size into “≥40mm” and “<40mm”. The morphology was classified as “Laterally spreading tumors” (LST) and “Protruding”. The cutoff of age is 70-year-old. The location consists of colon and rectum. The follow-up data such as period, perforation rate, local recurrence rate and rescued surgery rate would be extracted from references reporting the failure of en-bloc resection or R0 resection as the prognostic outcome.

Definition of outcomes

The primary outcome was to evaluate the preoperative and intraoperative predictors of the non-en bloc resection or R0 resection for colorectal neoplastic lesions. Inconsistent with the data in our center, we have also enrolled references which reported “R0 resection” as the primary outcome for retrieving data as much as possible. Secondary prognostic outcome was follow-up outcomes in non-en bloc resection group and en-bloc resection group: 1) Local recurrence was defined as the cancer has recurred on the primary resection site during the follow-up period. 2) Rescued surgery referred that the lesion cannot be treated under endoscopy, so that they underwent open surgery or laparoscopy for resection.

Statistical analysis

For retrospective analysis, continuous parameters were analyzed using Student’s t-test or the Mann-Whitney U test, whereas categorical variables were compared using the χ^2 test and Fisher’s exact test, as appropriate. Values of $p < 0.05$ were considered statistically significant. Risk factors for the non-en bloc resection were analyzed using univariate method. A logistic regression model was used for the multivariate analysis of significant factors detected by univariate analysis, defined as $p < 0.05$, with forward stepwise selection. SPSS version 25 for Mac (IBM Corp.; Armonk, NY, USA) was used for the statistical analysis.

For meta-analysis, all pooled odds ratio (OR) and 95% confidence intervals (CIs) of risk factors were calculated and compared using Review Manager (RevMan version 5.3). χ^2 test and I^2 statistics were used to evaluate heterogeneity. It was considered to have minor heterogeneity if $I^2 \leq 25\%$; if $25\% < I^2 \leq 75\%$, it was considered to have moderate heterogeneity; if $I^2 > 75\%$ and $p < 0.1$, it was considered to be significant heterogeneity; When there was no statistically significant heterogeneity among the studies ($I^2 < 75\%$, $P > 0.1$), a fixed-effects model was used to calculate the pooled estimates, otherwise a random effects model was used. Multiple sensitivity analyses were conducted to explore the potential heterogeneity and the possible causes. For potential publication bias, a comprehensive literature search and removal of the duplicated data were conducted to minimize the reporting biases and funnel plots were also constructed to explore the publication bias.

Results

Retrospective study and Meta-analysis

Baseline characteristics and outcomes of ESD

The baseline characteristics between the en bloc resection and non-en bloc resection groups were described in Table 1. Among 287 ESD cases (278 patients) for CRNs, 253 (86.8%) cases were completed en bloc. For demographic factors (age, gender, smoking, alcohol-consuming), the comparison didn’t show prominent difference between non-en bloc resection and en-bloc resection groups ($P > 0.5$). As to some preoperative factors (location, flexure, inexperienced

endoscopists, previous abdominal surgeries, family history of cancer), there was no significant difference between two groups ($P > 0.5$). However, as to other preoperative factors such as morphology, tumor size, fold convergence, underlying semilunar fold, Bauhin's valve/dentate line, diagnosis of ulcerative colitis, statistical difference could be observed ($P < 0.05$). For intraoperative factors, submucosal fibrosis and non-lifting sign showed significantly difference ($P < 0.0001$). The ratio of two factors mentioned above was obviously higher in non-en bloc resection group (52.9% vs 7.9%; 47.1% vs 5.5%).

Table 1

Comparison of preoperative and intraoperative factors between successful and non en-bloc resection groups.

	En bloc resection n, (%)	Non en bloc resection n, (%)	P value
Case number	253	34	
Age \geq 70yr	86(34)	13(38.2)	0.625
Gender Male/Female	142(56.1)/111(43.9)	18(52.9)/16(47.1)	0.726
Morphology			0.024
LST-GH	114(45.1)	9(26.5)	
LST-GM	58(22.9)	13(38.2)	
LST-NG-PD	8(3.2)	4(11.8)	
LST-NG-F	19(7.5)	3(8.8)	
Protruding	54(21.3)	5(14.7)	
Tumor location			0.524
Right Colon	80(31.6)	14(41.2)	
Left Colon	74(29.9)	8(23.5)	
Rectum	99(39.1)	12(35.3)	
Tumor size			0.041*
20 \leq Tumor size < 30 mm	165(65.2)	17(50)	
30 \leq Tumor size < 40 mm	49(19.4)	6(17.6)	
40 \leq Tumor size < 50 mm	16(6.3)	4(11.8)	
Tumor size \geq 50 mm	23(9.1)	7(20.6)	
Fold convergence	2(0.8)	2(5.9)	0.017*
Underlying semilunar fold	63 (24.9)	15(44.1)	0.018*
Flexure	28 (11.1)	3 (8.8)	0.692
Bauhin's valve/dental line	5(2)	5(14.7)	0.000*
Fibrosis	20(7.9)	18(52.9)	0.000*
Non-lifting sign	14(5.5)	16(47.1)	0.000*

***P value \leq 0.05**

LST-GH: laterally spreading tumors-granular-homogenous type

LST-GM: laterally spreading tumors-granular- nodular mixed type

LST-NG-PD: laterally spreading tumors-non-granular (pseudodepressed type)

LST-NG-F: laterally spreading tumors-non-granular (flat type)

	En bloc resection n, (%)	Non en bloc resection n, (%)	P value
Histology	198(78.3)	24(70.6)	0.536
Adenoma	47(18.6)	8(23.5)	0.000*
Adenocarcinoma-M	8(3.1)	2(5.9)	
Adenocarcinoma-SM1	234(92.5)	11(32.4)	
R0 resection			
Complications			
Perforation	7(2.8)	5(14.7)	0.001*
Postprocedural bleeding	4(1.6)	1(2.9)	0.569
Electrocoagulation syndrome	9(3.6)	1(2.9)	0.854
Fever	17(6.7)	5(14.7)	0.100
Inexperienced endoscopist	15(5.9)	4(11.8)	0.199
Ulcerative colitis	4(1.6)	3(8.8)	0.01*
Previous abdominal surgeries	71(28.1)	16(47.1)	0.077
Family history of cancer	48(19.0)	6(17.6)	0.903
Smoking	76(30)	7(20.6)	0.254
Alcohol consuming	40(15.8)	6(17.6)	0.784
*P value ≤0.05			
LST-GH: laterally spreading tumors-granular-homogenous type			
LST-GM: laterally spreading tumors-granular- nodular mixed type			
LST-NG-PD: laterally spreading tumors-non-granular (pseudodepressed type)			
LST-NG-F: laterally spreading tumors-non-granular (flat type)			

Possible procedure-related variables associated with non-en bloc resection

Next, we attempted to identify risk factors before and during ESD procedure in our center. Univariate analysis indicated that the non-en bloc resection was associated with preoperative factor: diagnosis of ulcerative colitis (6.024, 1.288–28.179; $P = 0.023$), previous abdominal surgeries (1.770, 1.034–3.029; $P = 0.037$), fold convergence (OR:7.844, 95%CI: 1.068–57.622; $P = 0.043$), Bauhin's valve/dentate line (OR:6.571, 95%CI: 2.181–19.802; $P = 0.001$), semilunar fold (OR:2.381, 95%CI: 1.142–4.963; $P = 0.021$); intraoperative predictors such as non-lifting sign (OR:15.175, 95%CI: 6.405–35.951; $P < 0.0001$) and submucosal fibrosis (13.106, 5.809–29.570; $P < 0.0001$). Multivariate analysis revealed that diagnosis of ulcerative colitis (10.518, 1.423–77.744; $P = 0.021$), semilunar fold (3.805, 1.480–9.782; $P = 0.006$), Bauhin's valve/dentate line (OR:10.764, 95%CI: 1.603–72.263; $P = 0.014$), non-lifting sign (OR:4.854, 95%CI:

1.421–16.584; $P = 0.012$) and submucosal fibrosis (5.666, 1.775–18.088; $P = 0.003$) were independently risk factors for non-en bloc resection. Details of factors associated with the non-en bloc resection were presented in Table 2.

Table 2

Predictors of incomplete en bloc resection in colorectal endoscopic submucosal dissection: univariate and multivariate analysis

Variable categories, and variables	Non-en Bloc Resection					
	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
Age (≤ 70 vs > 70), years	0.832	0.397–1.742	0.625			
Gender (Female vs Male)	1.137	0.555–2.311	0.726			
Location (Rectum vs colon)						
Rectum	1	1	0.528			
Left Colon	0.693	0.303–1.581	0.383			
Right Colon	0.618	0.245–1.557	0.307			
Ulcerative colitis	6.024	1.288–28.179	0.023*	10.518	1.423–77.744	0.021*
History of abdominal surgery	1.770	1.034–3.029	0.037*			
Inexperienced endoscopists	2.116	0.659–6.792	0.208			
Tumor size						
$20 \leq$ Tumor size < 30 mm	1	1	0.119			
$30 \leq$ Tumor size < 40 mm	0.339	0.127–0.904	0.031*			
$40 \leq$ Tumor size < 50 mm	0.402	0.121–1.333	0.136			
Tumor size ≥ 50 mm	0.821	0.206–3.279	0.781			
Morphology						
LST-GH	1	1	0.039*			
LST-GM	0.853	0.273–2.666	0.784			
LST-NG-PD	2.421	0.809–7.243	0.114			
LST-NG-F	5.400	1.193–24.443	0.029*			
Protruding	1.705	0.372–7.827	0.492			
Flexure	0.778	0.223–2.710	0.693			
Underlying semilunar fold	2.381	1.142–4.963	0.021*	3.805	1.480–9.782	0.006*
Fold convergence	7.844	1.068–57.622	0.043*			
Bauhin's valve or dentate line	6.571	2.181–19.802	0.001*	10.764	1.603–72.263	0.014*
Non-lifting sign	15.175	6.405–35.951	0.000*	4.854	1.421–16.584	0.012*
Submucosal fibrosis	13.106	5.809–29.570	0.000*	5.666	1.775–18.088	0.003*
Infiltration Depth						
IM	1	1	0.417			

Variable categories, and variables	Non-en Bloc Resection		
	Univariate analysis		Multivariate analysis
	OR	95%CI	OR95%CI
SM < 1000um	1.914	0.389–9.411	0.424

***P value<0.05**
LST-GH: laterally spreading tumors-granular-homogenous type
LST-GM: laterally spreading tumors-granular- nodular mixed type
LST-NG-PD: laterally spreading tumors-non-granular (pseudodepressed type)
LST-NG-F: laterally spreading tumors-non-granular (flat type)
IM: intramucosal infiltration
SM: submucosal infiltration

Search results

Initial search in database mentioned above (Pubmed, EMBASE, Cochrane library, Wanfang MedOnline, CNKI and CBM) yielded 3076 references in total. The data from consecutive patients in our center were added on this meta-analysis. After removing duplicated studies, 1668 references were screened at first. 1607 studies were excluded according to the following criteria: 127 items were excluded due to the irrelevant title, 894 abstracts didn't report the outcomes of interest, 13 studies were not written in English or Chinese. The other 573 studies were excluded since we didn't have the accessibility to the full text. Then we assessed the 61 full-text studies. Finally, 13 studies reporting the prognostic outcome "non-en bloc resection" or "non-R0 resection" (OR, 95%CI) were included in meta-analysis.(Fig. 1)

Synthesis and assessment of factors for the non-en bloc resection or R0 resection

Thirteen studies came from Japan, USA, Korea, China and Russia. All these studies were from single tertiary setting, and twelve studies were case-control studies(see Additional file 1). The average quality of all included studies was moderate assessed by the Newcastle–Ottawa scale. OR and 95%CI of preoperative and intraoperative factors for non-en bloc resection or non-R0 resection were pooled and assessed. For submucosal fibrosis and tumor size, statistical heterogeneity was observed ($I^2 > 50\%$, $P < 0.05$) and a random-effects model was used because exclusion of the studies cannot explain the source of heterogeneity. As to remaining factors, no significant heterogeneity was observed ($I^2 < 75\%$, $P > 0.05$) that a fixed-effects model can be used.

For preoperative predictors, the pooled OR reporting the association between gender, location (colon vs rectum) and the failure of en bloc resection/R0 resection was 1.26(95% CI 0.92–1.72; $P = 0.14$) and 1.35 (95% CI 1.00–1.83; $P > 0.05$). No significant heterogeneity was observed in both factors ($I^2 = 0\%$, $p = 0.48$; $I^2 = 0\%$, $p = 0.82$). The pooled OR of studies reporting the association between morphology, tumor size, Bauhin's valve/dentate line and non-en bloc resection/non R0 resection was 1.58 (95% CI 1.12–2.22; $P = 0.008$), 2.86 (95% CI 1.71–4.77; $P < 0.0001$) and 5.09 (95% CI 2.09–12.44; $P = 0.0004$), respectively. The heterogeneity of these three factors was insignificant ($I_2 = 0\%$, $p = 0.84$; $I^2 = 10\%$, $p = 0.34$; $I^2 = 0\%$, $p = 0.52$). The pooled OR of studies reporting the association between flexure and N-EBR/non R0 resection was 2.11 (95% CI 1.03–4.35; $P = 0.04$). No obvious heterogeneity was denoted ($I^2 = 48\%$, $p = 0.14$).

We have retrieved two intraoperative factors as follows for comparison with the data in our center. The pooled OR reporting the association between submucosal fibrosis, non-lifting sign and non-en bloc resection/non R0 resection was 7.17(95% CI 4.36–11.79, $P < 0.0001$) and 4.43(95% CI 1.11–17.74, $P = 0.04$). The heterogeneity of non-lifting sign

was significant ($I^2 = 81\%$, $p = 0.006$), therefore a sensitivity analysis was performed to explore the heterogeneity and we found that the source was from the data in our center. As to the submucosal fibrosis, no significant difference was observed ($I^2 = 44\%$, $p = 0.06$). (Fig. 2)

Follow-up outcomes

Five literatures(see Additional file 2) reporting follow-up period, perforation, recurrence or rescued surgery and current study were enrolled to analyze adverse events and follow-up outcomes of none en bloc resection(Table 3). A total of 1750 cases of en bloc resection and 233 cases of the non-en bloc resection were included in total. Details of outcomes reported in literatures and current study were described in Table 3. Among these, 4 studies supplied the follow-up period. The longest period can last for 31 months while in the study carried out by Mikhail et al, the period only last for 3 months. According to three literatures reporting perforation, the rates of perforation were obviously higher in N-EBR group compared to EBR group (21.9 vs 4.8, 8.3 vs 7.6, 14.7 vs 2.8). No significant results can be observed on the local recurrence based on these studies. Considering the 4 references reporting the rescued surgery rate, although the study conducted by Phillip S et al uncovered that the only 3 cases of surgery were all within EBR group. The rest of all 3 publications showed that it was significantly higher in N-EBR groups compared to their controls which underwent en bloc ESD (11.1 vs 2.3, 17.6 vs 9.0, 2.9 vs 0.4).

Authors (Year)	Mikhail <i>et al.</i> (2014)	Kenichiro <i>et al.</i> (2015)	Xin <i>et al.</i> (2017)	Myeongsook <i>et al.</i> (2018)	Phillip S <i>et al.</i> (2019)	Current study (2019)
Study design	Retrospective study	Retrospective study	Retrospective study	Retrospective study	Prospective RCT	Retrospective study
Cases(n)	N-EBR EBR (n=7) (n=37)	N-EBR EBR (n=73) (n=643)	N-EBR EBR (n=9) (n=132)	N-EBR EBR (n=108) (n=648)	N-EBR EBR (n=2) (n=37)	N-EBR EBR (n=34) (n=253)
Follow-up Period(month)	3	NR*	13.2±8.6	13.7(6.9-31.0) 15.4(12.3-29.3)	17.3±8.7	NR*
Perforation (n, %)	NR*	16(21.9) 31(4.8)	NR*	9(8.3) 49(7.6)	NR*	5(14.7) 7(2.8)
Local recurrence rate (n)	0	NR*	0	4 3	0	NR*
Rescued surgery rate (n, %)	NR*	NR*	1(11.1) 3(2.3)	19(17.6) 58(9.0)	0 3	1(2.9) 1(0.4)
*No record						

Table 3
Outcomes of non-en bloc resection of included publications

Discussion

Currently, ESD has been widely accepted as the standard therapy for early-stage colorectal neoplasms. However, due to the anatomical structure of colon, it's more challenging to resect lesions in complete fashion. Previous single-center studies have contributed greatly to the knowledge of risk factors for non-en bloc resection, but a full overview of current evidence on which factors should be focused on before or during the ESD procedure was lacking. In this study, we conducted a meta-analysis which demonstrated that preoperative factors such as laterally spreading tumors, tumor size larger than 40 mm, special anatomical regions such as Bauhin's valve/dentate line, flexure and intraoperative factors such as non-lifting sign, submucosal fibrosis were the risk factors for the failure of en bloc resection or R0 resection. This meta-analysis can assist endoscopists in improving care for patients who require ESD for treatment.

Lately, some investigators have explored the feasibility and efficacy of ESD for ulcerative colitis. Kinoshita et al. recruited 25 dysplastic cases at one tertiary referral center in Japan and found that the rate of en bloc resection for lesions (mean size: 35 ± 17 mm) were 100% (25/25) [13]. Similarly, another study reported that the rate of en bloc resection can even reach 91% (29/32) [14]. However, in our center, by analyzing the retrospective data in one tertiary setting, the rate of en-bloc resection can only reach 57% within 7 ulcerative colitis patients. Furthermore, the multi-variate analysis showed that the diagnosis of ulcerative colitis was an independent risk factor for non-en bloc resection. We reported here to illustrate that no matter the satisfying results in highly-experienced centers in Japan mentioned above, it was still a strong barrier in other centers like us. Disparity of the rate of en-bloc resection may lie in different levels of ESD techniques among centers. As in China, the clinical practice of colorectal ESD began not that early as in Japan. In the future, it may need a larger-scale cohort to validate whether the diagnosis of UC is indeed one of the risk factors for non-en bloc resection.

It has been discussed for a long time whether the morphology of colorectal lesions should be assessed before ESD procedure. In 2015, Jung et al analyzed 220 ESD cases for colorectal tumors (67, protruding tumors; 153, LSTs) in a single Korean center and reported that en bloc resection rate was much lower in protruding tumors than in LSTs (76.1 vs. 92.8%, P = 0.001) [15]. Contrary to this, majority of studies denoted that no matter comparing the ratio of the LST and protruding in non-en bloc resection group and successful ESD group or analyzing the association between morphology and non-en bloc resection, there were no significant difference [12, 13, 14]. In this meta-analysis, the pooled estimates of morphology (LST vs Protruding) demonstrated no significant relationship with non-en bloc resection or R0 resection. The data we get in this study may support that morphology shall not be an important indicator for difficult ESD.

Previous studies reported that the presence of fibrosis may prevent complete resection. In 2009, Isomoto has firstly reported that the finding of fibrosis contributed to the incomplete resection [4]. Since then, this factor has always been focused and regarded as a potent risk factor responsible for the difficulty of performing ESD. Consistent with these studies, we also confirmed that submucosal fibrosis were the risk factors for the failure of en bloc resection by retrospective analysis and meta-analysis. However, as the severity of submucosal fibrosis can only be detected during ESD instead of predicting before the procedure. It mainly depends on the experience of endoscopists whether can achieve en-bloc resection under this situation. Therefore, it should be put more focus on the preoperative prediction of submucosal fibrosis.

Colorectal ESD for large-sized lesions has been always considered to be a difficult and time-consuming procedure compared with conventional EMR. But no agreement has reached yet on the definition of "large lesions". In our study, we defined lesions larger than 40 mm as the large lesions. Koichiro, Hisashi and Yuqi have all reported previously that lesions larger than 40 mm can cause the difficulty of successful ESD or perforation in Japan and China,

respectively^[16, 17, 18]. However, in our center, towards to lesions larger than 40 mm, no significant difference can be seen between non-en bloc resection and successful ESD. Contrary to the results of retrospective analysis, meta-analysis showed that lesions larger than 40 mm was a risk factor for non-en bloc or R0 resection. Taken together, although there is no consensus on the exact size to define “large lesion”, lesions larger than 4 cm would be still regarded as a risk factor for the failure of ESD.

The summarized data of follow-up outcomes showed that the perforation rate and rescued surgery rate were much higher in non-en bloc resection. Dealing with patients with risk factors mentioned in this study, the endoscopists should avoid non-en bloc resection through various approaches such as pocket-creation method ESD, traction so that the incidence of unsatisfactory outcomes can be lowered to the fullest extent. The local recurrence showed that no significant difference between both groups. We believed that it was due to the limitation of literatures reporting that. More references need to be traced to get a convincing result.

As the development of strategies for treating colorectal ESD, endoscopists have focused on whether or not achieving en-bloc resection. The primary strength of this investigation is that we firstly found that UC was one of risk factors for the failure of en-bloc resection. Second, the strength of this study was that we enrolled references to make a meta-analysis on the risk factors for the failure of successful ESD. This may be significant in a higher-level evidence for guiding a better prognosis in future clinical practice. Keeping these factors in mind could remind endoscopists to prepare the endoscopic ancillary attachment devices to avoid the failure of ESD before procedure or abort in time and then transfer for surgery to avoid futile efforts and serious complications due to long procedure time.

However, there were some limitations in this study. First, some abstracts in Embase just reported the final conclusion instead of showing the detailed data such as OR value or exact number of each group. Hence, these cannot be recruited into our meta-analysis. Second, some indicators like age (> 70 or ≤ 70), the history of abdominal surgery, the experience of endoscopists were reported no more than 3 references so that cannot be analyzed.

Conclusions

All in all, our study has validated the importance of some risk factors such as tumor size ≥ 40 mm, Bauhin's valve/dentate line, non-lifting sign, submucosal fibrosis for non-en bloc resection by retrospective description adding on meta-analysis. What's more, the diagnosis of ulcerative colitis was also the independent factor for difficult ESD procedure. More focus should be on the improvement of techniques and the exploration of more advanced ancillary devices to achieve better post-ESD prognosis.

List Of Abbreviations

Colorectal neoplastic lesions, CRNs Endoscopic submucosal dissection, ESD Laterally spreading tumors, LST.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Beijing Friendship Hospital has approved this retrospective review (2017-P2-047-02). As to the nature of this study, the informed consent was waived.

Consent for publication

Not applicable

Availability of data and materials

The retrospective datasets used and analysed during the current study are available from the corresponding author on reasonable request. In meta-analysis part, the published literatures are available in Pubmed, EMBASE, Cochrane library and large bibliographic database in China such as Wanfang MedOnline, China National Knowledge Infrastructure (CNKI) and China Biology Medicine disc (CBMdisc).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors have contributed to and agreed on the content of the manuscript, and each author's contribution is as follows

GY : Study design, data collection, statistical analysis and drafting paper

JW: Study design, data collection, statistical analysis and drafting paper

ZHH: Study design and revising paper;

XJJ: Data collection and figure editing;

WSS: Statistical analysis;

ZST: Study design, revising the manuscript and making final decision to submit it.

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Figures

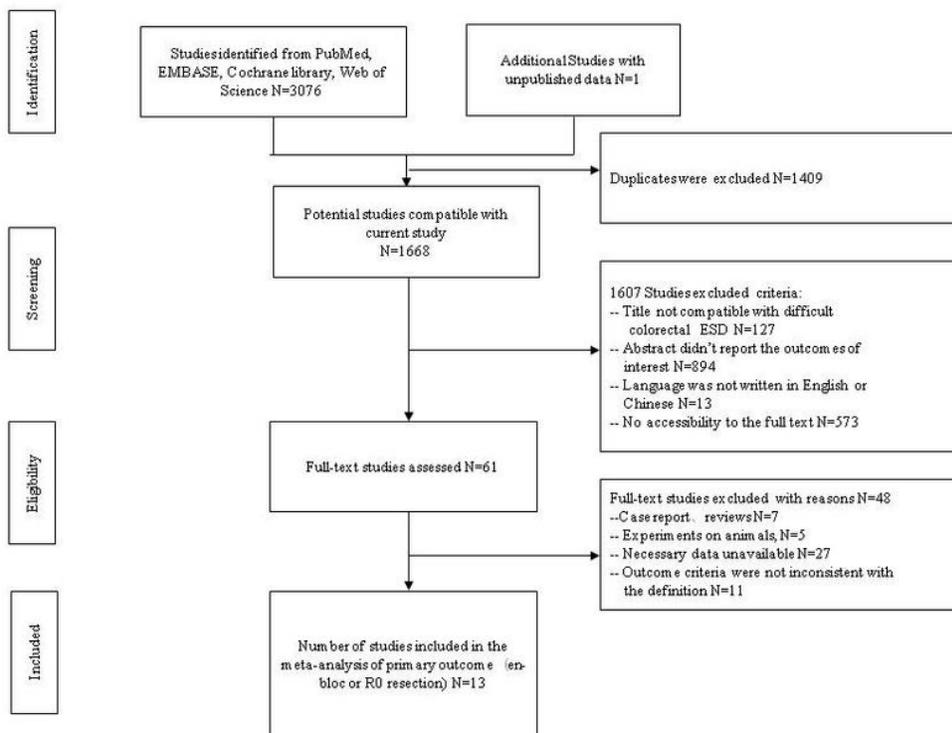


Figure 1

Flow chart on the selection of studies.

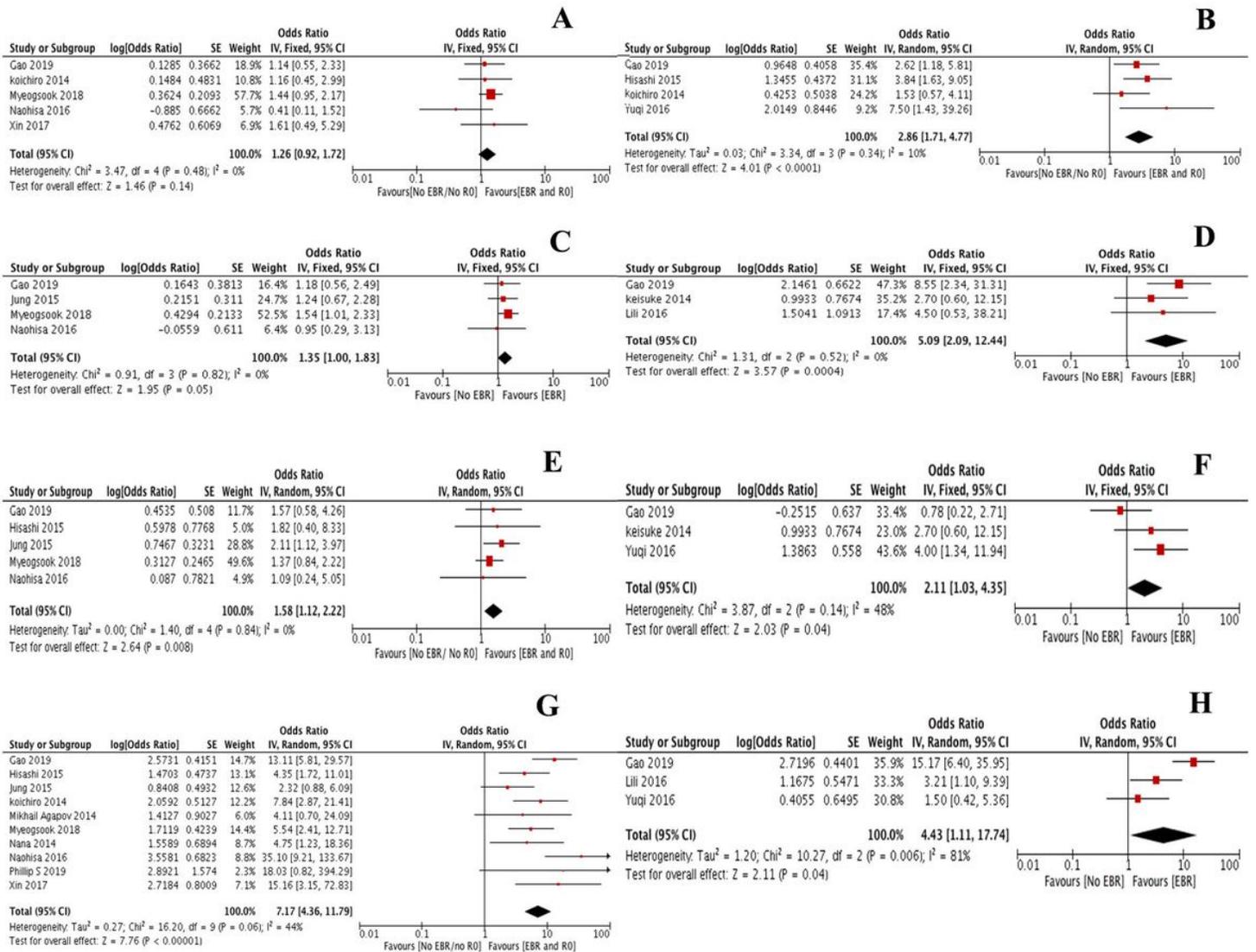


Figure 2

Forest Plot of pre- and perioperative factors for non en-bloc resection or R0 resection: A. Gender; B. Diameter; C. Location; D. Bauhin's valve/Dentate line; E. Morphology; F. Flexure; G. Fibrosis; H. Non-lifting sign.

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