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REVIEW ARTICLE

Endoscopic submucosal dissection for early neoplastic lesions in the surgically altered stomach: a systematic review and meta-analysis

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Abstract

Introduction and aim Endoscopic submucosal dissection (ESD) for early gastric cancer is highly effective and well established. Performing ESD in the surgically altered stomach (SAS) is challenging. The aim of this meta-analysis is to assess the safety and efficacy of ESD for patients with early neoplastic lesions occurring in the SAS with a subgroup analysis of lesions occurring on the suture line compared to non-suture line lesions and outcomes in the remnant stomach compared to the gastric tube.

Methods We performed a literature search of the PubMed, Embase, and CINAHL electronic databases from January 2000 to November 2017 for articles reporting the safety and efficacy of ESD in the surgically altered stomach. SAS was defined as the remnant stomach following gastrectomy and gastric tube following esophagectomy. Meta-analysis was performed using Review Manager version 5.3 software.

Results A total of 21 articles, with 903 lesions occurring in the remnant stomach or gastric tube, were included in this study. There was no significant difference between en bloc (RR 0.99, 95% CI 0.91–1.08), curative resection (RR 1.03, 95% CI 0.84–1.26), or bleeding rates (RR 1.40, 95% CI 0.18–10.72) between lesions in the remnant stomach and gastric tube. However, perforation was significantly higher in the gastric tube (RR 5.19, 95% 1.27–21.25). Suture line lesions had a significantly higher risk of perforation (RR 4.55, 95% CI 2.13–9.74).

Conclusion ESD for early neoplastic lesions occurring in the SAS is a safe and efficacious with similar en bloc and curative resection rates compared to the anatomically normal stomach. ESD for lesions on the suture line or in the gastric tube is associated with an increased risk of perforation which can be managed endoscopically.

Keywords ESD · Endoscopic submucosal dissection · Early gastric cancer · Remnant stomach · Gastric tube

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Remnant gastric cancer (RGC) comprises nearly 1–2% of all gastric neoplasms [1]. Its incidence, however, is increasing due to the advanced surgical techniques and treatment options which have prolonged survival. Most cases are diagnosed on routine periodic surveillance after gastrectomy [2, 3]. Patients who have undergone previous gastric surgery are at a higher risk of developing remnant gastric cancer [4]. Gastric tube cancer (GTC) occurs in the gastric tube after esophagectomy. One of the distinct features of esophageal cancers is the metachronous cancer occurring in other organs with an incidence rate of 12% [5, 6].

Endoscopic resection is a widely accepted modality of treatment for early gastric cancer with low risk of lymph node metastasis [7]. Endoscopic submucosal dissection (ESD) has replaced traditional endoscopic mucosal resection

(EMR) as it allows for en bloc resection of lesions as a single piece with intact margins for evaluation of complete and subsequently curative resection [8]. ESD also allows the resection of larger more irregular lesions in addition to lesions that have minimal submucosal invasion (sm1) [9]. However, there is a slight increase in perforation risk with ESD compared to EMR [10].

Total gastrectomy is associated with a higher morbidity and mortality in the remnant stomach and gastric tube [11]. Endoscopic resection, primarily ESD, is a promising therapy for the resection of early gastric cancer occurring in the remnant stomach and gastric tube. Several studies evaluating its efficacy have shown preliminary results that are similar to results in the anatomically normal stomach. In the surgically altered stomach, the limited workspace available makes ESD more challenging. Lesions occurring on the suture line or anastomosis site are also more difficult to resect en bloc due to increased fibrosis, adhesions, and staples.

Optimal treatment for early gastric neoplasms occurring in the surgically altered stomach remains unknown. In this meta-analysis, we aimed to assess the efficacy and safety of ESD for early gastric neoplasms occurring in the surgically altered stomach.

Methods

Definitions

Remnant stomach (gastric stump)

The portion of stomach remaining following Billroth I or II partial or subtotal gastrectomy (partial or distal).

Gastric tube

The reconstructed stomach after esophagectomy.

En bloc resection

Single piece resection of neoplastic lesion.

Complete resection

En bloc resection with vertical and horizontal margins free of neoplasm.

Curative resection

Complete resection with no evidence of neoplastic lymphovascular invasion [12].

Search strategy

We performed a systematic and comprehensive review of three electronic reference databases (Medline, Embase, and CINAHL) for studies that reported one or more outcomes of ESD for early gastric neoplasm in the surgically altered stomach (remnant stomach and/or gastric tube). The search was restricted to human studies published in any language. Major conference and meeting abstracts were included in the search. Articles were compiled into a database, duplicates were removed and abstracts were then screened for relevance. In addition, the references of relevant trials and reviews were hand-searched. Reference lists of the retrieved literature were cross searched manually for additional publications.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The search strategy was developed from inception through December 10, 2017. Search terms included "early gastric cancer," "endoscopic submucosal dissection," "submucosal invasion," "remnant stomach," "remnant gastric cancer," "gastric stump," "gastric tube," "gastric tube cancer," and "gastric conduit."

The study received institutional review board (IRB) exemption by the hospital IRB committee as the study authors collected data from previous clinical trials in which informed consent had already been obtained by the trial investigators.

Selections of studies

Inclusion and exclusion criteria

Inclusion criteria: Studies (randomized, prospective observational, and retrospective observational) were eligible for inclusion in the meta-analysis if they met the following criteria: (1) Patients included in the study were diagnosed with early neoplastic lesions (EGC or adenoma) by histopathology and underwent ESD. (2) ESD for early neoplastic lesions was performed in the remnant stomach or in the gastric tube. (3) Sufficient data were presented on any one of the following outcomes; en bloc resection, complete resection, curative resection, perforation rate, or bleeding rate.

Data extraction and study quality assessment

Data from the studies included were extracted independently by two reviewers (M. B. and M. S.) on data collection sheets. Details extracted from each article included study design, country, year of publication, patient demographics, en bloc resection rates, complete resection rates,

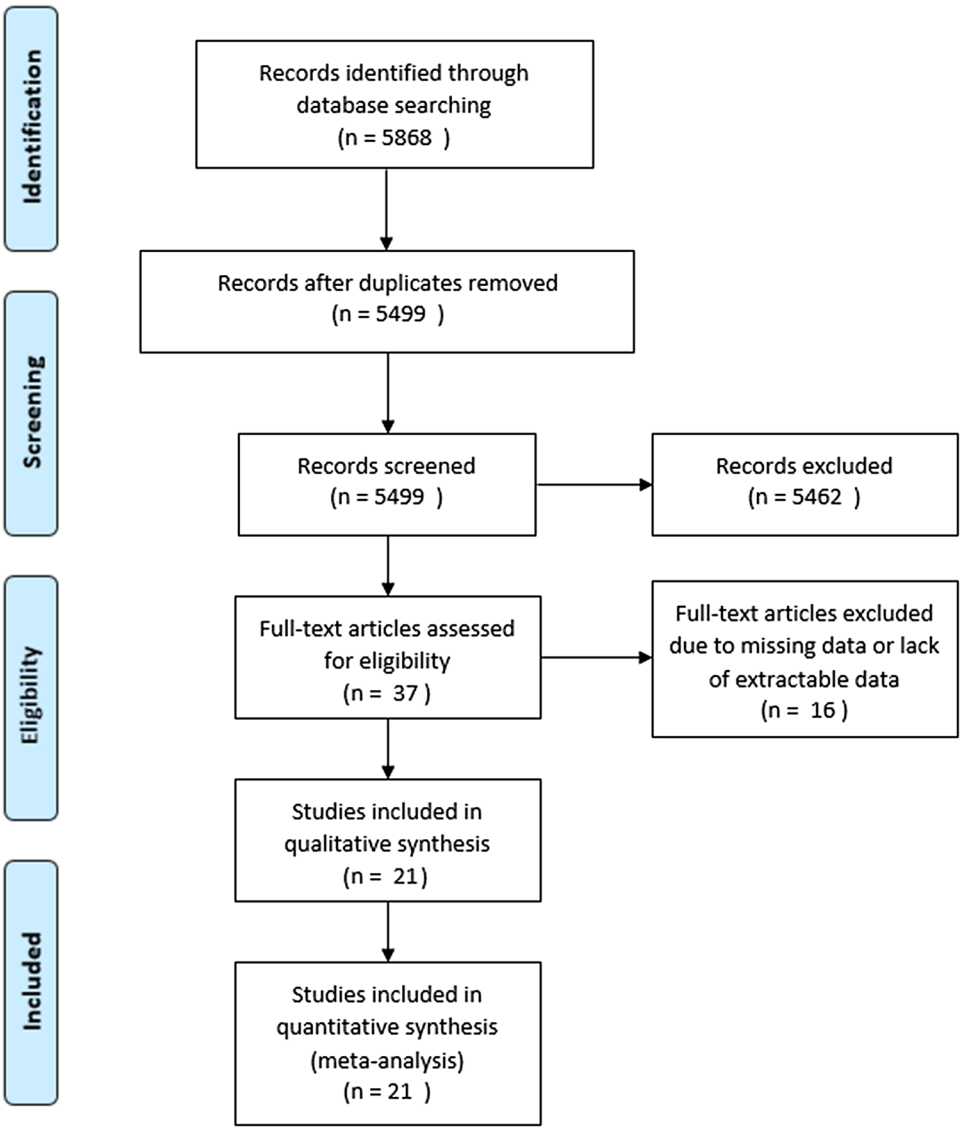


Fig. 1 PRISMA diagram

curative resection rates, perforation rates, and bleeding rates. The two investigators independently assessed study quality using the Newcastle–Ottawa scale for cohort studies, to avoid bias. In the case of disagreement, a third investigator made a consensus decision "M.O."

Statistical analysis

Meta-analysis was conducted using Review Manage (RevMan) 5.3 software (Cochrane Collaboration) and Comprehensive Meta-Analysis Software (version 3.3.070; Biostat Inc, Englewood, NJ, USA). Relative risk was used to compare the outcomes of interest for lesions occurring on the suture line compared to non-suture line lesions. Relative risk was used to compare the outcomes of interest between lesions occurring in the remnant stomach and the gastric tube. Confidence interval (CI) of 95% and a p value of < 0.05 was considered significant. In order to provide an approximation of the overall, remnant gastric cancer and gastric tube cancer en bloc resection rate, complete resection rate, curative resection rate, bleeding and perforation rates, pooling proportions from raw cells with Freeman–Tukey double arcsine transformation and exact confidence intervals for the individual studies were utilized using the random-effects model.

Author, year, country	Study design	Operation years	Type of surgery	Gender M/F	Age (mean or median)	Lesion size (mm, mean)	En bloc resection (%)	Complete resection (%)	Curative resection (%)
Song[14], 2017, Korea	Retrospective	2006 - 2016	Distal gastrectomy & esophagectomy	24/5	69 (44–80)	15 (5–40)	28/31 (90)	24/31 (77)	22/31 (71)
Jung[15], 2016, Korea	Retrospective	NA	Subtotal gastrectomy	NA	NA	NA	20/20 (100)	19/20 (95)	16/20 (80)
Lee J[16], 2016, Korea	Retrospective	2007 - 2013	Gastrectomy	17/1	72 (52–81)	13 (4–22)	16/18 (89)	16/18 (89)	11/12 (92)
Mukasa[17], 2015, Japan	Retrospective	2007 - 2012	Esophagectomy	12/1	70.5 (65-78)	26.1 (10-68)	11/11 (100)	NA	NA
Nishimura[18], 2014, Japan	Retrospective	2006 - 2012	Distal & proximal gastrectomy, esophagectomy	21/2	71.4	NA	NA	19/23 (83)	16/23 (70)
Niwa[19], 2014, Japan	Retrospective	2003 - 2013	Distal gastrectomy	16/5	67.1 ± 11.2	13 (4-45)	20/24 (83)	NA	16/24 (67)
Nonaka[20], 2014, Japan	Retrospective	1998 - 2011	Esophagectomy	47/4	67.4 ± 6.7	15 (3-50)	73/79 (92)	59/79 (75)	51/79 (65)
Ojima[21], 2014, Japan	Retrospective	2002 -2013	Distal, proximal & partial gastrectomy, esophagectomy	36/7	70 (47–84)	11 (1 – 25)	49/49 (100)	42/49 (86)	40/49 (82)
Suzuki[22], 2014, Japan	Retrospective	1999 - 2012	NA	NA	NA	NA	NA	NA	NA
Tanaka[23], 2014, Japan	Retrospective	2008 - 2012	Gastrectomy	12/20	NA	NA	33/33 (100)	31/33 (94)	31/33 (94)
Tawaraya[24], 2014, Japan	Retrospective	2004 - 2012	Esophagectomy	13/2	70 (61-79)	18.6 (5-42)	16/16 (100)	16/16 (100)	14/16 (88)
Lee[25], 2013, Korea	Retrospective	2007 - 2012	NA	NA	NA	NA	22/23 (96)	16 (70)	15 (65)
Nonaka[26], 2013, Japan	Retrospective	1997 - 2011	Distal, proximal & pylorus-preserving gastrectomy	116/12	69.6 ± 8.9	13 (1-60)	131/139 (94)	118/139 (85)	109/139 (78)
Nishide[27], 2012, Japan	Retrospective	2002 - 2009	Distal gastrectomy and esophagectomy	56 /3	74 (53–84)	22 (5 – 59)	59/62 (95)	53/62 (85)	53/62 (85)
Bamba[28], 2010, Japan	Retrospective	2004 - 2007	Esophagectomy	NA	NA	20.6 (6 -52)	9/10 (90)	9/10 (90)	9/10 (90)
Hoteya[29], 2010, Japan	Retrospective	2005 - 2008	Gastrectomy & esophagectomy	37/3	71.3 (56–81)	18.8 (3–53)	NA	38/40 (95)	32/40 (80)
Lee[30], 2010, Korea	Retrospective	2004 - 2008	Gastrectomy	11/2	63 (39–81)	10 (5–27)	13/13 (100)	12/13 (92)	11/13 (85)
Mochizuki[31], 2009, Japan	Retrospective	2002 - 2007	Distal, proximal & partial gastrectomy	15/2	68 (54-80)	11 (6-28)	16/17 (94)	NA	14/17 (82)
Osumi[32], 2009, Japan	Retrospective	2003 - 2007	Esophagectomy	6m 1f	70.6 (56–80)	NA	7/8 (86)	6/8 (75)	NA
Hirasaki[33], 2008, Japan	Retrospective	1998 - 2007	Distal gastrectomy	N/A	73.1 (64-84)	15.5 ± 5.6	17/17 (100)	14/17 (82)	14/17 (82)
Takenaka[34], 2008, Japan	Retrospective	2001 - 2007	Gastrectomy	27/3	73 (51-87)	NA	30/31 (97)	NA	23/31 (74)

Fig. 2 Study characteristics

Heterogeneity among the studies was assessed with the Chi-square test. p value 0.05 was considered to be significantly heterogeneous. I^2 values 0–40%, 30–60%, 50–90%, and 75–100% were reflective of low, moderate, substantial, and considerable heterogeneity, respectively. Meta-analysis was to be calculated by using a random-effects model. Publication bias for the outcomes of interest was detected by a funnel plot. The symmetry of the funnel plot was confirmed by the Egger test, with a p value of 0.05.

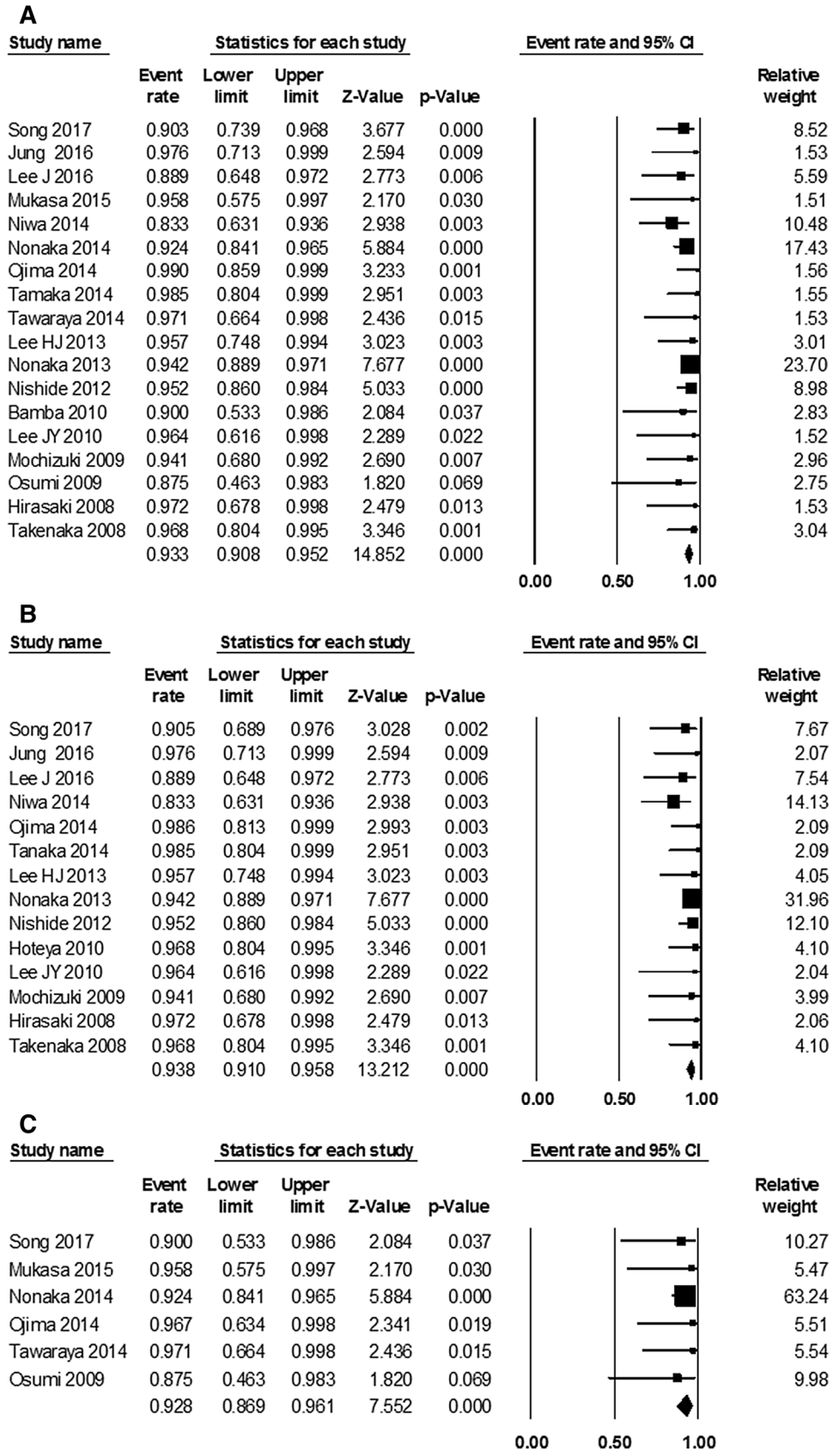


Fig. 3 **A** Overall en bloc resection rate in the surgically altered stomach. **B** Remnant gastric cancer en bloc resection rate. **C** Gastric tube cancer en bloc resection rate

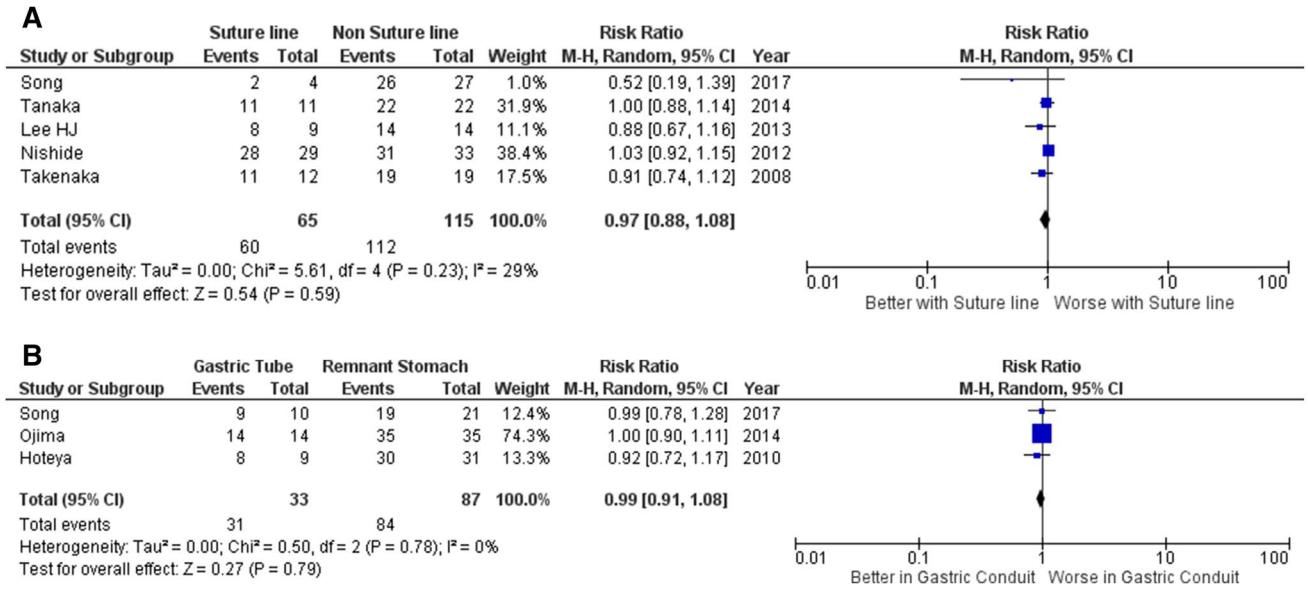


Fig. 4 **A** Suture line versus non-suture line lesion en bloc resection rate. **B** Remnant gastric cancer versus gastric tube en bloc resection rate

Results

Identification of studies and study characteristics

Our search yielded 5499 studies, of which 5462 studies were excluded after abstract or method, and result sections were reviewed. After reviewing a total of 37 full-text articles, 16 articles were excluded due to missing data on outcomes of ESD in the surgically altered stomach (Fig. 1). The final analysis included 21 studies (all retrospective), with a total of 903 neoplastic lesions [14–34]. Among the 21 studies included in the analysis, 16 were published articles while five were major conference abstracts (Fig. 2). The studies originated from Japan and Korea.

Study outcomes

En bloc resection rate

Eighteen studies included data on en bloc resection rates. The overall en bloc resection rate for 601 lesions treated with ESD in the surgically altered stomach was 0.93 (95% CI 0.91–0.95) (Fig. 3A). The en bloc resection rate for 14 studies (484 lesions) with data on remnant gastric neoplasms treated with ESD was 0.94 (95% CI 0.91–0.96) (Fig. 3B). The en bloc resection rate for six studies (138 lesions) with data on gastric tube neoplasms treated with ESD was 0.93 (95% CI 0.87–0.96) (Fig. 3C). There was no difference in the en bloc resection rates of lesions occurring on the suture line (60/65) compared to non-suture line lesions (112/115) (RR 0.97, 95% CI 0.88–1.08) (Fig. 4A). There was no difference in the en bloc resection rates of lesions occurring in the remnant stomach (84/87) compared to the gastric tube (31/33) (RR 0.99, 95% CI 0.91–1.08) (Fig. 4B).

Complete resection rate

Sixteen studies included data on complete resection rates. The overall complete resection rate for 581 lesions treated with ESD in the surgically altered stomach was 0.84 (95% CI 0.80–0.87) (Fig. 5A). The complete resection rate for 11 studies (412 lesions) with data for remnant gastric neoplasm treated with ESD was 0.85 (95% CI 0.80–0.89) (Fig. 5B). The complete resection rate for seven studies (146 lesions) with data for gastric tube neoplasm treated with ESD was 0.79 (95% CI 0.71–0.85) (Fig. 5C). There was no difference in the complete resection rates of lesions occurring on the suture line (53/73) compared to non-suture line lesions (137/156) (RR 0.87, 95% CI 0.76–1) (Fig. 6A). There was no difference in the complete resection rates of lesions occurring in the remnant stomach (46/56) compared to the gastric tube (20/24) (RR 1.02, 95% CI 0.82–1.26) (Fig. 6B).

Curative resection rate

Eighteen studies included data on curative resection rates. The overall curative resection rate for 645 lesions treated with ESD in the surgically altered stomach was 0.78 (95% CI 0.73–0.82) (Fig. 7A). The curative resection rate for 14 studies (478 lesions) with data for remnant gastric neoplasm treated with ESD was 0.79 (95% CI 0.75–0.82) (Fig. 7B). The curative resection rate for five studies (128 lesions) with

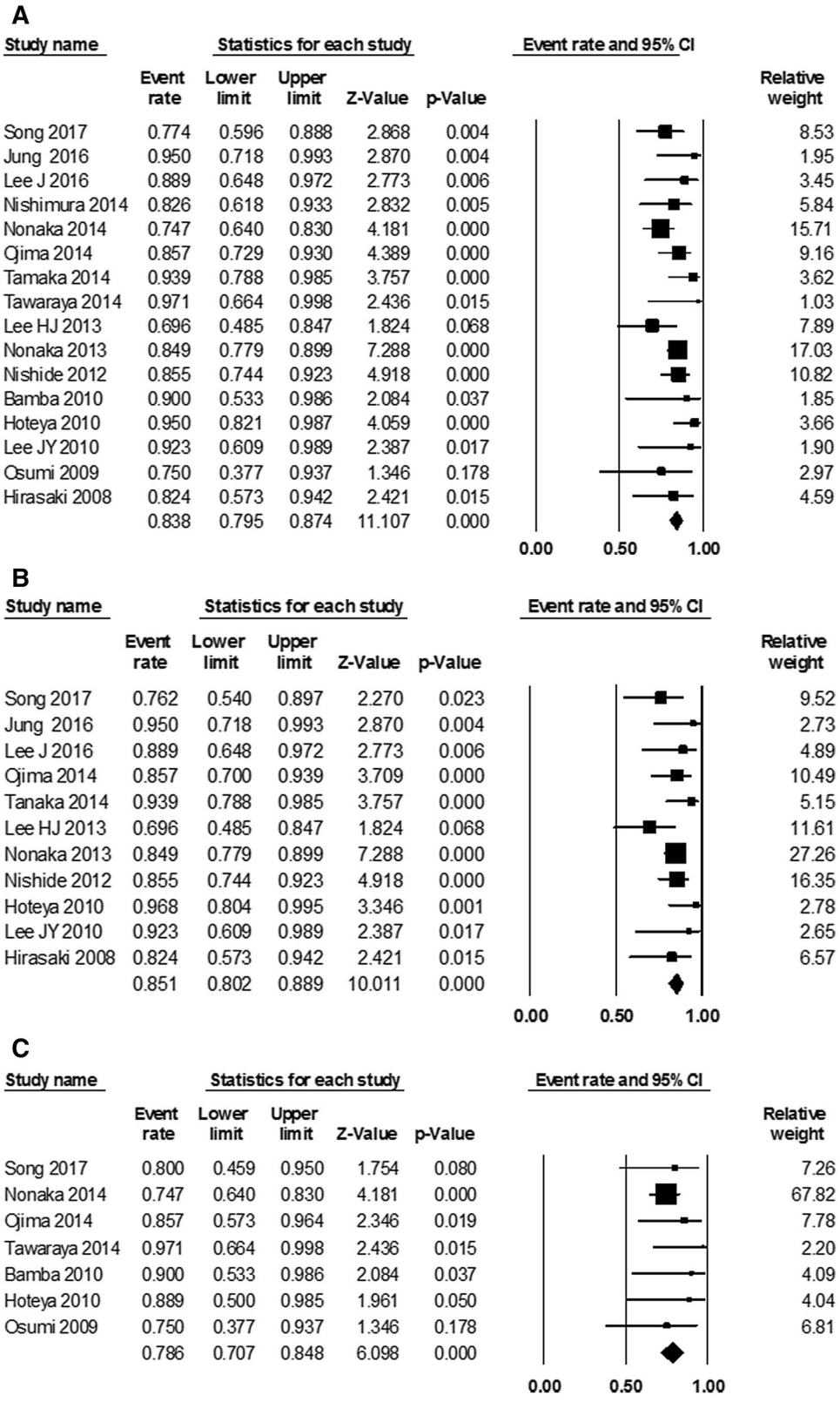


Fig. 5 **A** Overall complete resection rate in the surgically altered stomach. **B** Remnant gastric cancer complete resection rate. **C** Gastric tube cancer complete resection rate

data for gastric tube neoplasm treated with ESD was 0.73 (95% CI 0.61–0.82) (Fig. 7C). There was no difference in the curative resection rates of lesions occurring on the suture line (14/23) compared to non-suture line lesions (67/80) (RR 0.74, 95% CI 0.35–1.56) (Fig. 8A). There was no difference in the curative resection rates of lesions occurring in

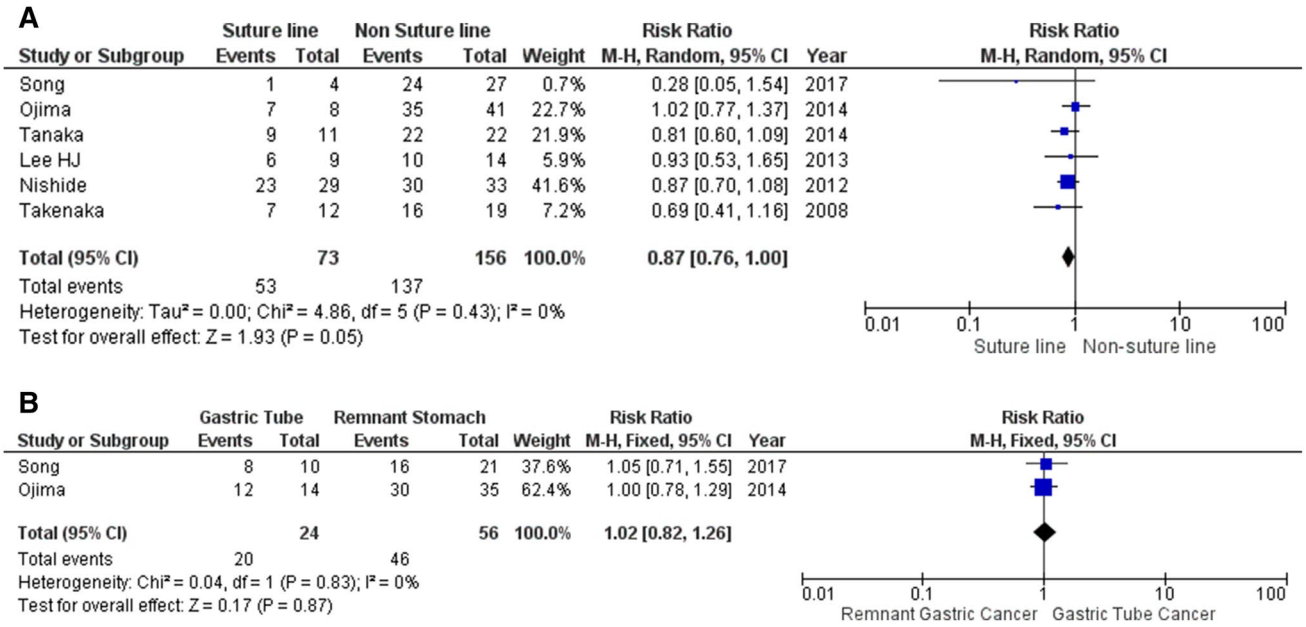


Fig. 6 **A** Suture line versus non-suture line lesion complete resection rate. **B** Remnant gastric cancer versus gastric tube complete resection rate

the remnant stomach (68/87) compared to the gastric tube (26/33) (RR 1.03, 95% CI 0.84–1.26) (Fig. 8B).

Bleeding rate

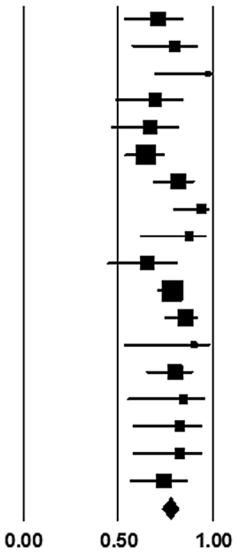
Twenty studies included data on bleeding rates. The overall bleeding rate for 664 lesions treated with ESD in the surgically altered stomach was 0.05 (95% CI 0.03–0.09) (Fig. 9A). The bleeding rate for 13 studies (453 lesions) with data for remnant gastric neoplasm treated with ESD was 0.05 (95% CI 0.03–0.08) (Fig. 9B). The bleeding rate for seven studies (148 lesions) with data for gastric tube neoplasm treated with ESD was 0.09 (95% CI 0.03–0.27) (Fig. 9C). There was no difference in the bleeding rates of lesions occurring on the suture line compared (4/67) to non-suture line lesions (4/113) (RR 1.97, 95% CI 0.47–8.87) (Fig. 10A). There was no difference in the bleeding rates of lesions occurring in the remnant stomach (2/56) compared to the gastric tube (1/24) (RR 1.40, 95% CI 0.18–10.72) (Fig. 10B).

Perforation rate

Twenty-one studies included data on perforation rates. The overall perforation rate for 903 lesions treated with ESD in the surgically altered stomach was 0.06 (95% CI 0.04–0.09) (Fig. 11A). The perforation rate for 14 studies (692 lesions) with data for remnant gastric neoplasm treated with ESD was 0.06 (95% CI 0.03–0.10) (Fig. 11B). The perforation rate for seven studies (148 lesions) with data for gastric tube neoplasm treated with ESD was 0.09 (95% CI 0.04–0.19) (Fig. 11C). There was a statistically significant increase in perforation rates of lesions occurring on the suture line (19/75) compared to non-suture line lesions (7/154) (RR 4.55, 95% CI 2.13–9.74) (Fig. 12A). There was a statistically significant increase in the perforation rate for lesions occurring in the gastric tube (5/24) compared to the remnant stomach (2/56) (RR 5.19, 95% CI 1.27–21.25) (Fig. 12B).

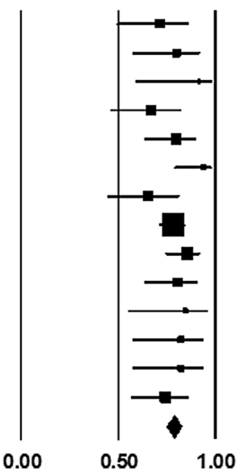
A

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Song 2017	0.710	0.530	0.841	2.259	0.024	6.94
Jung 2016	0.800	0.572	0.923	2.480	0.013	4.20
Lee J 2016	0.974	0.690	0.998	2.519	0.012	0.78
Nishimura 2014	0.696	0.485	0.847	1.824	0.068	5.76
Niwa 2014	0.667	0.461	0.824	1.601	0.109	6.14
Nonaka 2014	0.646	0.535	0.743	2.549	0.011	12.02
Ojima 2014	0.816	0.683	0.902	4.043	0.000	7.59
Tamaka 2014	0.939	0.788	0.985	3.757	0.000	2.70
Tawaraya 2014	0.875	0.614	0.969	2.574	0.010	2.54
Lee HJ 2013	0.652	0.443	0.816	1.436	0.151	6.05
Nonaka 2013	0.784	0.708	0.845	6.258	0.000	13.25
Nishide 2012	0.855	0.744	0.923	4.918	0.000	7.80
Bamba 2010	0.900	0.533	0.986	2.084	0.037	1.39
Hoteya 2010	0.800	0.648	0.897	3.507	0.000	6.95
Lee JY 2010	0.846	0.549	0.961	2.218	0.027	2.47
Mochizuki 2009	0.824	0.573	0.942	2.421	0.015	3.41
Hirasaki 2008	0.824	0.573	0.942	2.421	0.015	3.41
Takenaka 2008	0.742	0.563	0.865	2.573	0.010	6.61
	0.775	0.728	0.816	9.607	0.000	



B

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Song 2017	0.714	0.492	0.866	1.897	0.058	5.71
Jung 2016	0.800	0.572	0.923	2.480	0.013	4.26
Lee J 2016	0.917	0.587	0.988	2.296	0.022	1.22
Niwa 2014	0.667	0.461	0.824	1.601	0.109	7.11
Ojima 2014	0.800	0.636	0.902	3.281	0.001	7.46
Tanaka 2014	0.939	0.788	0.985	3.757	0.000	2.50
Lee HJ 2013	0.652	0.443	0.816	1.436	0.151	6.95
Nonaka 2013	0.784	0.708	0.845	6.258	0.000	31.34
Nishide 2012	0.855	0.744	0.923	4.918	0.000	10.25
Hoteya 2010	0.806	0.631	0.910	3.139	0.002	6.45
Lee JY 2010	0.846	0.549	0.961	2.218	0.027	2.25
Mochizuki 2009	0.824	0.573	0.942	2.421	0.015	3.29
Hirasaki 2008	0.824	0.573	0.942	2.421	0.015	3.29
Takenaka 2008	0.742	0.563	0.865	2.573	0.010	7.91
	0.787	0.747	0.823	11.325	0.000	



C

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Song 2017	0.700	0.376	0.900	1.228	0.220	13.42
Nonaka 2014	0.646	0.535	0.743	2.549	0.011	53.50
Ojima 2014	0.857	0.573	0.964	2.346	0.019	11.27
Tawaraya 2014	0.875	0.614	0.969	2.574	0.010	11.47
Hoteya 2010	0.778	0.421	0.944	1.562	0.118	10.35
	0.729	0.611	0.822	3.603	0.000	

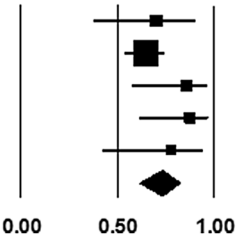


Fig. 7 **A** Overall curative resection rate in the surgically altered stomach. **B** Remnant gastric cancer curative resection rate. **C** Gastric tube cancer curative resection rate

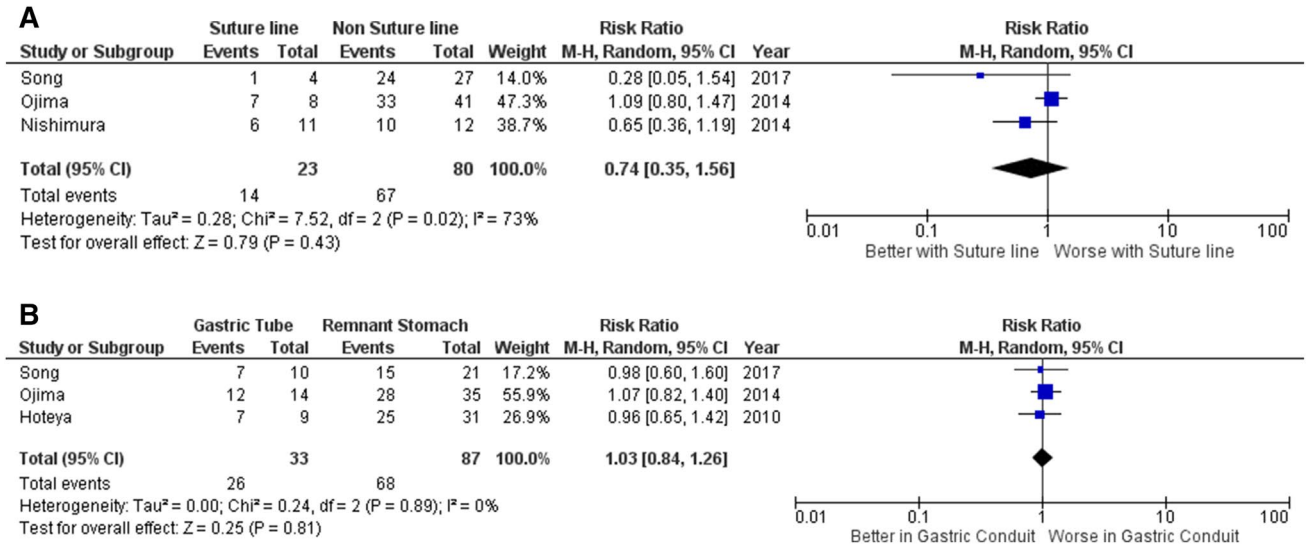


Fig. 8 **A** Suture line versus non-suture line lesion curative resection rate. **B** Remnant gastric cancer versus gastric tube curative resection rate

Discussion

In our meta-analysis, we found that ESD for early gastric neoplastic lesions in the SAS had high en bloc, complete and curative resection rates, similar to previously published outcomes in the unaltered stomach. In our analysis of adverse events, we found bleeding rates to be similar, however, the perforation rates were slightly higher in the surgically altered stomach, especially in the gastric tube when compared to results of previously published cohorts. Perforation remains one of the most crucial complications of ESD, whether it is performed in the normal or surgically altered stomach. Most ESD-related perforations can be treated endoscopically with very few requiring surgical intervention.

We noted that the en bloc, complete, and curative resection rates were not statistically significant when comparing lesions that occurred on the suture line versus non-suture line lesions in the surgically altered stomach. While bleeding events were not statistically significant, we found an increase in the risk of perforation when ESD was performed for lesions occurring on the suture line in the surgically altered stomach. As expected, suture lines are associated with fibrosis which is less amenable to manipulation leading to an increase in the risk of perforation [35].

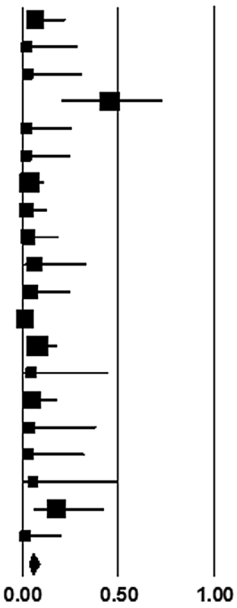
In our comparison between the safety and efficacy of ESD for neoplastic lesions occurring in the remnant stomach or gastric tube, we did not find a significant difference between en bloc, complete, or curative resection rates. There was no difference in bleeding rates, however, there was a statistical significance in perforation rates occurring in the gastric tube compared to the remnant stomach. The gastric tube involves a larger number of sutures and suture lines which are known to increase the technical difficulty of ESD and could potentially lead to viscous organ perforations.

Previous studies evaluating the outcomes of total gastrectomy for remnant gastric cancer have reported high mortality rates (19–59%). Mortality of surgical removal of gastric tube cancers in the reconstructed gastric tube were reported to be 24–33% [11, 20]. These high mortality rates make ESD a favorable alternative given the limited morbidity and mortality owing to the procedures minimal invasiveness [36–38]. While there is limited data available on the survival rate of RGC or GTC treated with ESD, the current literature supports a 100% disease-specific survival rate at 5 years [20, 26]. Local recurrence has also been reported to be minimal to non-existent in RGC treated with ESD [14, 16, 33].

The incidence of lymph node metastasis (LNM) in RGC and GTC remains a considerable challenge which must be considered during the treatment of these tumors with ESD

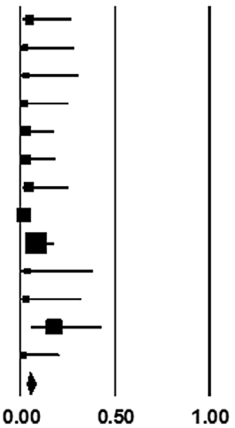
A

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Song 2017	0.065	0.016	0.224	-3.658	0.000	6.93
Jung 2016	0.024	0.001	0.287	-2.594	0.009	2.89
Lee J 2016	0.026	0.002	0.310	-2.519	0.012	2.88
Mukasa 2015	0.455	0.203	0.732	-0.301	0.763	8.20
Nishimura 2014	0.021	0.001	0.259	-2.694	0.007	2.90
Niwa 2014	0.020	0.001	0.251	-2.724	0.006	2.90
Nonaka 2014	0.038	0.012	0.111	-5.491	0.000	8.38
Ojima 2014	0.020	0.003	0.131	-3.831	0.000	4.78
Tanaka 2014	0.030	0.004	0.186	-3.413	0.001	4.75
Tawaraya 2014	0.063	0.009	0.335	-2.622	0.009	4.65
Lee HJ 2013	0.043	0.006	0.252	-3.023	0.003	4.71
Nonaka 2013	0.014	0.004	0.056	-5.934	0.000	7.11
Nishide 2012	0.081	0.034	0.180	-5.218	0.000	9.79
Bamba 2010	0.045	0.003	0.448	-2.103	0.035	2.84
Hoteya 2010	0.050	0.013	0.179	-4.059	0.000	6.98
Lee JY 2010	0.036	0.002	0.384	-2.289	0.022	2.86
Mochizuki 2009	0.028	0.002	0.322	-2.479	0.013	2.88
Osumi 2009	0.056	0.003	0.505	-1.947	0.052	2.81
Hirasaki 2008	0.176	0.058	0.427	-2.421	0.015	7.87
Takenaka 2008	0.016	0.001	0.206	-2.907	0.004	2.91
	0.053	0.032	0.088	-10.499	0.000	



B

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Song 2017	0.048	0.007	0.271	-2.924	0.003	6.02
Jung 2016	0.024	0.001	0.287	-2.594	0.009	3.09
Lee J 2016	0.026	0.002	0.310	-2.519	0.012	3.08
Niwa 2014	0.020	0.001	0.251	-2.724	0.006	3.10
Ojima 2014	0.029	0.004	0.177	-3.476	0.001	6.14
Tanaka 2014	0.030	0.004	0.186	-3.413	0.001	6.13
Lee HJ 2013	0.043	0.006	0.252	-3.023	0.003	6.05
Nonaka 2013	0.014	0.004	0.056	-5.934	0.000	12.47
Nishide 2012	0.081	0.034	0.180	-5.218	0.000	29.07
Lee JY 2010	0.036	0.002	0.384	-2.289	0.022	3.05
Mochizuki 2009	0.028	0.002	0.322	-2.479	0.013	3.07
Hirasaki 2008	0.176	0.058	0.427	-2.421	0.015	15.62
Takenaka 2008	0.016	0.001	0.206	-2.907	0.004	3.11
	0.049	0.031	0.078	-11.757	0.000	



C

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Song 2017	0.100	0.014	0.467	-2.084	0.037	14.21
Mukasa 2015	0.455	0.203	0.732	-0.301	0.763	20.22
Nonaka 2014	0.038	0.012	0.111	-5.491	0.000	20.46
Ojima 2014	0.033	0.002	0.366	-2.341	0.019	10.28
Tawaraya 2014	0.063	0.009	0.335	-2.622	0.009	14.47
Bamba 2010	0.045	0.003	0.448	-2.103	0.035	10.21
Osumi 2009	0.056	0.003	0.505	-1.947	0.052	10.14
	0.087	0.029	0.236	-3.932	0.000	

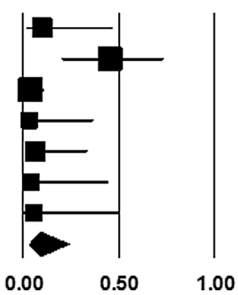


Fig. 9 **A** Overall bleeding rate in the surgically altered stomach. **B** Remnant gastric cancer bleeding rate. **C** Gastric tube cancer bleeding rate

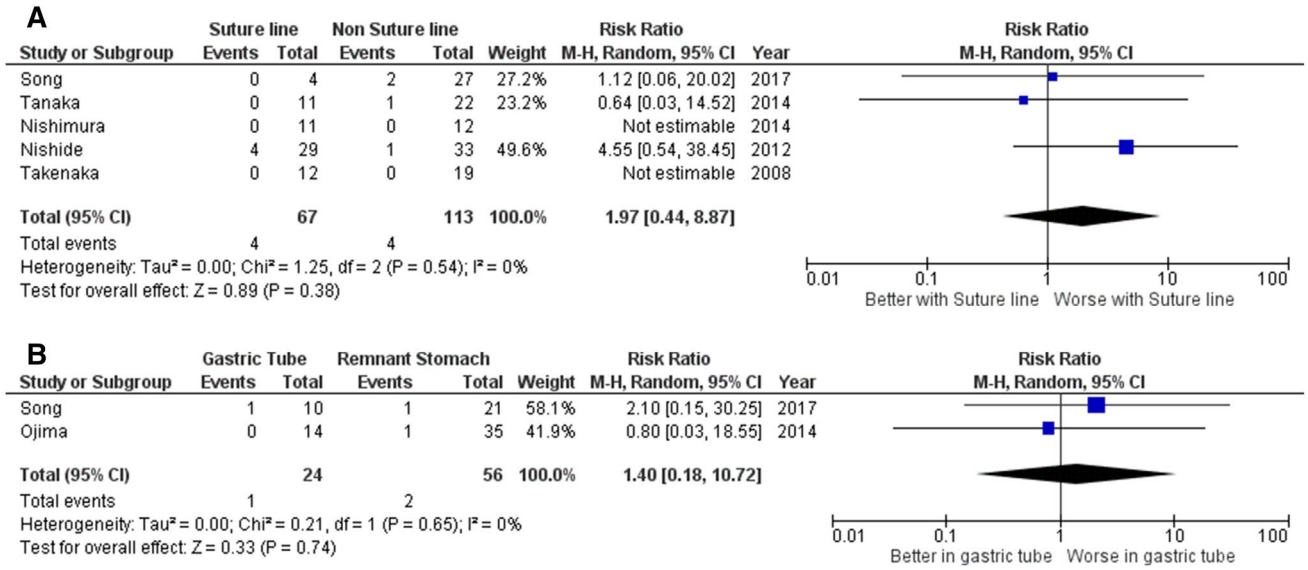


Fig. 10 **A** Suture line versus non-suture line lesion bleeding rate. **B** Remnant gastric cancer versus gastric tube bleeding rate

[39, 40]. Prior surgical intervention for malignant disease with gastrectomy is usually associated with regional lymph node dissection while benign disease is not [41]. Esophagectomy also includes disruption on the lymphatics which can reduce the incidence of lymph node metastasis. These prior surgical interventions seem to be associated with a lower risk of LNM. Currently, the applicability of the JGCA criteria for early gastric cancer occurring in the remnant stomach or the gastric tube remains unknown.

Our study has several limitations. Most endoscopists performing ESD in the cohorts including are experienced with over 2000 procedures each. The applicability of our results may not be generalizable to other endoscopists. These procedures were performed in large and specialized tertiary centers and the patient cohorts originated from Asian countries. These data may limit the use of ESD in similar patients in Western countries. A small number of adenomas (24/903) were included in the analysis which could potentially affect the application of our results to EGC. The strength of our study is the large number of cohorts with a relatively large number of patients included, given the rarity of remnant gastric cancer and gastric tube cancers. We included various types of surgically altered stomachs to reflect the wide variety of surgical interventions performed in practice.

Conclusion

Our results are encouraging as they show that ESD is both safe and efficacious for the treatment of early neoplastic lesions occurring in the remnant stomach or gastric tube. Despite the technical difficulty of ESD in the surgically altered stomach owing to the narrow work space, fibrosis, and sutures, ESD should be considered as a first-line

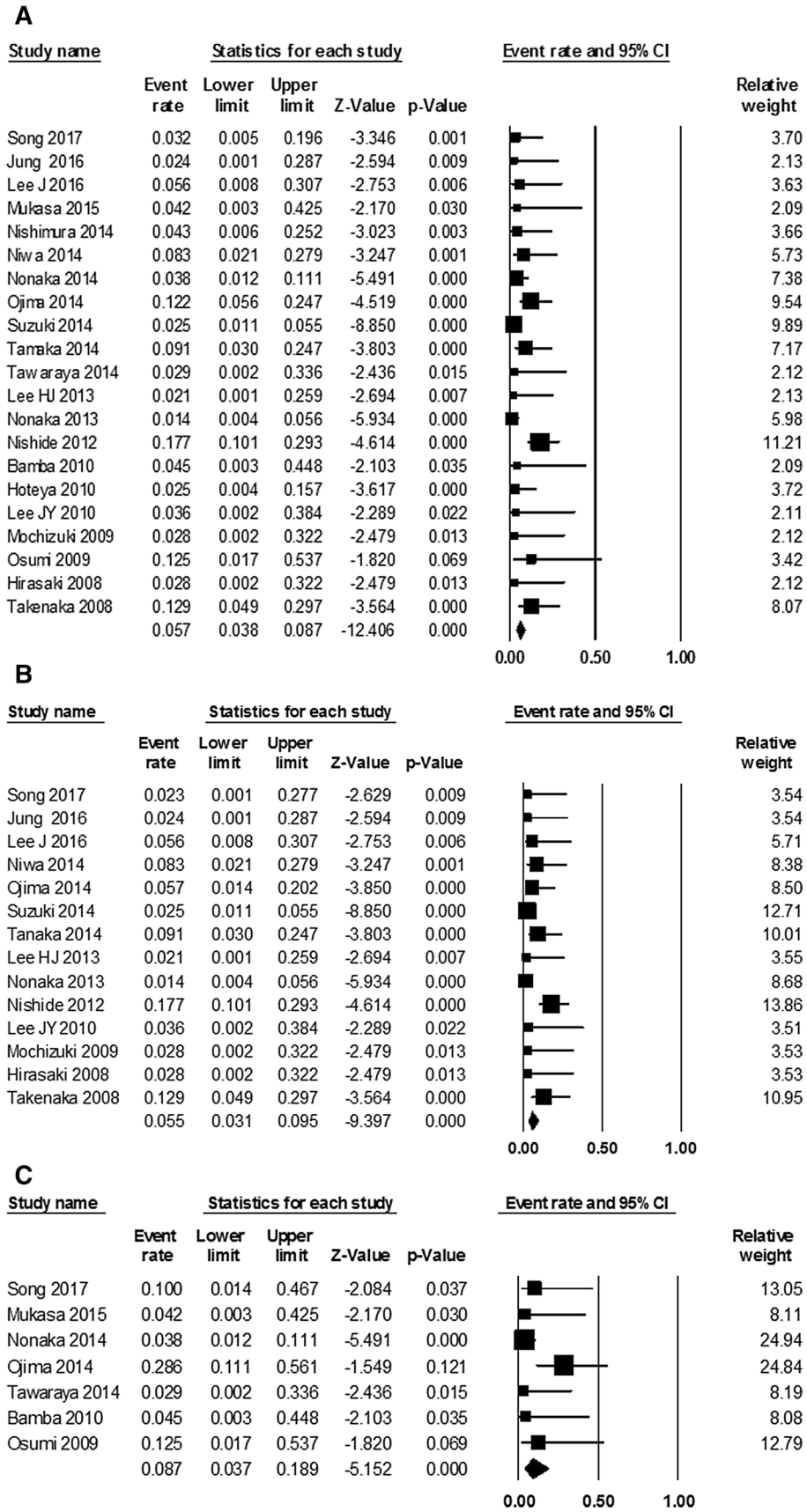


Fig. 11 **A** Overall perforation rate in the surgically altered stomach. **B** Remnant gastric cancer perforation rate. **C** Gastric tube cancer perforation rate

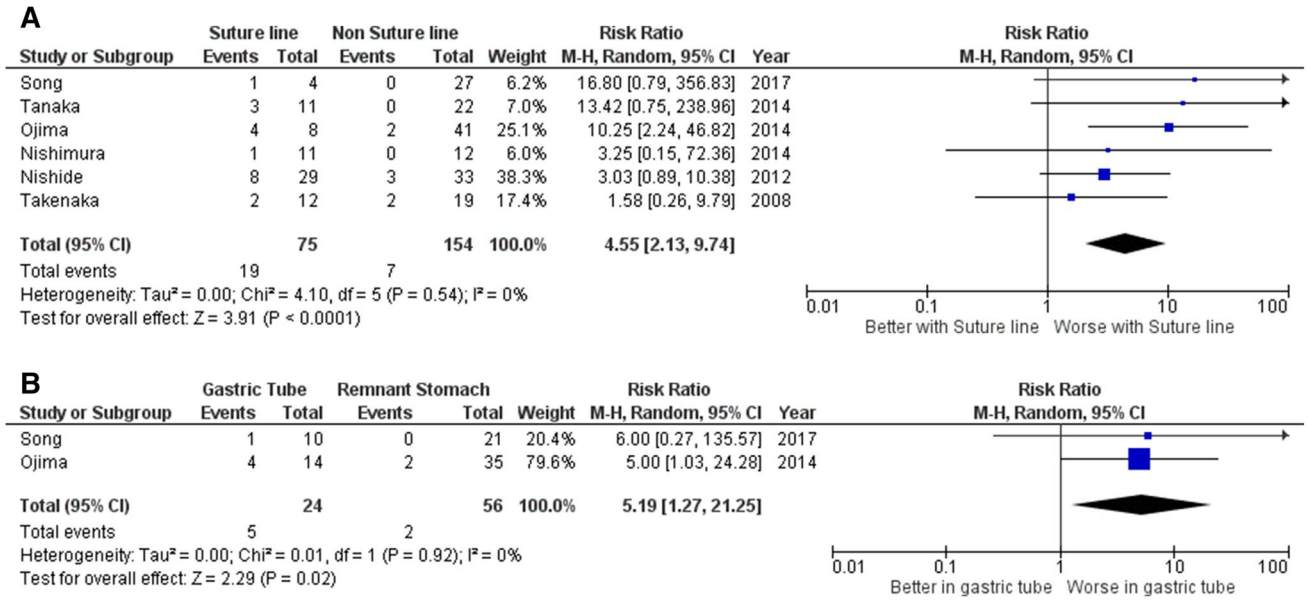


Fig. 12 **A** Suture line versus non-suture line lesion perforation rate. **B** Remnant gastric cancer versus gastric tube perforation rate

treatment when performed by an experienced endoscopist. Special consideration should be given to lesions occurring in the gastric tube or on the suture line.

Author contribution Literature search was performed by MB and MA. Data collection was performed by MB and MS. Data analysis was performed by AO and MB. The manuscript was written by MB. The manuscript was edited and revised by DCL and MO. Overall supervision was done by DCL and MO.

Compliance with ethical standards

Disclosure Dr. David L. Carr-Locke is a consultant for Boston Scientific, Maura Kea Technologies and receives royalties from Telemed and Steris. Dr. Mohamed Othman is a consultant for Boston Scientific and Olympus. Doctors Mohamed Barakat, Mohamed Seif, Mohamed Abdelfatah, and Andrew Ofosu have no conflicts of interest or financial ties to disclose.

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