Long-Term Outcomes of Additional Surgery After Noncurative Endoscopic Resection in Patients with Early Gastric Cancer: A Meta-Analysis

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Abstract

Background

The influence of additional surgery on the prognosis of early gastric cancer who underwent noncurative endoscopic resection was controversial. Different results were observed in different studies. Therefore, this meta-analysis was conducted to evaluate whether additional surgery could produce survival benefits for these patients.

Methods

A systematic search was conducted in the PubMed, Embase, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure and Wanfang databases for relevant articles published until 31 March 2021 to investigate the differences in long-term results between the additional surgery group and the observation group.

Results

Sixteen studies including 3877 patients were included in this meta-analysis. The results had shown that the surgery group were younger and more male, higher undifferentiated type, higher rate of SM2, lymphatic and vascular invasion, lower recurrence and metastasis than the observation group. Good survival benefits were observed in additional surgery group with obvious significant differences in the 5-year OS, 5-year DSS and 5-year DFS. Similar results were obtained in the subgroup analysis, such as elderly patients (aged ≥70 years) in 5-year OS.

Conclusion

This meta-analysis illustrated that significant survival benefits, including 5-year OS, 5-year DSS and 5-year DFS, could be obtained with additional gastrectomy in patients with EGC after noncurative ER, and patients ≥70 years could also benefit from surgery.

1. Introduction

Gastric cancer, one of the most common malignant tumors in the world(1), is a major problem endangering human health. Early gastric cancer (EGC) is defined as tumor confinement to the mucosa or submucosa, regardless of lymph node metastasis(2). Endoscopic submucosal dissection (ESD) has become an important treatment for EGC in Japan because of its safety and low trauma(3, 4). However, ESD only allows the removal of the primary tumor without lymph node dissection, the minority of patients require additional surgery after noncurative endoscopic resection (ER)(2, 5). A large number of studies had researched the differences between additional surgery group and observation group after noncurative ER, nevertheless, which treatment was more effective for improving the long-term survival rate was still controversial. Iwai et al.(6) showed that the surgery group achieved better survival benefits in terms of overall survival (OS) than the observation group, while the disease-specific survival (DSS) were not significantly different. Yano et al.(7) revealed that the rate of overall survival (OS) and disease-specific survival (DSS) were significantly higher in the surgery group than in the observation group. So far, a unified conclusion had not been reached.

Two existing meta-analyses(8, 9) focused on the survival benefits have caught our attention; however, some limitations were observed after careful reading. First of all, the included studies were not insufficient which may lack some important studies. Moreover, only two long-term results of OS and DFS were included in one study(8). Therefore, we systematically screened the literatures in databases with the guidance of new standards that were reformulated and excluded some articles that were inappropriate. A new meta-analysis was conducted by comparing the long-term survival outcomes between two groups to clarify the most suitable treatment for patients with EGC after noncurative ER.

2. Materials And Methods

Our meta-analysis was registered in PROSPERO with registration number CRD42021226554 and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(10).

2.1 Literature search

A systematic online search of the PubMed, Embase, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure and Wanfang databases was conducted for relevant articles. Some of the MESH terms used were “Stomach Neoplasms”, “Gastric Cancer”, “Endoscopic Mucosal Resection”, “EMR”, “Endoscopic Submucosal Dissection”, “ESD”, “Surgery” and “Gastrectomy”. The complete search strategy was detailed in appendix 1, and no limitations on language or publication time were applied. This strategy was also applied in the other databases. In addition, manual searches were performed by two researchers independently to determine suitable papers, as shown in Fig. 1.

2.2 Selections of studies

The inclusion criteria were as follows: (1) the research design included all randomized controlled trials (RCTs), prospective studies and retrospective studies; (2) the articles were published in English or Chinese as of 31 March 2021; (3) comparisons were made between the additional surgery group and the observation group. Patients with EGC who underwent additional gastrectomy after noncurative ER were included in the surgery group, while patients without additional surgery belonged to the observation group; and (4) at least one target result was included in the article, with participants more than 20.

The exclusion criteria were as follows: (1) patients with EGC after curative ER; (2) studies did not have sufficient data in terms of long-term prognosis and studies such as case reports, reviews or discussions; and (3) full texts were unavailable. If several articles contained similar authors or research cohorts, more comprehensive articles were included in this meta-analysis.

2.3 Definition of noncurative endoscopic resection

Based on clinical practice, the JGCA(2) divides the indications of ER into absolute indications and expanded indications. Absolute indications are suitable for (1) differentiated intramucosal tumors of unlimited size without the formation of ulcers; (2) differentiated intramucosal tumors with the formation of ulcers, size ≤ 30 mm. These indicators are in line with the expanded indications, including the following: (1) undifferentiated intramucosal carcinoma without ulcerations, size ≤ 20 mm; (2) differentiated carcinoma, size ≤ 30 mm, pT1b (< 500 μm from the muscularis mucosa). When (1) not matching the criteria for absolute or expanded indications; (2) positive lymphatic or vascular infiltration; and (3) positive transverse or longitudinal margins; and (4) piecemeal resection are met, the diagnosis of noncurative ER is established.

2.4 Outcomes assessed

The primary outcomes of interest are long-term survival benefits, including 5-year OS, 5-year DSS and 5-year DFS, in patients with EGC after noncurative ER between two groups. The overall survival (OS) is defined as the time from the end of ER to death from any cause. The disease-specific survival (DSS) is defined as the time from the end of ER to death due to gastric cancer. The disease-free survival (DFS) is defined as the time from the end of ER to tumor recurrence or death. The secondary results are characteristics of the patients.

2.5 Data management

The target data from the included studies were extracted and summarized by two researchers independently. Articles were assessed by a third researcher if the opinions of the two researchers were not uniform. The following items were screened: (1) characteristics of the patients, including number of patients, age, sex, tumor location, tumor size, tumor morphology, histologic type, tumor depth of invasion, presence of ulcer, lymphovascular invasion, lymphatic invasion, venous invasion, positive vertical margin, en bloc resection, recurrence, beyond ER indication, distant metastasis, etc.; and (2) long-term outcomes, including 5-year OS, 5-year DSS and 5-year DFS.

2.6 Quality assessment

Two reviewers independently conducted research quality assessment using the Jadad scoring system or the Newcastle–Ottawa Scale (NOS)(11, 12), and any differences were resolved by discussion. The Jadad scoring system was used for the quality assessment of RCTs. The quality of the nonrandomized studies was evaluated using the NOS. Articles with a score of 6 or more points were considered high-quality articles according to selection, comparability, and exposure.

2.7 Statistical analysis

Review Manager 5.3 software was used for this meta-analysis. Weighted mean differences (WMDs) and odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess continuous data and dichotomous data, respectively. Statistical heterogeneity among the studies was evaluated by the chi-square test and was considered to be significant with values of $P < 0.05$. The I^2 value was also used to assess heterogeneity, and I^2 value □50% was determined to indicate low heterogeneity. Subgroup or sensitivity analyses were conducted on studies with high heterogeneity, and if necessary, subgroup analysis was performed based on research characteristics. Given that there was no significant heterogeneity, a fixed-effects model was applied to analyze the data. Funnel plots were used to estimate potential publication bias (Fig. 2).

3. Results

3.1 Study selection and characteristics

After the preliminary searches and screenings of the relevant databases, a total of 9005 articles were included in our study, of which 1653 studies were excluded on account of duplication and 7247 articles were excluded after reading the titles and abstracts. Then, 89 studies were excluded for various reasons. Ultimately, 16 studies(6, 7, 13–26) were included in this meta-analysis (Tables 1 and 2).

Table 1
Characteristics of the included studies

Study, year	Reference	Country	Study period	Study type	Cases		Results matching*	Reasons for not undergoing addition surgery	Level of evidence	Nos quality scale
					Surgery (n)	Observation (n)				
Choi, 2015	[13]	South Korea	2003–2010	RS	28	61	1,3	N/A	[illegible]b	7
Hoteya, 2016	[14]	Japan	2005–2011	RS	109	56	1	refusal of surgery, high surgical risk	[illegible]b	7
Iwai, 2020	[6]	Japan	2007–2012	RS	49	46	1	N/A	[illegible]b	8
Jeon※, 2018	[15]	Japan	2007–2016	RS	264	198	1,2,3	adverse events or advanced age	[illegible]b	7
Kawata, 2017	[16]	Japan	2002–2012	RS	323	183	1,2	N/A	[illegible]b	8
Kikuchi, 2017	[17]	Japan	2004–2013	RS	73	77	1	refusal of surgery, high surgical risk	[illegible]b	7
Kim, 2019	[18]	South Korea	2005–2016	RS	113	175	1,2,3	refusal of surgery, high surgical risk	[illegible]b	7
Kusano, 2011	[19]	Japan	1999–2005	RS	38	82	1	refusal of surgery, high surgical risk	[illegible]b	7
Noh, 2015	[20]	South Korea	2005–2013	RS	45	38	3	refusal of surgery, high surgical risk	[illegible]b	8
Pyo, 2017	[21]	South Korea	2000–2013	RS	87	51	1,2	refusal of surgery, high surgical risk	[illegible]b	7
Sumiyoshi, 2017	[22]	Japan	2003–2010	RS	15	17	1	N/A	[illegible]b	7

Results matching: 1 = 5-year OS; 2 = 5-years DSS; 3 = 5-years DFS

N/A: Not available; RS: Retrospective study

※: Although the author was Korean, the research objects come from Japan and were included in the subgroup of Japan.

Study, year	Reference	Country	Study period	Study type	Cases		Results matching*	Reasons for not undergoing addition surgery	Level of evidence	Nos quality scale
Suzuki, 2017	[23]	Japan	2000–2011	RS	553	553	1,2	N/A	□b	8
Toya, 2017	[24]	Japan	2002–2010	RS	45	21	1,2	N/A	□b	7
Yamanouchi, 2016	[25]	Japan	2001–2012	RS	28	51	1,2	refusal of surgery, high surgical risk	□b	7
Yang, 2015	[26]	South Korea	2005–2013	RS	123	144	2	N/A	□b	8
Yano, 2018	[7]	Japan	2002–2015	RS	118	113	1,2	refusal of surgery, high surgical risk	□b	8

Results matching: 1 = 5-year OS; 2 = 5-years DSS; 3 = 5-years DFS

N/A: Not available; RS: Retrospective study

※: Although the author was Korean, the research objects come from Japan and were included in the subgroup of Japan.

Table 2
Results of meta-analysis

Outcome of interests	Studies (n)	Surgery (n)	Observation (n)	WMD/OR (95%CI)	P value	Study heterogeneity			
						Chi^2	df	I^2, %	P value
Perative related outcomes									
Age, years	8	1237	1204	-3.31	< 0.01	68.25	7	90	< 0.01
Sex, male	15	1519	1331	1.16	0.05	20.96	14	33	0.10
Tumor location, upper third	7	271	254	1.00	0.98	0.87	6	0	0.99
Tumor size, mm	5	822	732	-0.48	0.28	0.49	4	0	0.97
Tumor morphology, elevated	8	289	216	1.04	0.83	16.49	7	58	0.02
Histologic Type,undifferentiated	11	414	458	0.74	0.09	28.24	10	65	< 0.01
Tumor depth of invasion, SM2	12	1049	712	2.25	< 0.01	50.88	11	78	< 0.01
Presence of ulcer	9	330	359	0.74	0.15	27.76	8	71	< 0.01
Lymphovascular invasion	9	489	177	2.76	< 0.01	21.36	8	63	< 0.01
Lymphatic invasion	7	552	347	2.22	0.02	64.46	6	91	< 0.01
Venous invasion	7	269	165	2.23	0.02	32.83	6	82	< 0.01
Positive Vertical margin	9	343	177	1.89	0.10	89.64	8	91	< 0.01
En bloc resection	5	501	480	1.53	0.08	2.51	4	0	0.64
Recurrence	4	17	53	0.26	< 0.01	4.57	3	34	0.21
Beyond endoscopic resection indication	3	54	71	0.73	0.46	4.56	2	56	0.10
Distant metastasis	6	14	26	0.48	0.03	2.71	5	0	0.75
Long-term survival outcomes									
5-year overall survival (5-year OS)	14	147	386	0.28	< 0.01	13.07	13	1	0.44
5-years disease-specific survival (5-year DSS)	10	22	82	0.23	< 0.01	8.48	9	0	0.49
5-years disease-free survival (5-year DFS)	3	24	136	0.13	< 0.01	2.15	2	7	0.34
WMD/OR/HR: Weighted mean difference/odds ratio/hazard ratio;									
CI: Confidence interval;									
df: Degrees of freedom.									

All studies included in this study were conducted in East Asia: 11 studies(6, 7, 14–17, 19, 22–25) were conducted in Japan, 5 studies(13, 18, 20, 21, 26) were conducted in South Korea. The results revealed that additional surgery would bring better long-term prognosis in terms of 5-year OS, 5-year DSS and 5-year DFS between two groups. Meanwhile, the surgery group were younger and more male, higher undifferentiated type, higher rate of SM2, lymphatic and vascular invasion, lower recurrence and metastasis than the observation group. The most common reasons for not undergoing additional surgery were refusal of surgery or high surgical risks, such as adverse events or advanced age (Tables 1 and 2).

3.2 Long-term survival outcomes

Five-year OS: The pooled data of 14 studies(6, 7, 13–19, 21–25) showed that significant difference was observed in terms of 5-year OS, and the surgery group had better prognosis. The fixed-effects model was applied based on no significant heterogeneity (OR = 0.28; 95% CI:

0.23, 0.35; $P < 0.01$)($P = 0.44$, $I^2 = 1\%$) (Fig. 3).

Despite showing low heterogeneity, subgroup analysis of elderly patients (age ≥ 70 years) was performed, 4 studies(7, 19, 21, 22) showed additional surgery brought better prognosis for the elderly. There was low heterogeneity, and the fixed-effects model was used (OR = 0.27; 95% CI: 0.15, 0.46; $P < 0.01$)($P = 0.40$; $I^2 = 0\%$).

Five-year DSS: Ten articles(6, 7, 15, 16, 18, 21, 23–26) reported data in 5-year DSS, showing a significant difference between the two groups. No significant heterogeneity was found and a fixed-effects model was used (OR = 0.23; 95% CI: 0.14, 0.36; $P < 0.01$)($P = 0.49$, $I^2 = 0\%$)(Fig. 4).

Five-year DFS: Three studies(13, 15, 18) showed the surgery group had higher the rate of 5-year DFS than the observation group. The fixed-effects model was applied to analyze the data because of low heterogeneity (OR = 0.12; 95% CI: 0.07, 0.19; $P < 0.01$) ($P = 0.34$, $I^2 = 7\%$) (Fig. 5).

3.3 Publication bias

Publication bias was evaluated based on survival benefits using funnel plots, and little potential publication bias was observed in this pooled meta-analysis with obvious symmetry (Fig. 2).

4. Discussion

Patients with noncurative ER were recommended additional surgery for better survival benefits. Nevertheless, the existing researches had different perspectives and some patients would not be able to undergo additional surgery for various reasons. Therefore, this study was conducted to evaluate whether additional surgery was beneficial for patients with EGC who underwent noncurative ER.

This meta-analysis of 16 studies reported that surgery group had higher undifferentiated type, higher rate of SM2, lymphatic and vascular invasion, which indicated that these patients were more frequently selected for additional gastrectomy, yet, patients were older, the rate of the 5-year OS, 5-year DSS and 5-year DFS were lower in the observation group. The above factors may suggest that advanced age or additional surgery may be one of the important reasons that affected the prognosis. Although the long-term prognosis may be closely related to the age factor, the fact that the lower rate of recurrence or metastasis and the survival benefits of elderly patients in additional surgery group could strongly prove the advantages of additional gastrectomy. The study written by Suzuki et al.(23)with the help of propensity score matching that controlled different clinicopathological factors such as age, concomitant diseases showed similar results. The elderly tended to have more concomitant diseases or higher surgical risks, and the probability of rejecting subsequent surgery was greater, this may be an important reason for the age difference between the two groups. In short, additional gastrectomy may be one of the independent predictors for long-term results, and could improved survival benefits for these patients.

As shown in this article, the common reasons why part of elderly patients could not be treated with additional surgical treatment were that refusal of surgery or high surgical risks, including advanced age or adverse events(7, 14, 15, 17–21, 25). One article(27) demonstrated that after full considerations, only approximately 20% of patients would choose further gastrectomy among patients ≥ 80 years. The possible explanations were that ESD could keep the anatomy of the stomach intact, maintain normal physiological functions and a high quality of life, while various adverse events may arise due to the destruction of the integrity of the stomach after gastrectomy. Moreover, the aging process degrades physical conditions, the non tumor-related prognosis of the super-elderly patients (age ≥ 80 years) may be worse. In principle, we still strongly recommend additional gastrectomy for patients without obvious contraindications for better long-term survival. Significant evidences showed that advanced age, undifferentiated type, tumor size ≥ 2 cm, and presence of ulceration were important factors in causing noncurative ER(28, 29). If the elderly did not want to undergo surgery, the above individual characteristics should be evaluated in detail, fully communicated with the patients, and the benefits and risks should be weighed before finally deciding on the treatment plan.

However, the existing included studies seldom discuss whether the interval would affect the results. It had been reported that ulcers and fibrosis caused by ESD may affect subsequent gastrectomy(30). This was also a question worth pondering. One published study(31) reported that the survival benefit of delayed surgery after noncurative ER for EGC was equal to that of directed surgery with an average delay of 21.5 days. Similar result indicated that a better prognosis was obtained when the operation time was delayed by 1 month(32). In a word, it was recommended that the time interval between the completion of noncurative ER and the time of delayed surgery be at least 1 month to reduce its impact on the long-term outcomes. This theory may has important reference value for patients with noncurative ER who were hesitant about undergoing additional surgery, they could take longer to decide the next treatment plan. Endoscopic ultrasonography (EUS), infrared video endoscopy, magnifying endoscopy with narrow-band imaging (ME-NBI) and high-spatial-resolution MR provided further robust information in the diagnosis of EGC(33–36). Changes in the neutrophil-to-lymphocyte ratio (NLR) and the loss of fat and muscle after treatment had a high diagnostic accuracy for predicting the OS of patients(37, 38). These factors seemed to be sufficient for patient decision making. In summary, patients with noncurative ER should be reviewed in a timely manner through various methods and make the best decision to achieve longer survival times.

Our meta-analysis had some highlights as follows. Given the systematic searches and investigations of relevant data, more comprehensive articles that investigated the differences in the long-term survival rate between the additional surgery group and the observation group in patients with EGC after noncurative ER were included. Moreover, we performed subgroup analyses to discuss the influences of age on the long-term prognosis. Finally, we confirmed that additional surgery may be a better option among these patients.

Nevertheless, the limitations in this research cannot be ignored. First, the included studies were performed in the East. The results in the East may not be applicable to the West. More worldwide research was needed to verify the validity of the results. Second, all the included studies were retrospective studies and the differences were observed in the clinicopathological characteristics of the two groups, the results may be affected by potential bias. Finally, patients in the observation group did not undergo additional surgery for various reasons. The doctor's diagnosis and treatment plan tend to be largely affected by the patient’s willingness, advanced age, concomitant diseases and other factors. Selectivity bias may eventually lead to a poor long-term survival rate in the observation group.

In conclusion, this meta-analysis emphasized the evidences, increased the credibility of the outcomes that extra survival benefits exist with additional surgery among patients with EGC after noncurative ER and had clinical significance to guide patients to make the best treatment plan. This view also applied to the elderly. Although some elderly refused additional surgery for some reasons, timely follow-up should also be carried out for better prognosis.

Abbreviations

CI
Confidence interval; df:Degrees of freedom; EGC:early gastric cancer; ER:endoscopic resection; JGCA:the Japanese Gastric Cancer Association; NOS:Newcastle–Ottawa quality assessment scale; SM2:depth of invasion from the muscularis mucosa ≥ 500 μm;WMD/OR/HR:Weighted mean difference/odds ratio/hazard ratio; 5-year OS:5-year overall survival; 5-year DSS:5-year disease-specific survival; 5-year DFS:5-year disease-free survival.

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Authors’ contributions

All authors contributed to this research, research planning and design: Jian Jiao, Han Li; data collection, analysis and collation: Hao Wu, Fengying Du, Huicheng Ren; article drafting and revision: Liang Shang, Ronghua Zhang, Kun Xiao, Kangdi Dong, ; final review: Jin Liu, Leping Li.

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Declaration of interest

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Ethics approval and consent to participate

This study does not need ethics approval.

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Availability of data and materials

The data and materials are all provided in this manuscript, such as the tables and texts.

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Figures

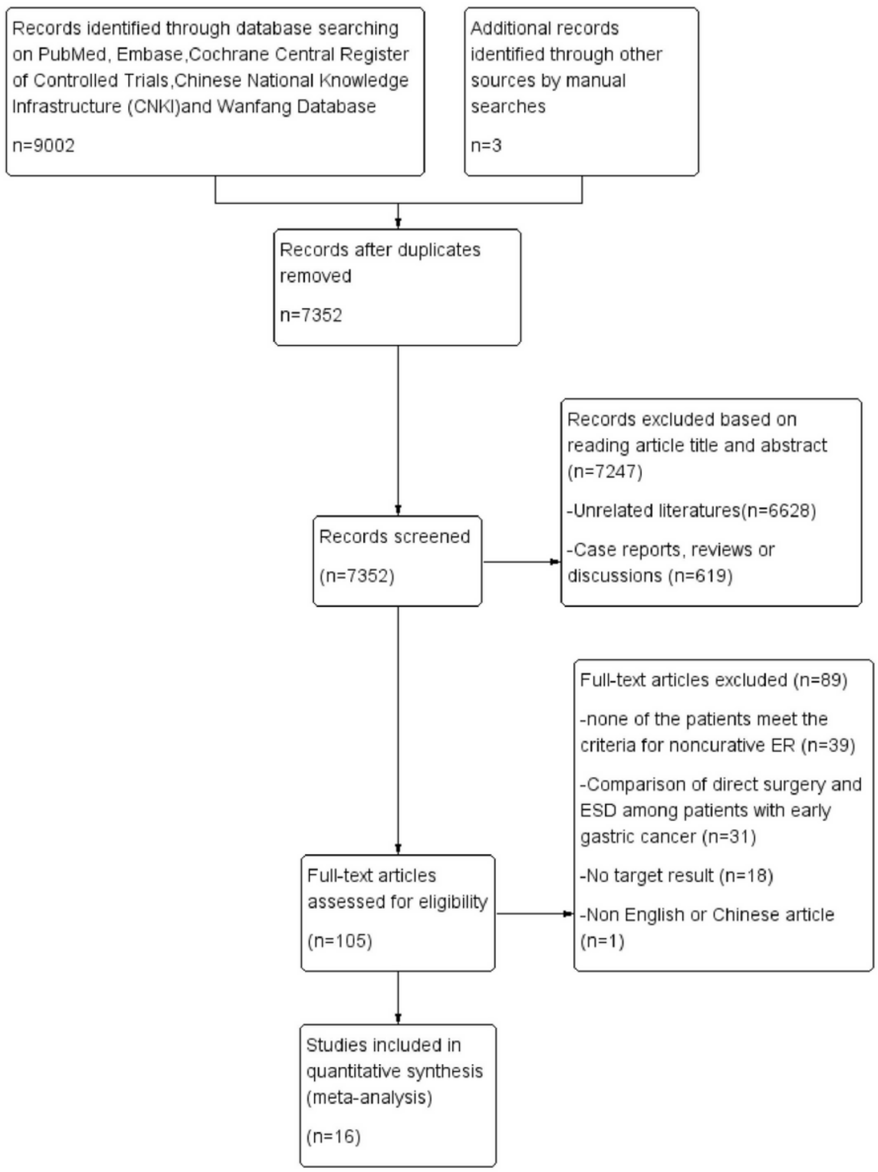

Figure 1

Flow diagram of study selection.

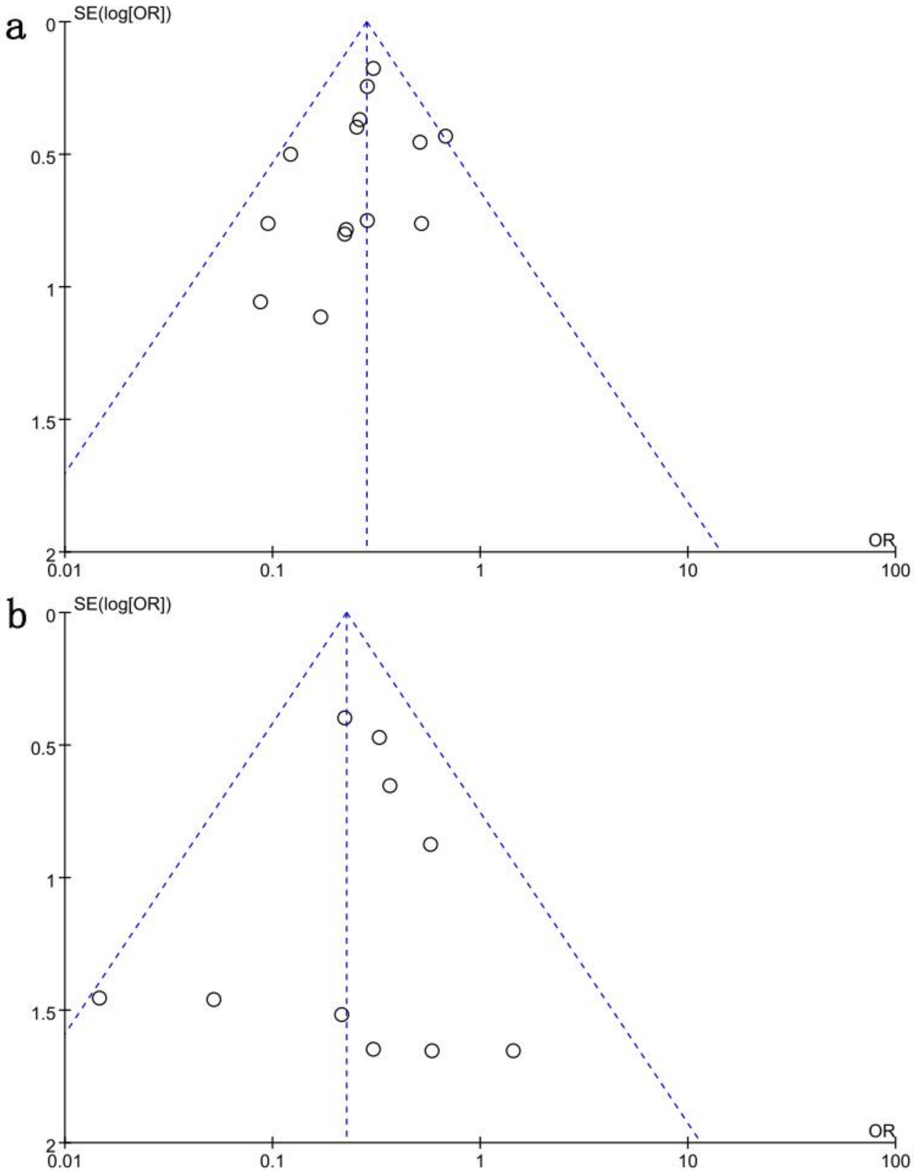

Figure 2

Funnel plot in all included studies. A: 5-year OS; B: 5-year DSS.

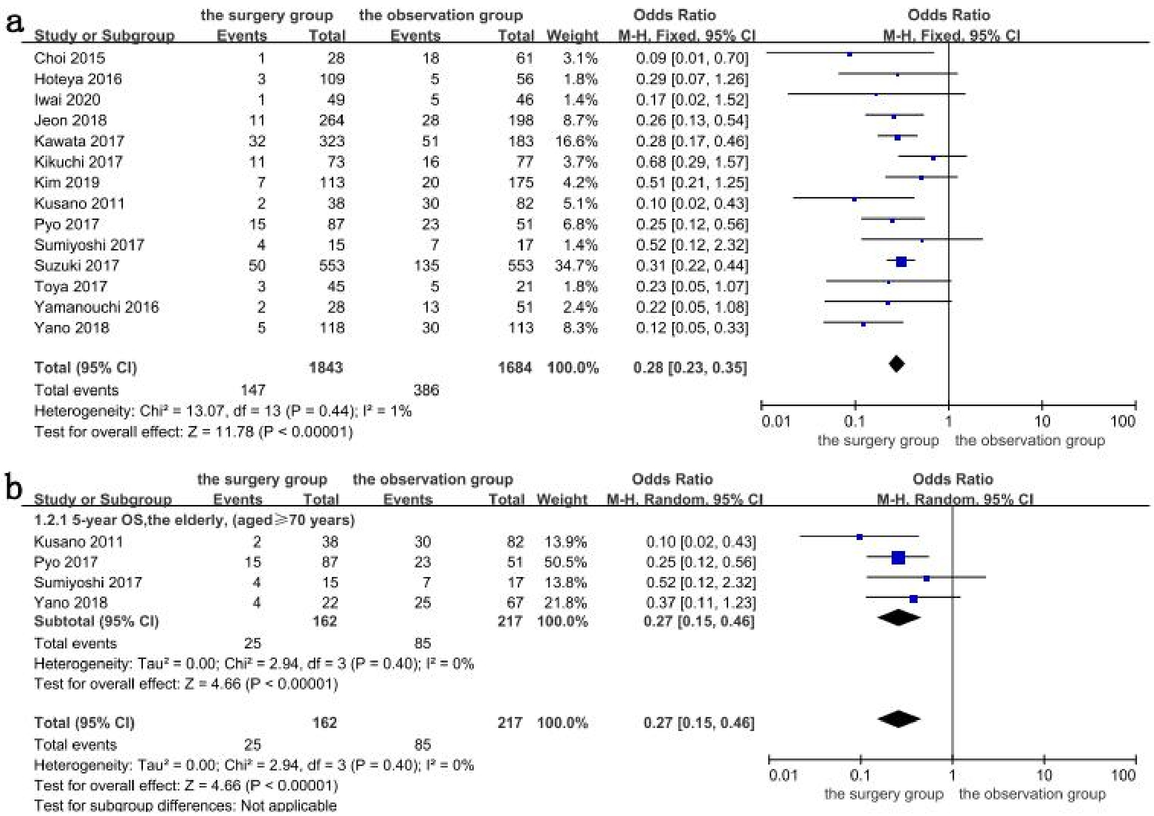

Figure 3

Forest plot and meta-analysis of long-term outcomes. A:5-year OS; B: the subgroup analysis, 5-year OS, the elderly, (age ≥70 years);

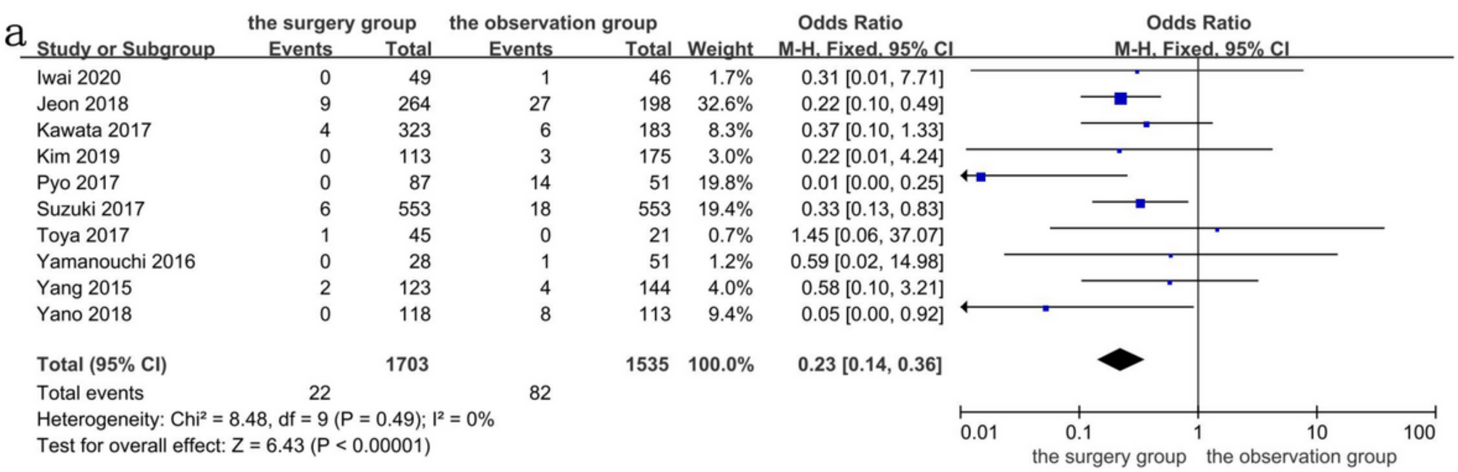

Figure 4

Forest plot and meta-analysis of long-term outcomes. A: 5-year DSS.

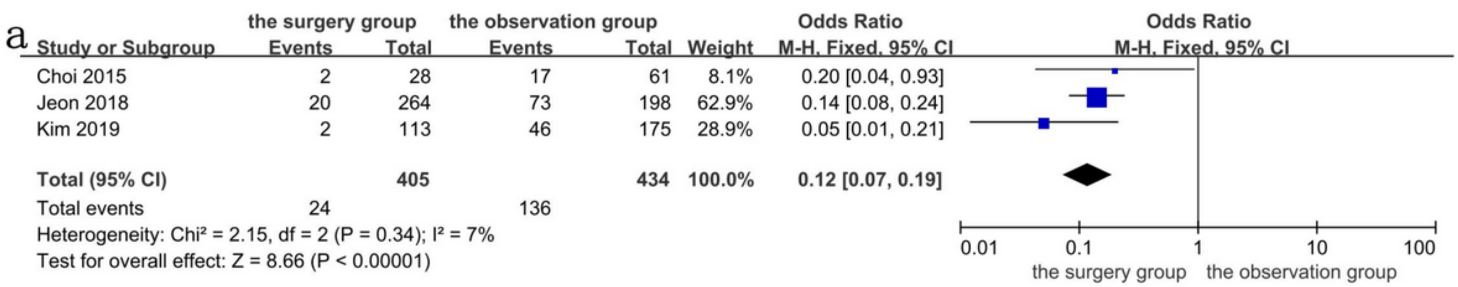

Figure 5

Forest plot and meta-analysis of long-term outcomes. A: 5-year DFS.

Supplementary Files

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- Appendix1.ThecompletesearchstrategyinPubmed.docx