SYSTEMATIC REVIEWS

Endoscopy *vs* surgery in the treatment of early gastric cancer: Systematic review

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Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at andrekondo@gmail.com. No additional data are available.

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Abstract

AIM: To report a systematic review, establishing the available data to an unpublished 2a strength of evidence, better handling clinical practice.

METHODS: A systematic review was performed using MEDLINE, EMBASE, Cochrane, LILACS, Scopus and CINAHL databases. Information of the selected studies was extracted on characteristics of trial participants, inclusion and exclusion criteria, interventions (mainly, mucosal resection and submucosal dissection *vs* surgical approach) and outcomes (adverse events, different survival rates, mortality, recurrence and complete resection rates). To ascertain the validity of eligible studies, the risk of bias was measured using the Newcastle-Ottawa Quality Assessment Scale. The analysis of the absolute risk of the outcomes was performed using the software RevMan, by computing

risk differences (RD) of dichotomous variables. Data on RD and 95%CIs for each outcome were calculated using the Mantel-Haenszel test and inconsistency was qualified and reported in χ^2 and the Higgins method (I^2). Sensitivity analysis was performed when heterogeneity was higher than 50%, a subsequent assay was done and other findings were compiled.

RESULTS: Eleven retrospective cohort studies were selected. The included records involved 2654 patients with early gastric cancer that filled the absolute or expanded indications for endoscopic resection. Three-year survival data were available for six studies (n = 1197). There were no risk differences (RD) after endoscopic and surgical treatment (RD = 0.01, 95%CI: -0.02-0.05, P = 0.51). Five-year survival data (n = 2310) showed no difference between the two groups (RD = 0.01, 95%CI: -0.01-0.03, P = 0.46). Recurrence data were analized in five studies (1331 patients) and there was no difference between the approaches (RD = 0.01, 95%CI: -0.00-0.02, P = 0.09). Adverse event data were identified in eight studies (n = 2439). A significant difference was detected (RD = -0.08, 95%CI: -0.10--0.05, P < 0.05), demonstrating better results with endoscopy. Mortality data were obtained in four studies (n = 1107). There was no difference between the groups (RD = -0.01, 95%CI: -0.02-0.00, P = 0.22).

CONCLUSION: Three-, 5-year survival, recurrence and mortality are similar for both groups. Considering complication, endoscopy is better and, analyzing complete resection data, it is worse than surgery.

Key words: Gastric cancer; Endoscopy; Gastroscopy; Gastrectomy; Surgery; Systematic review

Core tip: As clinical and oncological outcomes of endoscopic resection of early gastric cancer compared to surgery have not been reported in systematic reviews, this study adds an important value to scientific literature, as it establishes and unifies data regarding this comparison. There are only retrospective cohort studies on this topic (2b evidence-level according to Oxford Centre). This review brings the information to an unpublished 2a strength of evidence, better handling nowadays clinical practice.

INTRODUCTION

Rationale
Almost one million new cases of stomach cancer were estimated to have occurred in 2012 (952000 cases, 6.8% of the total), making it the fifth most common malignancy in the world, after cancers of the lung, breast, colorectum and prostate[1]. Despite advances in diagnosis and treatment, prognosis of gastric cancer remains poor, usually attributed to diagnosis at a late stage.

Early gastric cancer (EGC) was defined by the Japanese Society of Gastroenterological Endoscopy in 1962 as adenocarcinoma involving mucosa or sub-mucosa irrespective of nodal status[2]. While radical gastrectomy can achieve adequate oncological clearance with wide resection margins and lymphadenectomy, it poses significant perioperative morbidities and compromises long-term gastrointestinal function as well as quality of life[3]. With the low risk of lymph node metastasis, methods of endoscopic treatment were pioneered for EGC[4].

According to current guidelines, absolute indi-cation for endoscopic treatment of EGC is defined as moderately or well-differentiated intramucosal adeno-carcinoma that is elevated and smaller than 2 cm in diameter or is depressed and smaller than 1 cm without ulceration[5]. The absolute (standard) indication criteria, however, is so strict that unnecessary sur-geries are likely performed[6]. Therefore, expanded criteria for endoscopic resection was suggested[5] and many reports have shown good results. Gotoda *et al*[6] proposed this criteria: (1) mucosal cancer without ulcer findings, irrespective of tumor size; (2) mucosal cancer with an ulcer $\leqslant$ 3 cm in diameter; and (3) minimal ($\leqslant$ 500 μm from the muscularis mucosa) submucosal invasive cancer $\leqslant$ 3 cm in size.

This study adds an important value to scientific literature as it establishes, unifies and, accordingly, set the available published data regarding the best way to treat ECG.

Objectives
Clinical and oncological outcomes of endoscopic resection in patients with EGC, compared to surgery, have not been reported in systematic reviews.

This systematic review and meta-analyses was developed to address the short- and long-term outcomes of endoscopic resection compared to surgery in the treatment of EGC.

MATERIALS AND METHODS

Protocol and registration
This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses)[7] recommendations. The

review was registered on PROSPERO international database (www.crd.york.ac.uk/prospero/)[8] under number CRD42014015127.

Eligibility criteria

Types of studies: Clinical trials and/or observational studies of adequate quality; Types of participants: Patients with EGC; Types of intervention: Endoscopic treatment and surgery; Types of outcome measures: Basically, procedure-related adverse event, short- and long-term survival rates.

Information sources

Studies were identified searching electronic databases and scanning reference lists of the selected articles. No limits were initially applied for language. This search was applied for Medline and EMBASE (considering all years), Cochrane and LILACS (*via* BVS), Scopus and CINAHL (*via* EBSCO). The last manual search was run on January, 20th, 2015 and automatic updates were evaluated for new studies monthly until April, 2015 for Medline.

Search

The following search strategy, stratified by the components Population (P), Intervention (I) and Comparison (C), based on MeSH terms, was first used for MEDLINE, named MAINMEDLINE for abbreviation purposes: P: "{[Gastric cancer (MeSH)] OR [(Adeno-carcinoma OR Carcinoma OR Early Detection of Cancer OR Carcinoma in Situ OR Polyps) AND (Stomach OR Gastric)] OR [(Gastric Mucosa OR Early Diagnosis) AND (Gastric Cancer)]} AND I: [Endoscopy (MeSH) OR Endoscopy, Digestive System (MeSH) OR Endoscopy, Gastrointestinal (MeSH)] AND C: [Gastrectomy (MeSH) OR Digestive System Surgical Procedures (MeSH) OR Surgery (Subheading) OR General Surgery (MeSH) OR Minimally Invasive Surgical Procedures (MeSH)]".

Aiming high quality studies, MAINMEDLINE was filtered twice (#1 and #2): #1 "(MAINMEDLINE AND random*)"; and #2 "(MAINMEDLINE AND therapy/broad [filter])". The totality of articles was obtained mixing the investigation in the Pubmed Advanced Search Builder: "(#1 OR #2)." The Medline search strategies were peer reviewed (Kondo A and Bernardo WM).

The EMBASE search was: "[(gastric cancer AND endoscopy AND surgery) AND ("clinical trial" OR "controlled study" OR "major clinical study" OR "prospective study" OR "retrospective study")]". For Cochrane, LILACS, Scopus and CINAHL, the search was: "(gastric cancer AND endoscopy AND surgery)".

Study selection

Eligibility assessment and the selection of screened records were performed independently in an unblinded standardized manner by the reviewers. Disagreements were resolved by consensus.

Data collection process

The method of data extraction consisted of filling out information sheets. A Scottish Intercollegiate Guidelines Network (SIGN)[9] based checklist was used. Relevant data were extracted from each included study using a standardized extraction form. Extracted data were double checked by the reviewers. Disagreements were resolved by discussion.

Data items

Information was extracted on: (1) characteristics of trial participants (including age and pattern of different types of EGC), trials' inclusion and exclusion criteria, length of follow-up; (2) interventions (considering different modalities in endoscopic treatment, mainly mucosal resection and submucosal dissection; *vs* surgical approach: tailored gastrectomy and respective lymphadenectomy, if necessary, according to tumor stage); and (3) outcomes (adverse events, different survival rates, mortality, recurrence and complete resection rates).

Overall 3- and 5-year survival rates included patients alive in these analyzed follow-up periods, despite the presence or absence of cancer.

Treatment-related morbidity and adverse events include any adverse procedure-related implication.

Complete resection was considered the total removal of gastric cancer, using surgical or endoscopic approach, with no residual viable cell on the local procedure lay.

Recurrence was characterized by the reappearance of gastric cancer after its treatment, and after a period of no clinical or imagenological detection. It was considered both local and distant recurrence for analysis. Metachronous gastric cancer was not considered in this set.

Mortality data are based on procedure-related death.

Statistical analysis

Risk of bias in individual studies: To ascertain the validity of eligible studies, the reviewers measured the risk of bias using the Newcastle-Ottawa Quality Assessment Scale[10] for cohort studies and the Scottish Intercollegiate Guidelines Network checklist[9]. The critical evaluation of the included trials should reveal a score $\geq$ 6, total of 9 highest possible score. The levels of evidence according to the Oxford Centre for Evidence-based Medicine[11] (2009 classification) were obtained.

Summary measures: The analysis of the absolute risk of survival rates, adverse event, complete resection, recurrence and mortality rates was performed. Also, data on absolute risk reduction (ARR) or increase (ARI) and number needed to treat (NNT) or harm (NNH) were analyzed on main outcomes, with 95%CI.

Planned methods of analysis: The analysis was performed using the software Review Manager (RevMan) 5.3[12], by computing risk differences (RD) of dichotomous variables using fixed-effects model and providing the respective forest and funnel plots. Data

on RD and 95%CIs for each outcome were calculated using the Mantel-Haenszel test and inconsistency (heterogeneity) was qualified and reported in χ^2 and the Higgins method, termed I^2. Data on ARR or ARI and NNT or NNH were obtained using the Critically Appraised Topic (CAT)[13] software. The statistical review of the study was performed by a biomedical statistician (Bernardo WM).

Risk of bias across studies: Risks of publication bias for outcomes across studies were plotted (funnel plots) and identified (outliers detection), along with I^2 quantitative analysis.

Additional analyses: The cut-off value for heterogeneity of 50% was assumed to be adequate for this meta-analysis. Trying to find out if the results from this meta-analysis are adequate and reliable for medical practice and not arbitrary or based in unclear data, sensitivity analysis was performed when heterogeneity (I^2) was higher than 50%. A subsequent assay was done, excluding the outliers, and other findings were compiled. When outliers were not detected, true heterogeneity was presumed, *i.e.*, publication bias was excluded.

RESULTS

Study selection
Six thousand, three hundred and eighty six (6386) studies were screened and the articles assessed for eligibility were selected after the title and abstract were read. Six thousand, three hundred and seventy six (6376) articles were excluded because they did not contemplate the following comparison. Ten studies compare endoscopic treatment *vs* surgery in the treatment of EGC. Scanning the reference lists of the selected articles, two more studies were found (Fukase *et al*[14] and Etoh *et al*[15]). These articles were not identified in the initial search strategy for two reasons. The study published by Fukase in 1994 did not have its journal (*Digestive Endoscopy*) indexed until then. The article written by Etoh in 2005 would be found if the Medline filter "[epidemiologic methods]", not used, was applied. A clinical series study was excluded (Teixeira *et al*, *Arq Gastroenterol,* 1992). Eleven studies were included in quantitative and qualitative synthesis. An adapted PRISMA flow diagram illustrates the study selection process (Figure 1)[7].

Study characteristics
Methods: The eleven studies selected were retrospective cohorts (RC). Ten were published in English and the other one was an article written in Japanese (translated by Yagi OK). No randomized controlled trials were found.

Participants: The included records involved 2654 patients. The inclusion criteria entailed adults with EGC

that filled the absolute (AI) or expanded indication (EI) for endoscopic resection. As the number of studies was relatively small, all follow-up periods, in months, were adopted. The studies published by Fukase and Nishida *et al*[16] considers the Kaplan Meier curve.

Intervention: Different endoscopic treatment modalities were analyzed, mainly endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Mucosectomy with ligation device (EMR-L) and high-frequency cauterization (HFC) was also verified.

Comparison: Tailored modalities of surgical procedures (mainly, gastrectomy ± lymphadenectomy) were compared to endoscopic approach.

Outcomes: The primary outcomes assessed were the short- and long-term survival rates (SR), *e.g.*, 3-, 5- and 10-year. The secondary and additional outcomes were: adverse event (AER), complete resection (CRR), recurrence (RR) and mortality rates (MR). A summary of the characteristics of the included studies is shown in Table 1[14-24].

Risk of bias within studies
Using a standard approach with defined criteria, risk of bias was assessed to define methodological quality and the levels of evidence were compiled, as shown in Table 2[14-24].

Two studies obtained score 7 according to the Newcastle-Ottawa Quality Assessment Scale[10] for cohort studies. Other two scored 8 points and seven studies reached 9 points.

Aiming to increase confidence in the strength of association between exposure and outcomes, other parameters were used. According to the Scottish Intercollegiate Guidelines Network checklist[9], all studies were considered acceptable, *i.e.*, having some flaws and an associated risk of bias (possibility of conclusion change in the light of further studies). The SIGN classification considers three category levels: 0 (low quality), + (acceptable) and ++ (high quality). The included studies were classified as having level of evidence 2b (2009 Oxford Centre for Evidence-based Medicine)[11].

Results of individual studies
The results of individual studies are show in absolute numbers in the next forest plots.

Synthesis of results (meta-analyses), risk of bias across studies and additional analyses
Three-year survival data were available for six studies, reporting information of 1197 patients, as shown in Figure 2. In the pooled analysis, there were no differences in 3-year survival data after endoscopic and surgical treatment of EGC [risk difference (RD) = 0.01, 95%CI: -0.02-0.05)]. Heterogeneity was low (I^2 = 31%).

Five-year survival data were identified in nine
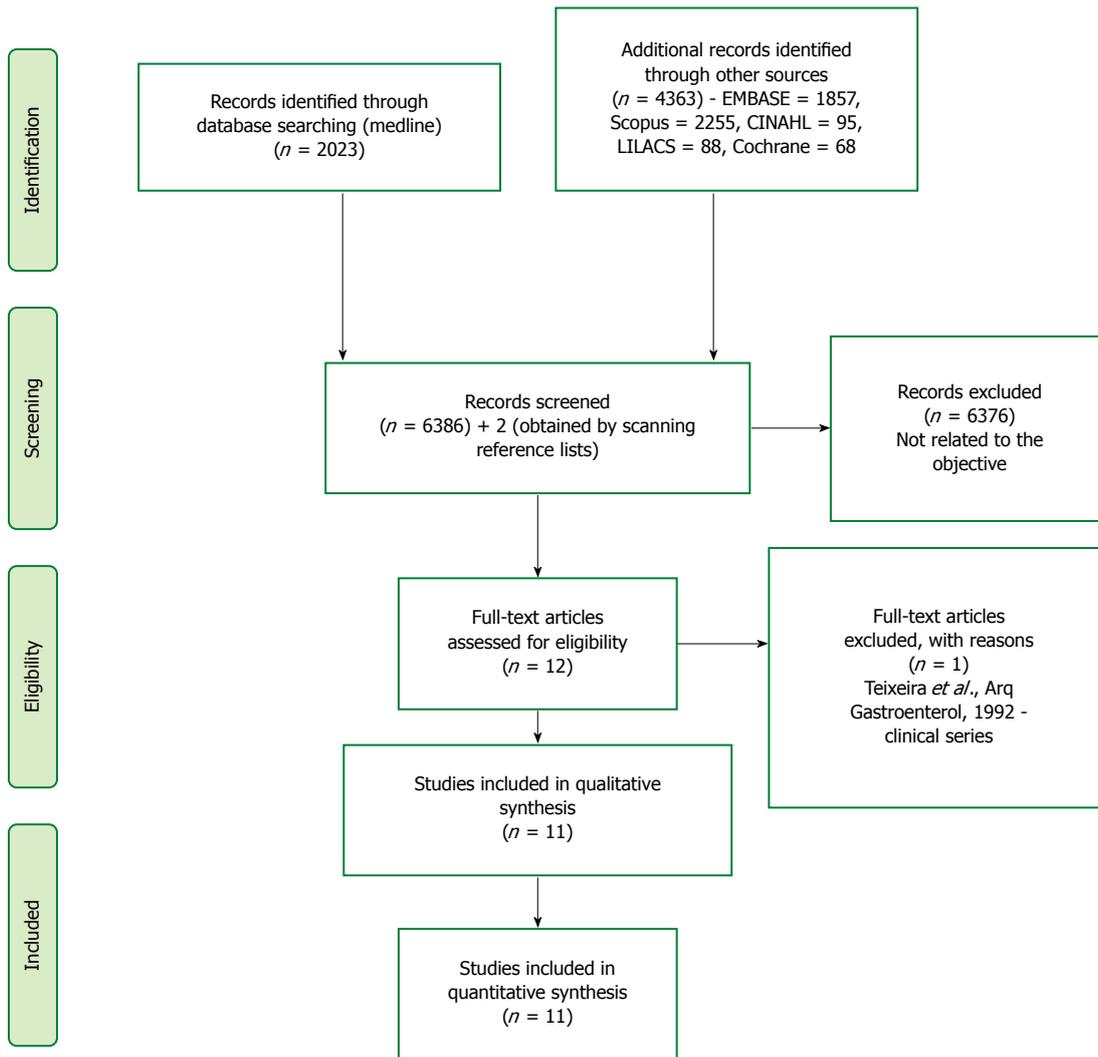
Figure 1 Search strategy and study selection flowchart.

Table 1 Summary of included studies evaluating the treatment of early gastric cancer

Ref.	Study design	No. of patients	Inclusion criteria	EA	SA	Follow-up (median) EA + SA	Outcomes
Nishida *et al*[16]	RC	109	AI	EMR, laser	Not specified	(2-3 yr)	3-5 yr SR + CRR
Fukase *et al*[14]	RC	175	AI	EMR, HFC, laser	Not specified	6 mo (5-10 yr)	5-10 yr SR + CRR
Kim *et al*[17]	RC	55	AI	EMR-L	Gastr + lymphadenect	35.3 mo + 29.3 mo	3 yr SR + CRR + RR
Etoh *et al*[15]	RC	93	AI	EMR	Gastrectomy	57 mo	3-5 yr SR + CRR + AER + MR
Choi *et al*[18]	RC	551	AI	EMR	Gastrectomy	81 mo + 88 mo	3-5-10 yr SR + RR + AER + MR
Chiu *et al*[19]	RC	114	AI	ESD	Gastr + lymphadenect	27 mo + 77.6 mo	3 yr SR + AER + MR
Fukunaga *et al*[20]	RC	287	AI or EI	ESD	Not specified	45.3 mo + 67.2 mo	5 yr SR + AER + RR
Park *et al*[21]	RC	225	AI or EI	ESD	Gastr + lymphadenect	17.6 mo + 24.2 mo	5 yr SR + RR + AER + MR
Kim *et al*[22]	RC	213	AI or EI	ESD	Gastr + lymphadenect	76.7 mo + 65.5 mo	3 yr + 5 yr SR + CRR + AER + RR
Choi *et al*[23]	RC	375	AI	EMR, ESD	Gastr + lymphadenect	76.4 mo	5 yr SR + RR + AER
Kim *et al*[24]	RC	457	EI	EMR, ESD	Gastr + lymphadenect	58.6 mo	5 yr SR + RR + AER

EA: Endoscopic approach; SA: Surgical approach.

studies. However, significant heterogeneity was initially detected ($\chi^2 = 20.87$ and $I^2 = 62\%$). Sensitivity analysis, through a funnel plot, identified one study (outlier) differing from the others (Fukase, 1994).

Exclusion of this study decreased the statistical heterogeneity to 0% (Figure 3) and did not affect the finding of no evidence of a difference in 5-year survival rate between endoscopic and surgical treatment of EGC (RD = 0.01, 95%CI: -0.01-0.03). Information of 2310 patients was obtained.

In a subgroup analysis, considering the available six studies comparing ESD *vs* surgery, four cohorts

| Table 2 Quality measures of the analyzed studies: Newcastle-Ottawa Scale - Bias measures							
Ref.	Representativeness of exposed cohort and selection of the non exposed cohort (max. 2 points)	Ascertainment of exposure (max. 1 point)	Demonstration that outcome of interest was not present at start of study (max. 1 point)	Comparability of cohorts on the basis of the design or analysis (max. 2 points)	Assessment of outcome (max. 1 point)	Length and adequacy of follow up (max. 2 points)	Score and levels of evidence
Nishida *et al*[16]	2	1	1	1	1	1	7 - 2b - acceptable (+)
Fukase *et al*[14]	2	1	1	1	1	1	7 - 2b - acceptable (+)
Kim *et al*[17]	2	1	1	2	1	2	9 - 2b - acceptable (+)
Etoh *et al*[15]	2	1	1	2	1	2	9 - 2b - acceptable (+)
Choi *et al*[18]	2	1	1	2	1	2	9 - 2b - acceptable (+)
Chiu *et al*[19]	2	1	1	1	1	2	8 - 2b - acceptable (+)
Fukunaga *et al*[20]	2	1	1	1	1	2	8 - 2b - acceptable (+)
Park *et al*[21]	2	1	1	2	1	2	9 - 2b - acceptable (+)
Kim *et al*[22]	2	1	1	2	1	2	9 - 2b - acceptable (+)
Choi *et al*[23]	2	1	1	2	1	2	9 - 2b - acceptable (+)
Kim *et al*[24]	2	1	1	2	1	2	9 - 2b - acceptable (+)
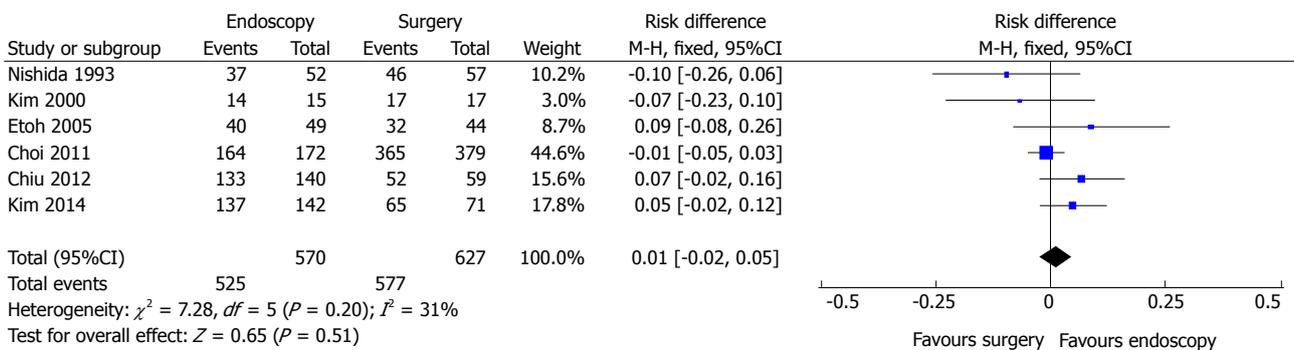
Figure 2 Three-year survival data after endoscopic and surgical treatment of early gastric cancer.

(1014 patients) evaluated the five-year survival. There was no difference between endoscopic and surgical treatment of EGC (RD = 0.02, 95%CI: -0.01-0.05), as shown in Figure 4.

Adverse events include any harmful procedure-related implications, such as anastomotic leakage, stenosis, perforation, hemorrhage, infection, mechanical ileus, herniation or, even, clinical illness decompensation (acute renal failure, pulmonary infection, myocardial infarction and so on).

Adverse event data were identified in eight studies (Figure 5). A high heterogeneity was initially detected ($\chi^2 = 34.50$ and $I^2 = 80\%$), a funnel plot was drawn and two outliers detected (Chiu, 2012 and Kim, 2014). As, excluding these studies, heterogeneity persisted high ($\chi^2 = 9.95$ and $I^2 = 50\%$) and there was no change in diamond trend, they were kept for meta-analysis. The same finding was obtained if the random effects model was applied. Data analysis of 2439 patients showed significant difference (RD = -0.08, 95%CI: -0.10--0.05), demonstrating better results with endoscopic approach. The pooled NNT (1/[RD]) was 12.

In the ESD subgroup analysis, five studies (1252 patients) evaluated the adverse event data. A high heterogeneity was initially detected ($\chi^2 = 28.79$ and $I^2 = 86\%$), a funnel plot was drawn and two outliers

detected (Park, 2014 and Choi, 2015). As, excluding these studies, heterogeneity persisted high and there was no change in diamond trend, they were kept for meta-analysis. Data analysis showed significant difference [RD = -0.12, 95%CI: -0.15-(-0.08)], favouring endoscopic approach (Figure 6).

Complete resection data comparing endoscopic and surgical treatment of EGC were seen in five studies. The heterogeneity was represented by $\chi^2 = 13.59$ and $I^2 = 71\%$. The funnel plot analysis showed an outlier (Nishida, 1993). Excluding this study, heterogeneity dropped ($I^2 = 41\%$) and there was no change in diamond trend. Data analysis, thus, was made considering a total amount of 536 patients and four studies. It showed significant difference in complete resection rates [RD = -0.13, 95%CI: -0.17-(-0.09)], exhibiting improved results in the surgical group (Figure 7). The pooled NNH (1/[RD]) was 7.

Recurrence data were identified in seven studies and the heterogeneity was represented by $\chi^2 = 16.51$ and $I^2 = 64\%$. The funnel plot analysis showed two outliers (Choi, 2015 and Kim, 2015). Excluding these studies, heterogeneity dropped ($I^2 = 13\%$) and there was a change in diamond trend. A total of 1331 patients were analyzed (Figure 8). There was no difference in terms of recurrence between endoscopic and surgical treatment of EGC (RD = 0.01, 95%CI:
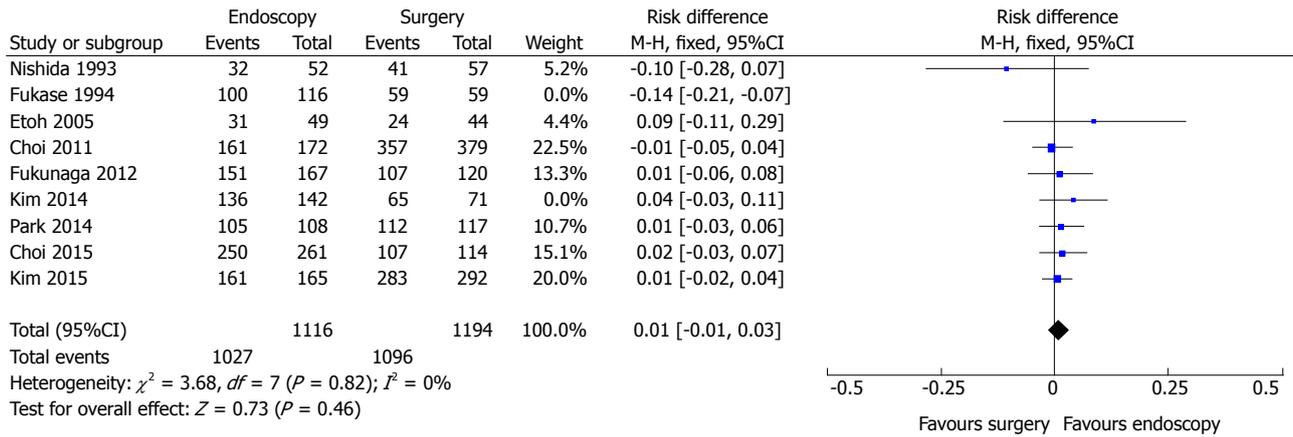
Study or subgroup	Endoscopy Events	Total	Surgery Events	Total	Weight	Risk difference M-H, fixed, 95%CI	Risk difference M-H, fixed, 95%CI
Nishida 1993	32	52	41	57	5.2%	-0.10 [-0.28, 0.07]	
Fukase 1994	100	116	59	59	0.0%	-0.14 [-0.21, -0.07]	
Etoh 2005	31	49	24	44	4.4%	0.09 [-0.11, 0.29]	
Choi 2011	161	172	357	379	22.5%	-0.01 [-0.05, 0.04]	
Fukunaga 2012	151	167	107	120	13.3%	0.01 [-0.06, 0.08]	
Kim 2014	136	142	65	71	0.0%	0.04 [-0.03, 0.11]	
Park 2014	105	108	112	117	10.7%	0.01 [-0.03, 0.06]	
Choi 2015	250	261	107	114	15.1%	0.02 [-0.03, 0.07]	
Kim 2015	161	165	283	292	20.0%	0.01 [-0.02, 0.04]	
Total (95%CI)		1116		1194	100.0%	0.01 [-0.01, 0.03]	
Total events	1027		1096				

Heterogeneity: $\chi^2 = 3.68$, $df = 7$ ($P = 0.82$); $I^2 = 0\%$
Test for overall effect: $Z = 0.73$ ($P = 0.46$)

Figure 3 Five-year survival data after endoscopic and surgical treatment of early gastric cancer (excluding outlier).

Study or subgroup	ESD Events	Total	Surgery Events	Total	Weight	Risk difference M-H, fixed, 95%CI	Risk difference M-H, fixed, 95%CI
Fukunaga 2012	151	167	107	120	28.8%	0.01 [-0.06, 0.08]	
Kim 2004	136	142	65	71	19.5%	0.04 [-0.03, 0.11]	
Park 2014	105	108	112	117	23.2%	0.01 [-0.03, 0.06]	
Choi 2015	167	175	107	114	28.5%	0.02 [-0.04, 0.07]	
Total (95%CI)		592		422	100.0%	0.02 [-0.01, 0.05]	
Total events	559		391				

Heterogeneity: $\chi^2 = 0.47$, $df = 3$ ($P = 0.93$); $I^2 = 0\%$
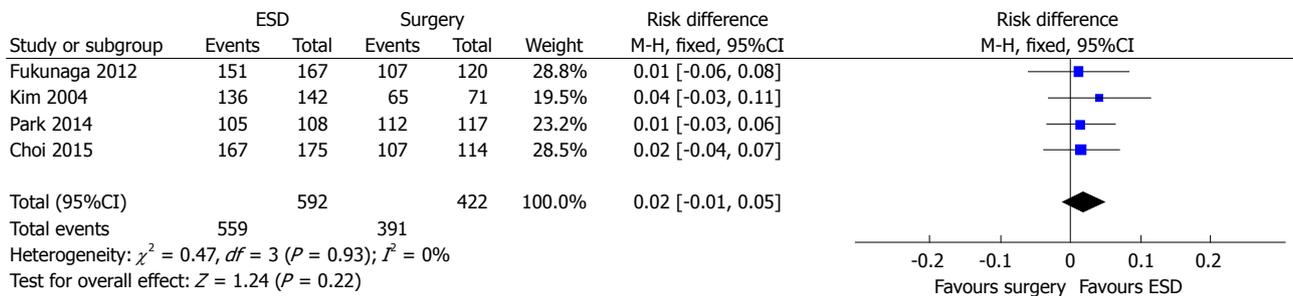Test for overall effect: $Z = 1.24$ ($P = 0.22$)

Figure 4 Five-year survival data after endoscopic submucosal dissection and surgical treatment of early gastric cancer.

Study or subgroup	Endoscopy Events	Total	Surgery Events	Total	Weight	Risk difference M-H, fixed, 95%CI	Risk difference M-H, fixed, 95%CI
Etoh 2005	0	49	4	44	4.2%	-0.09 [-0.18, 0.00]	
Choi 2011	11	172	29	379	21.5%	-0.01 [-0.06, 0.03]	
Fukunaga 2012	16	167	27	120	12.7%	-0.13 [-0.22, -0.04]	
Chiu 2012	7	140	20	59	7.5%	-0.29 [-0.42, -0.16]	
Kim 2014	12	142	20	71	8.6%	-0.20 [-0.31, -0.08]	
Park 2014	11	132	9	132	12.0%	0.02 [-0.05, 0.08]	
Choi 2015	7	261	9	114	14.4%	-0.05 [-0.11, 0.00]	
Kim 2015	9	165	29	292	19.1%	-0.04 [-0.09, 0.00]	
Total (95%CI)		1228		1211	100.0%	-0.08 [-0.10, -0.05]	
Total events	73		147				

Heterogeneity: $\chi^2 = 34.50$, $df = 7$ ($P < 0.0001$); $I^2 = 80\%$
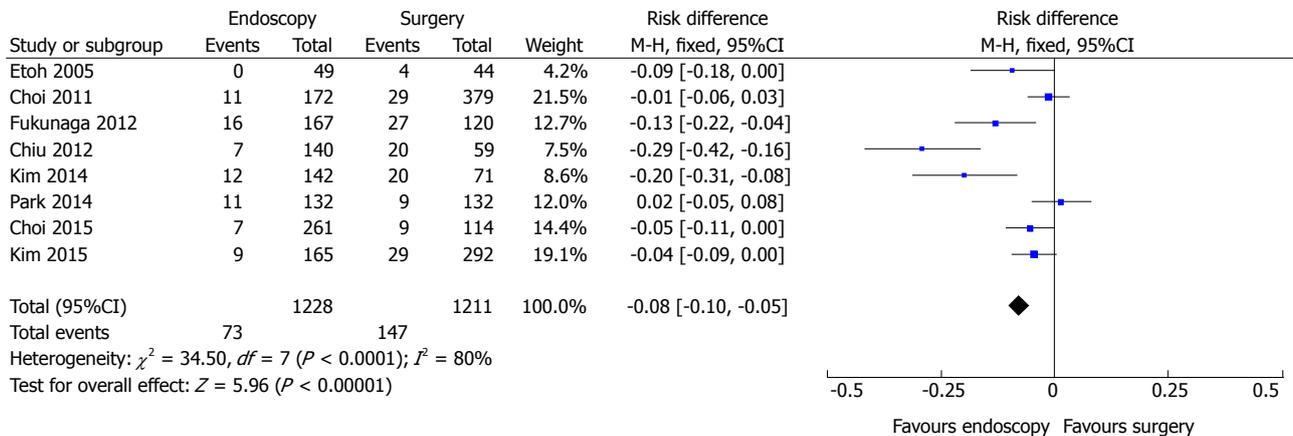Test for overall effect: $Z = 5.96$ ($P < 0.00001$)

Figure 5 Adverse event data after endoscopic and surgical treatment of early gastric cancer.

-0.00-0.02).

Mortality data include peritonitis due to perforation at the operation site, small bowel strangulation, splenic artery bleeding and anastomosis site leakage.

Mortality data were obtained in four studies and a total of 1107 patients were analyzed (Figure 9). No heterogeneity was detected ($\chi^2 = 0.85$ and $I^2 = 0\%$). In the pooled analysis, there was no evidence of a difference in terms of mortality between endoscopic and surgical treatment of EGC (RD = -0.01, 95%CI: -0.02-0.00).

DISCUSSION

The reported analysis combines data across studies in order to verify treatment effects with more precision than is possible in a single study. The greater advantage is that it increases the level of evidence of single retrospective cohort studies from 2b to 2a (systematic reviews of 2b studies) according to Oxford Centre[11].

Although gastrectomy (associated or not with lymphadenectomy) is the conventional oncologic surgical procedure to treat early gastric cancer, endo-
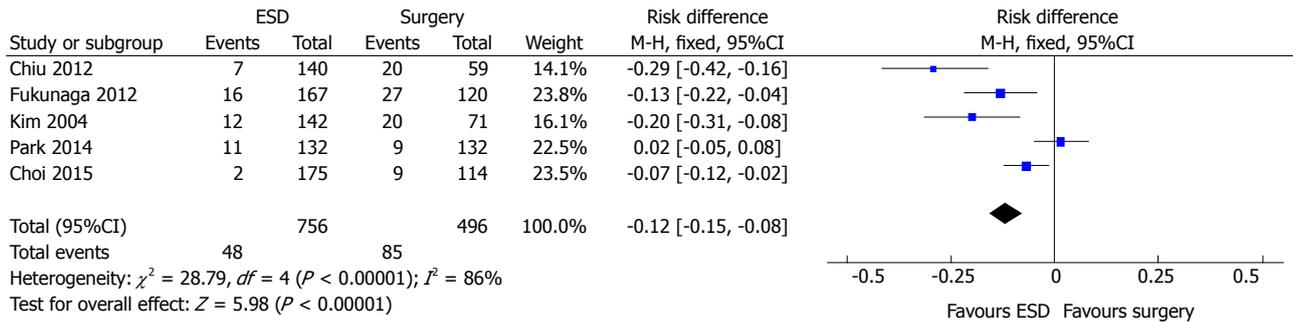
Study or subgroup	ESD		Surgery		Weight	Risk difference M-H, fixed, 95%CI	Risk difference M-H, fixed, 95%CI
	Events	Total	Events	Total			
Chiu 2012	7	140	20	59	14.1%	-0.29 [-0.42, -0.16]	
Fukunaga 2012	16	167	27	120	23.8%	-0.13 [-0.22, -0.04]	
Kim 2004	12	142	20	71	16.1%	-0.20 [-0.31, -0.08]	
Park 2014	11	132	9	132	22.5%	0.02 [-0.05, 0.08]	
Choi 2015	2	175	9	114	23.5%	-0.07 [-0.12, -0.02]	
Total (95%CI)		756		496	100.0%	-0.12 [-0.15, -0.08]	
Total events	48		85				

Heterogeneity: $\chi^2 = 28.79$, $df = 4$ ($P < 0.00001$); $I^2 = 86\%$
Test for overall effect: $Z = 5.98$ ($P < 0.00001$)

Figure 6 Adverse event data after endoscopic submucosal dissection and surgical treatment of early gastric cancer.

Study or subgroup	Endoscopy		Surgery		Weight	Risk difference M-H, fixed, 95%CI	Risk difference M-H, fixed, 95%CI
	Events	Total	Events	Total			
Nishida 1993	40	55	57	57	0.0%	-0.27 [-0.39, -0.15]	
Fukase 1994	106	116	59	59	32.0%	-0.09 [-0.14, -0.03]	
Kim 2000	17	20	35	35	10.4%	-0.15 [-0.31, 0.01]	
Etoh 2005	38	49	44	44	18.9%	-0.22 [-0.35, -0.10]	
Kim 2014	127	142	71	71	38.7%	-0.11 [-0.16, -0.05]	
Total (95%CI)		327		209	100.0%	-0.13 [-0.17, -0.09]	
Total events	288		209				

Heterogeneity: $\chi^2 = 5.13$, $df = 3$ ($P = 0.16$); $I^2 = 41\%$
Test for overall effect: $Z = 6.10$ ($P < 0.00001$)

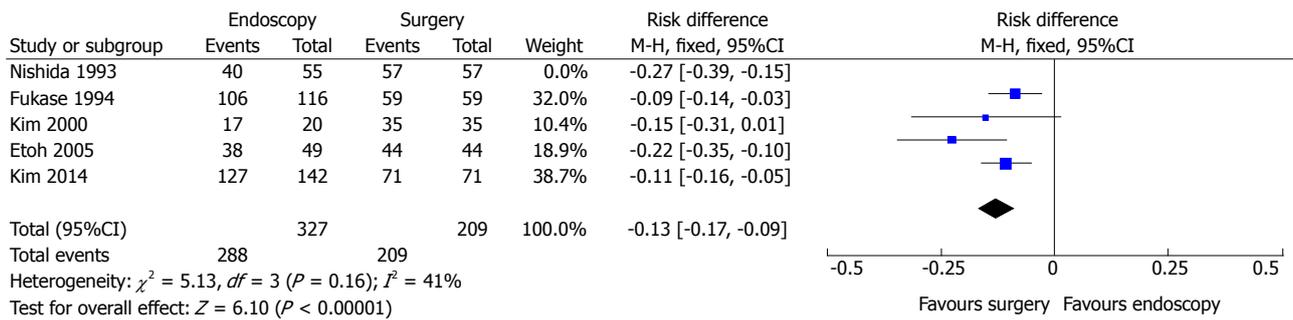**Figure 7 Complete resection data after endoscopic and surgical treatment of early gastric cancer (excluding outlier).**

Study or subgroup	Endoscopy		Surgery		Weight	Risk difference M-H, fixed, 95%CI	Risk difference M-H, fixed, 95%CI
	Events	Total	Events	Total			
Kim 2000	1	20	0	35	4.2%	0.05 [-0.07, 0.17]	
Choi 2011	2	172	4	379	38.9%	0.00 [-0.02, 0.02]	
Fukunaga 2012	2	167	0	120	22.9%	0.01 [-0.01, 0.03]	
Kim 2014	5	142	0	71	15.6%	0.04 [-0.00, 0.07]	
Park 2014	0	108	0	117	18.5%	0.00 [-0.02, 0.02]	
Choi 2015	13	261	1	114	0.0%	0.04 [0.01, 0.07]	
Kim 2015	8	165	1	292	0.0%	0.05 [0.01, 0.08]	
Total (95%CI)		609		722	100.0%	0.01 [-0.00, 0.02]	
Total events	10		4				

Heterogeneity: $\chi^2 = 4.61$, $df = 4$ ($P = 0.33$); $I^2 = 13\%$
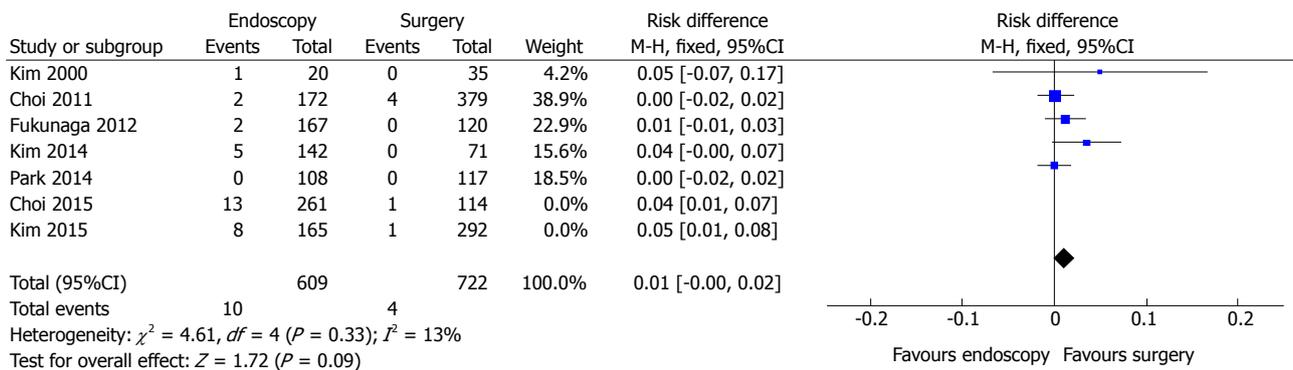Test for overall effect: $Z = 1.72$ ($P = 0.09$)

Figure 8 Recurrence data after endoscopic and surgical treatment of early gastric cancer (excluding outliers).

scopic approach has become an interesting and less invasive alternative for a select group of patients[5,6].

Basically, the two main endoscopic approaches consist of tumor resection, whether it is EMR or ESD. Many studies have demonstrated that endoscopic treatment of EGC is safe, even for elderly patients[25-29]. Nowadays, specially after 2004, EMR was replaced with ESD, which has higher rates of en bloc and complete endoscopic and pathological resection[30]. Even disregarding the oldest studies, published in the early 1990s by Nishida *et al*[16] and Fukase *et al*[14], when endoscopic resection was not completely and well-established, the three-, five-year survival rates and complete resection data did not significantly changed.

This systematic review fails to compare, on a subgroup analysis, the complete resection rates of ESD *vs* surgery. Although it is known that gastric tumor R0 resection is nearly 100% with surgical approach, no study regarding this comparison was found. According to Kim *et al*[22] and Choi *et al*[23], the complete resection rates, considering ESD, may reach 97.7% in some selected cases. These high total resection rates resulted, as seen previously in Figure 8, in lower recurrence rates, similar to surgery group. It is important to highlight that, even in situations of positive resection margins, an additional endoscopic treatment is feasible.

Although the expanded criteria proposed by Gotoda[6] was based on surgical specimens analysis, usually clinicians choose treatment modality based on limited information, such as endoscopic gross finding and histopathology of biopsy specimens[21]. It is known that, in some cases, a high rate of histologic discrepancy between endoscopic forceps biopsy and
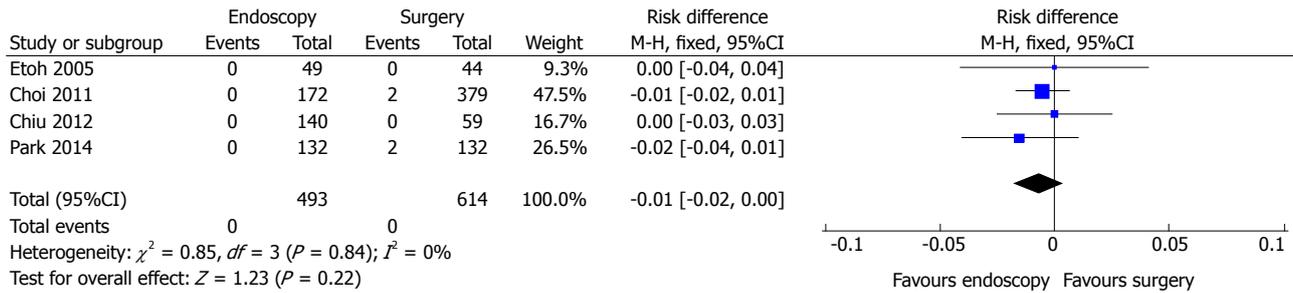
| Study or subgroup | Endoscopy | | Surgery | | Weight | Risk difference | Risk difference |
	Events	Total	Events	Total		M-H, fixed, 95%CI	M-H, fixed, 95%CI
Etoh 2005	0	49	0	44	9.3%	0.00 [-0.04, 0.04]	
Choi 2011	0	172	2	379	47.5%	-0.01 [-0.02, 0.01]	
Chiu 2012	0	140	0	59	16.7%	0.00 [-0.03, 0.03]	
Park 2014	0	132	2	132	26.5%	-0.02 [-0.04, 0.01]	
Total (95%CI)		493		614	100.0%	-0.01 [-0.02, 0.00]	
Total events	0		0				

Heterogeneity: $\chi^2 = 0.85$, $df = 3$ ($P = 0.84$); $I^2 = 0\%$
Test for overall effect: $Z = 1.23$ ($P = 0.22$)

Favours endoscopy   Favours surgery

Figure 9 Mortality data after endoscopic and surgical treatment of early gastric cancer.

endoscopic resection specimens may be present[31]. An important limitation of the available studies is that the obtainable data includes retrospective final pathology after endoscopic resection and surgery, rather than the criteria of pretreatment evaluation. Nevertheless, all data considered only patients with EGC, adding, on the other hand, more strength to the evidence. However, as previously cited, recent studies have implied that long-term outcomes of ESD for non-differentiated EGC are great[32,33].

Some recent studies indicate comparable results between absolute and expanded indications, and considering all variables involved in treatment decision, a less harmful position should be first considered and, if possible, adopted. Thus, a cautious and careful approach on patients filling the expanded criteria ought to be chosen, once a limited number of studies, reporting equivalent outcomes to surgery, are published. An unexpected inadequate endoscopic resection or recurrence identification would be inconveniences related to this practice. Thus, well-designed prospective randomized clinical trials are needed to evaluate the outcomes of endoscopic resection, considering the expanded indications.

The decision of which treatment modality is the best comprises a complex interaction of factors, such as patient clinical condition and age, tumor characteristics, physician expertise (surgeon, pathologist and endoscopist) and hospital infrastructure.

Summary of evidence
Overall, the evidence of survival rates seems to be enough to determine the comparative effectiveness of endoscopic resections over surgical procedures, once no statistically significant difference was seen.

Analyzing the nine studies contemplating 5-year survival, only one study (Fukase *et al*[14], 1994) was discrepant from the others. This study was removed from pooled analysis (outlier). In a subgroup analysis, considering the available six studies comparing ESD *vs* surgery (1014 patients), no difference was verified.

Some other reports have shown that endoscopic treatment for EGC can achieve survival rates similar to those seen in patients that undergo surgical procedures, irrespective the criteria adopted. However, well-designed prospective randomized controlled trials

should be performed to assign this statement properly.

Acceptable evidence was appointed regarding adverse event rates. Data analysis of 2439 patients showed significant difference favouring endoscopic treatment. The pooled NNT was 12. Considering that the selected studies were done in specialized centers, with high gastrointestinal surgical volume and excellence endoscopic units, reproducibility must be interpreted with caution. In the ESD *vs* surgery subgroup analysis (1252 patients), significant difference favouring endoscopic approach was also detected.

Data on complete resection rates confirm the advantages of surgical procedures in obtaining free resection margins, as they have wider boundaries. There was a significant difference favouring gastrectomy group (RD = 13%, $P < 0.0001$, NNH = 7). Although significantly more efficient in R0 resection, surgery incorporates an inherent risk of adverse events, even in experienced hands. It is reported a lower complete resection rates of EGC performing EMR[16,17]. More than one session was needed in some studies, although authors emphasize the possibility of sequential endoscopic resection procedures or, even, rescue surgery. Nowadays, enlarged dissections, such ESD, improve these results. This sequential approach seems to have no effect in survival rates, as evidenced.

Data on recurrence demonstrated no difference between endoscopic and surgical treatment after a complete tumor removal, *i.e.*, R0 resection (RD = 1%, $P = 0.09$), irrespective the number of endoscopic sessions needed to achieve this objective. As mentioned above, endoscopic retreatment or salvage surgery may be the choice according to tumor restaging.
Mortality data showed no evidence of a difference in the four meta-analyzed studies (RD = 1%, $P = 0.22$).

Important to remember is that statistical significance of the effect does not always suggest clinical relevance, or likewise, a non-significant result may not mean the ineffectiveness of a treatment. All data should be considered in the context of different patients and settings.

Nowadays, unnecessary surgeries seem to be performed in some early cancers and elderly patients, what could improve morbidity and mortality rates. Recent studies report a beneficial impact, favouring prognosis, in selected patients when considering age

and comorbidities. Although not addressed in this review, endoscopic treatment shows better perioperative outcomes in terms of procedure time, costs and hospital stay[18,19,21]. Thus, endoscopic treatment has its role increased in recent times due to technology development, indication expansion, tumor oncological aspects, patient clinical condition, early diagnosis and physician enthusiasm.

Despite the treatment guidelines, it is equally, or even more, important that these patients be treated in reference centers, used to a high-volume routine and host of specialized and meshed professionals, whatever the approach. Generalization to nonspecialized institutions requires discretion, aiming to improve outcomes.

Limitations

Publication bias regards to a problematic tendency of researchers to handle the reporting of results that are positive and good, leading to a misleading bias in the overall published literature[34]. It was detected on funnel plot analysis for the outcomes of 5-year survival, complete resection and recurrence data.

A limitation within this meta-analysis is the presence of heterogeneity detected within some outcomes and low number of studies in this topic. Although sensitivity analysis was done, some degree of heterogeneity is inevitable and it may undermine the quality and legitimacy of the results obtained. The categorization of values for I^2 considers adjectives of low, moderate and high to 25%, 50%, and 75%, respectively[35]. Quantification of heterogeneity is only one component of a wider investigation of variability across studies and the observed degree of inconsistency may have clinical implications.

The retrospective nature of the selected studies is also a limitation compared to prospectively and randomized collected database. The choice of endoscopic resection or surgery was not based on randomization. Although some studies used propensity-score matching to minimize selection biases, hidden ones may remain with the influence of unmeasured confounders.

In conclusion, addressing the outcomes of endoscopic resection compared to surgery in the treatment of early gastric cancer, this systematic review concludes that 3-, 5-year survival, recurrence and mortality rates are similar.

Considering procedure-related adverse event rates, endoscopic approach achieves significantly better results and, analyzing complete resection data, surgical procedures are preferred.

COMMENTS

Background

Early gastric cancer (EGC) was defined as adenocarcinoma involving mucosa or submucosa irrespective of nodal status. While radical gastrectomy can achieve adequate oncological clearance, it poses significant perioperative morbidities. Thus, methods of endoscopic treatment were pioneered for EGC. This study adds an important value to scientific literature as it establishes, unifies and, accordingly, set the available published data regarding the best way to treat ECG.

Research frontiers

Clinical and oncological outcomes of endoscopic resection in patients with EGC, compared to surgery, have not been reported in systematic reviews.

Innovations and breakthroughs

This systematic review and meta-analyses was developed to address the short- and long-term outcomes of endoscopic resection compared to surgery in the treatment of EGC. According to current guidelines, absolute indication for endoscopic treatment of EGC is so strict that unnecessary surgeries are likely performed. Therefore, expanded criteria for endoscopic resection was suggested. This study emphasizes the major points related to this topic, aiming to improve results in clinical practice.

Applications

This review suggests that, despite treatment guidelines, it is important that patients be treated in reference centers, used to a high-volume routine and host of specialized and meshed professionals, whatever the approach. Generalization to nonspecialized institutions requires discretion. The retrospective nature of the selected studies is a limitation. Prospective randomized controlled database is needed.

Terminology

EGC was defined as adenocarcinoma involving mucosa or submucosa irrespective of nodal status. It can be treated by surgery (even conventional, laparoscopic or robotic approach) or endoscopy (resection procedures such as mucosectomy or endoscopic submucosal dissection).

Peer-review

In this systematic review, the authors have presented the clinical and oncological outcomes of endoscopic resection in patients with EGC, compared to surgery, bringing the information to an unpublished 2a strength of evidence, better handling nowadays clinical practice.

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