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REVIEW ARTICLE

# Survival benefits of additional surgery after non-curative endoscopic resection in patients with early gastric cancer: a meta-analysis

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## Abstract

**Background** The survival benefit of additional surgery after non-curative endoscopic resection of early gastric cancer is a matter of debate. This meta-analysis is intended to draw a convincing conclusion on this issue based on data currently available.

**Methods** A systematic review of PubMed/Medline database was performed from 2010 to 2018 for studies comparing survival outcomes of additional surgery versus simple follow-up after non-curative endoscopic resection for early gastric cancer. Differences between groups were calculated using either the fixed effects model or random effects model.

**Results** Ten retrospective studies with 4225 patients met the inclusion criteria. Additional surgery significantly provided better 5 years overall survival [odds ratios (OR) 3.50, 95% confidence interval (95% CI) 2.89–4.24] and disease-specific survival (OR 3.99, 95% CI 2.50–6.36).

**Conclusions** Additional surgery offers survival benefits to patients undergoing non-curative endoscopic resection of early gastric cancer.

**Keywords** Endoscopic sub-mucosal dissection · Early gastric cancer · Non-curative resection · Additional surgery · Long-term outcomes

Early gastric cancer (EGC) is defined as invasive cancer existing within the submucosa, regardless of the presence of lymph node metastasis (LNM). Endoscopic resection (ER) has been accepted as the standard treatment for patients with EGC with a negligible risk of LNM, especially in Japan and Korea. According to the 2010 Japanese Gastric Cancer Association (JGCA) treatment guidelines [1], patients who have undergone non-curative ER are candidates for additional surgery. However, studies on the efficacy of additional surgery are relatively limited and have yielded conflicting results [2–10]. This tempted us to perform a systematic review and meta-analysis in order to determine whether additional surgery could improve survival of patients undergoing non-curative ER of EGC.

Debang Li and Haixin Luan have contributed equally to this work.

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## Methods

This meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11].

### Study selection

Using PubMed/Medline, studies comparing survival outcomes of additional surgery versus simple follow-up after non-curative ER for EGC published in the English langue between January 2010 and March 2018 were searched by using the following Mesh search headings: "early gastric cancer," "additional surgery," "endoscopic resection," and "endoscopic sub-mucosal dissection". Non-curative ER was diagnosed when the pathological findings did not fulfill the criteria for curative resection as defined by the JGCA guidelines [1]. Reference lists of the identified relevant articles were searched manually to identify any additional studies. If multiple publications from the same study cohort were presented, the largest and most recently updated data were chosen. Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and studies lacking control groups were excluded.

## Data extraction

From each included article, two reviewers independently extracted the following standard information: first author, year of publication, study location, study period, study design, sample size, participant characteristics, and survival outcomes. All relevant text, tables and figures were reviewed for data extraction. Discrepancies between the two reviewers were resolved by discussion and consensus.

The Newcastle-Ottawa Scale was used to quantify study quality, and those achieving 6 or more stars (out of 9) were considered to be of higher quality [12].

## Outcomes

The primary outcomes were 5-years overall survival (OS) and disease-specific survival (DSS). OS was determined from the date of ER to death, while DSS was determined from the date of ER to gastric cancer-related death. The secondary outcome was the independent effect of additional surgery on survival expressed as multivariate-adjusted hazard ratios (HR) with 95% confidence interval (95% CI). The characteristics of the patients were also assessed.

## Statistical methods

Data were analyzed using the RevMan 5.3.5 software for Windows® (http://ims.cochrane.org/revman/download). Dichotomous variables were analyzed using estimation of odds ratios (OR) with a 95% CI, and continuous variables using weighted mean difference (WMD) with a 95% CI. In addition, multivariable adjusted HR available in the articles was pooled separately to examine the independent effect of additional surgery on survival. Heterogeneity across studies was evaluated by $\chi^2$ and $I^2$. We considered heterogeneity to be present if the $I^2$ statistic was $> 50\%$. The fixed effect model was used for meta-analysis in cases of nonsignificant heterogeneity. If there was a significant heterogeneity, the random model was used. Publication bias was assessed with a funnel plot.

All statistical tests were performed two-sided, and $p < 0.05$ was considered statistically significant.

# Results

## Study and patient characteristics

Ten retrospective studies matched the inclusion criteria and were therefore included for review (Fig. 1). Characteristics of each study are shown in Table 1 [3–10, 13, 14]. The ten studies included a total of 4225 patients: 2455 in the additional surgery group and 1770 in the simple follow-up group. The sample size of each study varied from 66 to 1969 patients.

As Table 2 shows, there were significant differences between groups in terms of patient characteristics. Patients who underwent additional surgery were significantly younger, with smaller tumors, a lower proportion of comorbidity (Charlson comorbidity index 2 or greater), a higher proportion of SM2 invasion (depth of invasion from the muscularis mucosa ≥ 500 μm), and a higher proportion of lymphovascular invasion.

## Survival

Nine of the ten included studies provided data on 5-years OS, which was found to be significantly higher in the additional surgery group (OR 3.50, 95% CI 2.89–4.24; $p < 0.001$) (Table 2; Fig. 2A). Similarly, 5-year DSS was evaluated in seven studies, demonstrating that the survival outcome in

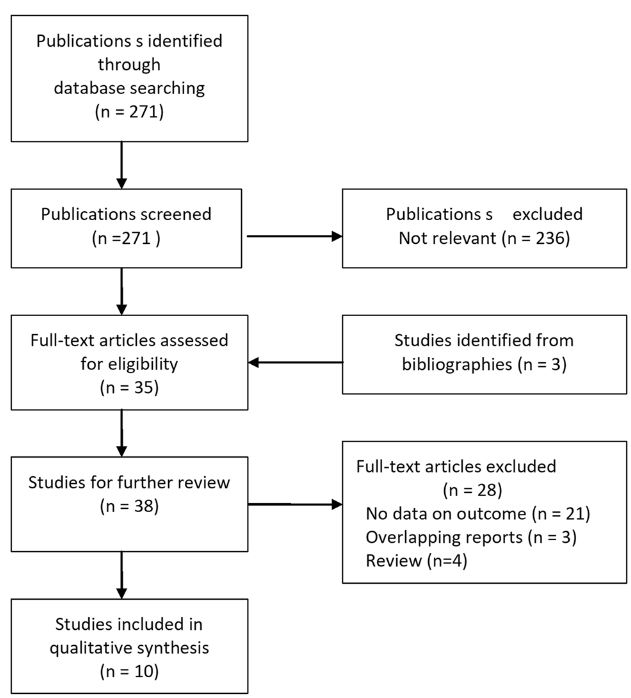


**Fig. 1** Flow chart illustrating the study selection process

**Table 1** Baseline characteristics of the studies included in the meta-analysis

| Author | Year | Country | Cases | | Outcomes | Study quality |
|---|---|---|---|---|---|---|
| | | | Surgery | F-Up | | |
| Kim et al. [3] | 2015 | South Korea | 194 | 80 | 5-year OS | 6 |
| Yang et al. [4] | 2015 | South Korea | 123 | 144 | 5-year DSS | 6 |
| Hoteya et al. [5] | 2016 | Japan | 109 | 56 | 5-year OS | 6 |
| Eom et al. [7] | 2016 | South Korea | 126 | 67 | 5-year OS, 5-year DSS | 6 |
| Yamanouchi et al. [6] | 2017 | Japan | 28 | 51 | 5-year OS, 5-year DSS | 7 |
| Kawata et al. [8] | 2017 | Japan | 323 | 183 | 5-year OS, 5-year DSS | 7 |
| Pyo et al. [9] | 2017 | Japan | 87 | 51 | 5-year OS, 5-year DSS | 7 |
| Suzuki et al. [10] | 2017 | Japan | 356 | 212 | 5-year OS, 5-year DSS | 7 |
| Suzuki et al. [13] | 2017 | Japan | 1064 | 905 | 5-year OS, 5-year DSS | 7 |
| Toya et al. [14] | 2017 | South Korea | 45 | 21 | 5-year OS | 6 |

*F-Up* follow-up; *5-y OS* 5-years overall survival; *5-y DSS* 5-years disease-specific survival

**Table 2** Outcomes of meta-analysis

| Variables | Studies used | Results | | OR/WMD (95% CI) | *p* value | $I^2$ (%) |
|---|---|---|---|---|---|---|
| | | Surgery | Follow-up | | | |
| Baseline characteristics | | | | | | |
| Male | 10 | 78.2% | 76.1% | 1.13 (0.98 to 1.31) | 0.10 | 17 |
| Age, years | 9 | 61.3 (68–77) | 65.1 (74.5–80) | − 5.55 (− 7.04 to − 4.06) | < 0.001 | 87 |
| Charlson comorbidity index ≥ 2 | 3 | 11.6% | 20.3% | 0.51 (0.35 to 0.74) | < 0.001 | 0 |
| Tumor location, antrum | 5 | 41.1% | 38.5% | 1.05 (0.90 to 1.24) | 0.52 | 0 |
| Tumor size, mm | 7 | 26 (21–34.7) | 27 (21.3–35) | − 1.59 (− 3.05 to − 0.13) | 0.03 | 55 |
| Depressed tumor morphology | 4 | 55.6% | 57.2% | 0.95 (0.81 to 1.11) | 0.49 | 0 |
| SM2 invasion | 8 | 65.0% | 44.1% | 2.46 (1.74 to 3.49) | < 0.001 | 78 |
| Lymphovascular invasion | 9 | 44.9% | 25.9% | 2.35 (1.77 to 3.11) | < 0.001 | 62 |
| Differentiated type | 8 | 11.2% | 14.7% | 0.72 (0.50 to 1.04) | 0.08 | 56 |
| Positive vertical margin | 7 | 19.5% | 11.7% | 1.80 (0.98 to 3.31) | 0.06 | 87 |
| Positive horizontal margin | 5 | 10.3% | 15.1% | 0.97 (0.41 to 2.29) | 0.94 | 72 |
| Long-term survival outcomes | | | | | | |
| 5-years overall survival | 9 | 91.9% | 76.3% | 3.50 (2.89 to 4.24) | < 0.001 | 0 |
| 5-years disease-specific survival | 7 | 98.9% | 95.9% | 3.99 (2.50 to 6.36) | < 0.001 | 16 |

*SM2* depth of invasion from the muscularis mucosa ≥ 500 µm, *OR* odds ratios, *WMD* weighted mean difference

patients of the additional surgery group was better than that in patients of the simple follow-up group (OR 3.99, 95% CI 2.50–6.36; $p < 0.001$) (Table 2; Fig. 2B).

### Multivariate-adjusted HR on survival

In our secondary analyses, we investigated whether using multivariate-adjusted HR had any significant impact on our results. It was found that additional surgery was associated with a significantly better OS (three studies [3, 7, 14]; HR 2.52, 95% CI 1.35–4.68, $p = 0.004$, $I^2 = 0\%$).

Only Pyo et al. [9] conducted a multivariable analysis for DSS. These authors found that additional surgery was the only independent predictor of DSS in patients who underwent non-curative ER of EGC (HR 72.38, 95% CI 7.08–739.68, $p = 0.001$).

### Publication bias

A funnel plot analyzing studies reported on 5-years OS showed no asymmetry (Fig. 3).

## Discussion

The wider use of endoscopic examinations and intensified monitoring of risk factors have greatly improved the diagnosis of EGC worldwide. ER is a minimally invasive and effective procedure for EGC with a negligible risk of

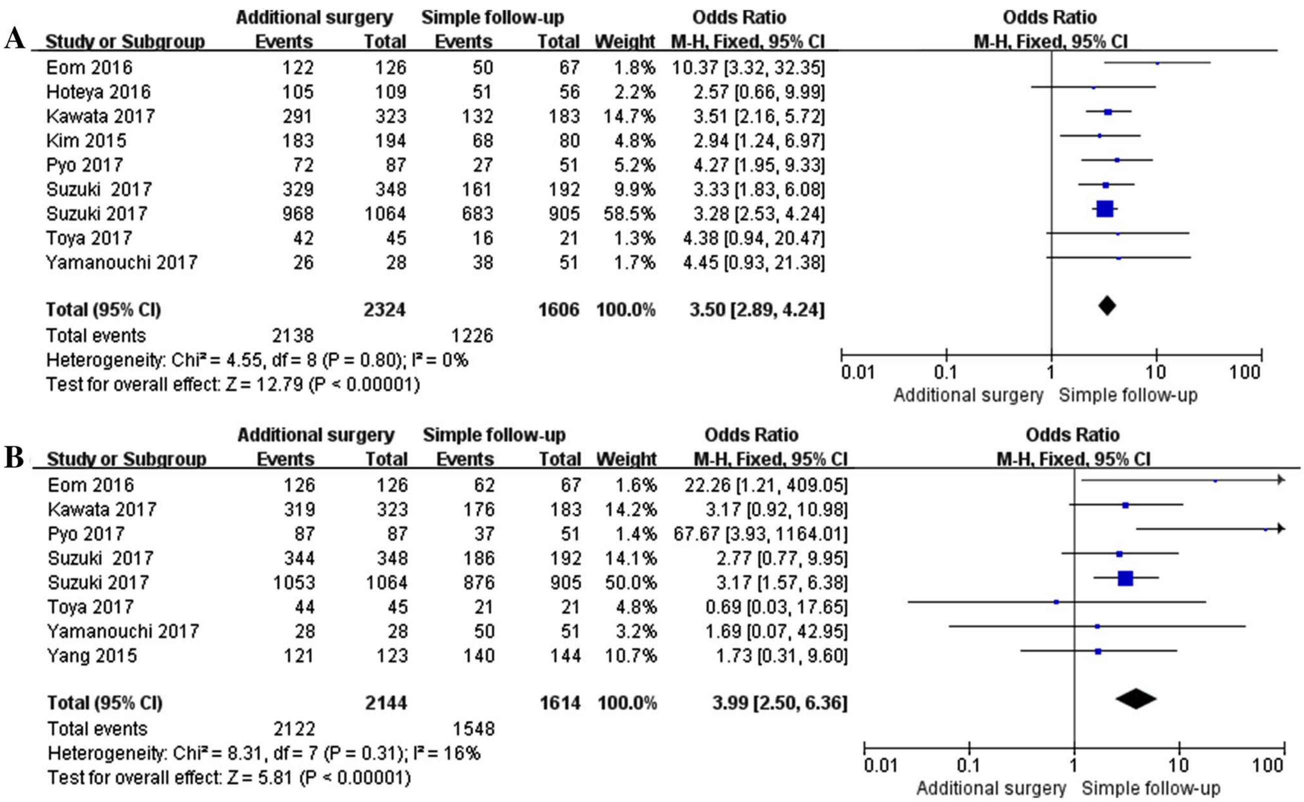


**Fig. 2** Forest plot comparing 5-year overall survival (**A**) and disease-specific survival (**B**) in patients who received and did not receive additional surgery

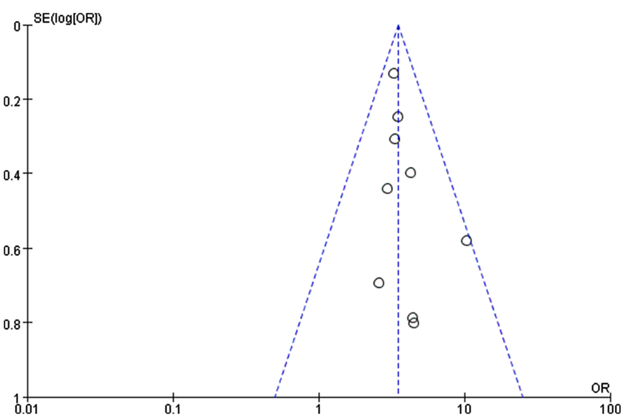


**Fig. 3** Funnel plot of studies that were compared for 5-year overall survival shows no evidence of publication bias

LNM. A thorough histological examination of the resected specimen is used to stratify patient management. Patients who have undergone non-curative ER generally need additional radical gastrectomy with lymph node dissection, but the real benefit of such procedure remains controversial. Hoteya et al. [5] reported that the 5-year OS rate and gastric cancer-related death were comparable between patients who received additional surgery and those who did not received additional surgery. However, another study [2] argued that additional surgery was superior to simple follow-up in terms of 5-year OS. One possible way to overcome such controversy is to consolidate evidence by meta- analysis of published data. The result of our meta-analysis clearly showed that additional surgery provided survival benefits to patients undergoing non-curative ER of EGC.

As might be expected, additional surgery was associated with a significant improvement in 5-year DSS. Nevertheless, it should be emphasized that many cases have neither LNM nor a local residual tumor in surgical specimens obtained by additional surgery [15]. It is therefore crucial to identify suitable candidates for additional surgery after non-curative ER for EGC. Sunagawa et al. [15] showed that a positive vertical margin and horizontal margin were predictors for a local residual tumor according to a multivariate analysis of 200 patients. Based on a multicenter retrospective study of 1101 patients, Hatta et al. [16] in 2017 developed a seven-point risk-scoring system (the eCura system) with three risk categories based on five clinicopathological factors (tumor size > 30 mm, positive vertical margin, lymphatic invasion, venous invasion, and SM2 invasion) for LNM in patients undergoing additional surgery after non-curative ER. Their recent updated data revealed that in the high-risk category, cancer recurrence was significantly higher and cancer-specific mortality tended to be higher in the additional surgery group than that in the simple follow-up group after non-curative ER of EGC, whereas no significant difference was observed in the intermediate-risk and low-risk categories. In addition, 5-year DSS in the low-risk category was high in both patient groups (99.6 and 99.7%) [17]; such histopathological factor-based assessment would help stratify patients for an appropriate treatment strategy.

It was found that the risk of death from other diseases in the additional surgery group was lowered that in the simple follow-up group [14]. The possible reason may be that patients in the additional surgery group were significantly younger with a lower proportion of comorbidity than those in the simple follow-up group. It is generally accepted older age is an independent risk factor for shorter survival of EGC patients treated by ER or surgery [18]. With the life expectancy increasing in recent years, more elderly adults with gastric cancer are subjected to aggressive treatments including surgery. However, elderly patients are more likely to be inflicted with co-morbidities, particularly cardiovascular and pulmonary diseases influencing their daily life. Compared with surgical intervention, ER for EGC improves the quality of life, owing to the preservation of the entire stomach and the maintenance of physiologic gastric motility [19]. Moreover, Abe et al. [20] have recently shown that the 5-year OS rate (66.7%) in the elderly patients with nonsurgical follow-up after non-curative ER for EGC was similar to the expected 5-year OS rate (65%) of the general population. It is possible that local control provided by ER alone may be significant even in such patients. Therefore, in the clinical setting, decision-making for additional surgery in patients after non-curative ER should be determined after considering the histopathology of EGC and the individual physiological status, and quality of life after surgery. Simple follow-up observation may be an acceptable alternative to additional gastrectomy in non-curative ER patients with a lower expectation of survival such as in elderly patients and patients complicated with high operative risks. On the other hand, additional surgery with lymphadenectomy is strongly recommended for non-curative ER patients without severe co-existing underlying disease and those who are young enough to tolerate surgical interventions according to the JGCA guidelines, knowing that additional surgery offers favorable survival outcomes in such patients.

Regarding peri-operative outcomes, a Korean study of 346 patients undergoing additional radical gastrectomy had zero mortality and only 5.6% associated morbidity [9]. Another Korean study found that the rate of surgery-related adverse events were similar between the ER with additional surgery and matched surgery subgroups [7]. These results suggest that such aggressive surgical treatment can be undertaken safely in selected patients by experienced surgeons.

One of the limitations of the present study is that all the studies in this meta-analysis are retrospective and uncontrolled, which may potentially produce patient selection bias. The baseline characteristics of the additional surgery group differed significantly from those of the simple follow-up group. However, the survival benefit of additional surgery remained significant when the analysis was restricted to studies reporting the multivariate-adjusted estimates. Another limitation is that all the included studies came from the East Asia region, which may affect the generalizability.

In conclusion, additional surgery offers a survival advantage in patients undergoing non-curative ER of EGC. Given the absence of randomized studies addressing this tissue, our study may provide the most convincing evidence on this subject.

## Compliance with ethical standards

**Disclosures** Debang Li, Haixin Luan, Shijie Wang, and Yanming Zhou have no conflicts of interest or financial ties to disclose.

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