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# Systematic evaluation of the safety and therapeutic effects of para-aortic lymphadenectomy for advanced gastric cancer: a systematic review and meta-analysis

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**Abstract. – OBJECTIVE: At present, there is still no definite conclusion on whether advanced gastric cancer (GC) requires additional para-aortic nodes dissection (PAND). The purpose of this study is to summarize current evidence on the potential benefits of the extended systemic lymphadenectomy (D2+) compared to D2 lymphadenectomy in the treatment of gastric cancer.**

**MATERIALS AND METHODS: Systematic literature search was performed across PubMed, Embase, Cochrane library, Web of Science, China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, VIP Database for Chinese Technical Periodicals, and China Biology Medicine disc using the following terms: gastric cancer, para-aortic lymphadenectomy, D2+ lymphadenectomy and D3 lymphadenectomy. RevMan 5.3 software was used for the meta-analysis.**

**RESULTS: A total of 20 studies involving 5,643 patients were included, consisting of 6 randomized controlled trials (RCT) and 14 non-randomized controlled trials (nRCT). Compared with the D2 group, the operating time in the D2+ group was longer [mean difference (MD)=99.45 min, 95% confidence interval (CI) (48.93, 149.97), $p<0.001$], with more intra-operative blood loss [MD=262.14 mL, 95% CI (165.21, 359.07), $p<0.001$]. There were no significant differences in five-year overall survival (OS) [HR=1.09, 95% CI (0.95, 1.25), $p=0.22$] and post-operative mortality [RR=0.96, 95% CI (0.59, 1.57), $p=0.88$] between the two groups. The rate of post-operative complications in group D2+ was higher than that in group D2 [RR=1.42, 95% CI (1.11, 1.81), $p<0.001$].**

**CONCLUSIONS: Prophylactic D2+ surgery is not recommended, since D2+ surgery is associated with an increased rate of post-operative complications and does not improve the long-term survival rate of patients with advanced gastric cancer. However, D2+ surgery (especially D2+PAND) has certain survival advantages for specific patients, and D2+PAND surgery combined with chemotherapy may potentially improve long-term survival rate.**

*Key Words:*
Gastric cancer, D2+ lymphadenectomy, D2 lymphadenectomy, Para-aortic lymphadenectomy.

## Introduction

Gastric cancer (GC) is associated with poor overall survival rates worldwide. It is ranked fifth in morbidity and third in mortality[1-3], and the morbidity rates are highest in east Asia and lowest in North America[4]. Although early diagnosis

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of gastric cancer has greatly improved due to the recent developments in endoscopy, the prognosis is still unsatisfactory[5]. At present, surgery is the main therapeutic option for GC[6]. As lymph node metastasis is likely to occur in gastric cancer patients, lymph node dissection is recommended during surgery. However, the optimal extent of lymphadenectomy remains unclear and controversial.

For D1 lymphadenectomy, the stomach with the primary tumor and perigastric (N1) lymph nodes are removed. For D2 lymphadenectomy, the nodes along the common hepatic, the splenic, the left gastric, and the left hepatic arteries are also removed, as well as some stations that differ for middle, proximal, and distal tumors (N2 nodes). This type of surgery was introduced by Japanese surgeons and is now considered the recommended standard practice[8,9]. During the late 1900s, 18%-40% patients with advanced GC were reported to have metastasis in the para-aortic nodes[7-9]. Therefore, some researchers assumed that removing these lymph nodes might improve the clinical outcome of advanced GC[7,10,11]. As a result, D2+ surgery progressed to the dissection of the lymph nodes beyond the N1, N2, such as station 10 or station 14v[12]. Para-aortic lymph node is considered as the outmost barrier before gastric cancer cells systemic metastasis. Therefore, No. 16 lymph nodes have been a focus of attention among gastrointestinal surgeons for a long time. However, there is still dispute regarding the scope of lymph node dissection. In 1999, two studies[13,14] were published in Europe, which showed that compared with D1 surgery, D2 surgery was not beneficial in terms of long-term survival rate and was associated with higher rate of post-operative complications and mortality. However, with further advances in the modern medical technology, a randomized controlled trial[15] (RCT), carried out in 2006, showed that D2 surgery had obvious survival advantages over D1 surgery. While a consensus has been reached on D2 surgery, there is still no definite conclusion on whether advanced gastric cancer requires additional para-aortic lymphadenectomy (D2+ surgery). Although a systematic review published in 2010 reported that D2+para-aortic nodes dissection (PAND) are similar to the standard D2 resection in terms of post-operative mortality, D2+PAND still do not increase overall survival in patients with advanced gastric cancer[16]. The present study aims to systematically evaluate relevant clinical studies comparing D2+PAND and D2 surgery alone in GC patients in terms of intra-operative and post-operative complications, mortality, and long-term survival, in an attempt to provide significant data to aid clinical decision-making.

## Materials and Methods

### Search Strategy

Relevant articles were retrieved from PubMed, Embase, Cochrane library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, VIP Database for Chinese Technical Periodicals, and China Biology Medicine disc databases. The deadline for retrieval was July 2021.

English language articles with the following subject terms and key words were retrieved: gastric cancer, gastric carcinoma, carcinoma of stomach, stomach cancer, para-aortic lymphadenectomy, D2+ lymphadenectomy, D2 lymphadenectomy and D2 plus. References of manuscripts were also screened for any additional relevant clinical controlled studies.

### Articles' Selection

The following inclusion criteria were used: (1) research type: randomized controlled trials (RCTs) and non-randomized controlled trials (nRCTs). (2) Research subject: curable patients with gastric cancer, with no limit regarding age or sex. (3) Intervention measure: the control group underwent D2 surgery, while the treatment group underwent D2+ (para-aortic lymphadenectomy) surgery. (4) Evaluation indicators: operation time, intra-operative blood loss, post-operative complications, 5-year overall survival (OS), post-operative mortality and intra-operative blood transfusion.

Exclusion criteria were as follows: (1) non-human study; (2) patients with metastatic gastric cancer; (3) D1 surgery.

### Literature Evaluation

Quality evaluation of the articles was conducted by two researchers independently. Any disagreements were resolved by discussion with a third researcher. The Newcastle-Ottawa Scale (NOS) was used for quality evaluation of nRCTs, and the Cochrane bias risk evaluation tool was used for quality evaluation of RCTs. Funnel plots were used to make a visual assessment of the publication bias. According to the Cochrane man-

ual, funnel plots are required when the number of studies enrolled in the meta-analysis is more than 10.

### Data Extraction

Two researchers independently evaluated all retrieved studies, read the titles and abstracts, selected potentially useful studies according to the inclusion and exclusion criteria, read the text thoroughly and decided which studies should be included in the meta-analysis. If there were several articles related to one study, the article containing the most complete data was included. In case of dispute on selected studies between the researchers, it was resolved by discussion.

### Statistical Analysis

RevMan 5.3 software (Cochrane Collaborative software Copenhagen, Denmark) was used to process the data[17]. Dichotomous variables were reported as hazard risk (HR) or relative ratio (RR) value with 95% confidence interval (CI). Continuous variables were reported as mean difference (MD) and 95% CI. $p<0.05$ was considered statistically significant. The Q statistics test and $I^2$ test were used to evaluate heterogeneity. If $p>0.1$ and $I^2<50\%$, no heterogeneity was present. We assessed clinical heterogeneity by examining the type of participants, interventions, and outcomes in each study. We assessed statistical heterogeneity using the Chi$^2$ test to determine whether the observed differences in the results were compatible with chance alone. The $I^2$ statistic was used to determine the impact of heterogeneity on the meta-analysis. When the heterogeneity was large, the random-effects model was used. Otherwise, the fixed-effects model was used.

## Results

### Article Retrieval and Selection

The process of literature search and study design is shown in Figure 1. In total, 219 articles were retrieved. Of them, 60 articles remained after removal of duplicates, and 35 papers remained after title and abstract screening. Eleven articles that met the eligibility criteria of the study were selected for inclusion. Additional two papers were identified in the reference section of relevant review articles. Finally, 13 studies involving 3,056 patients were selected[17-29].

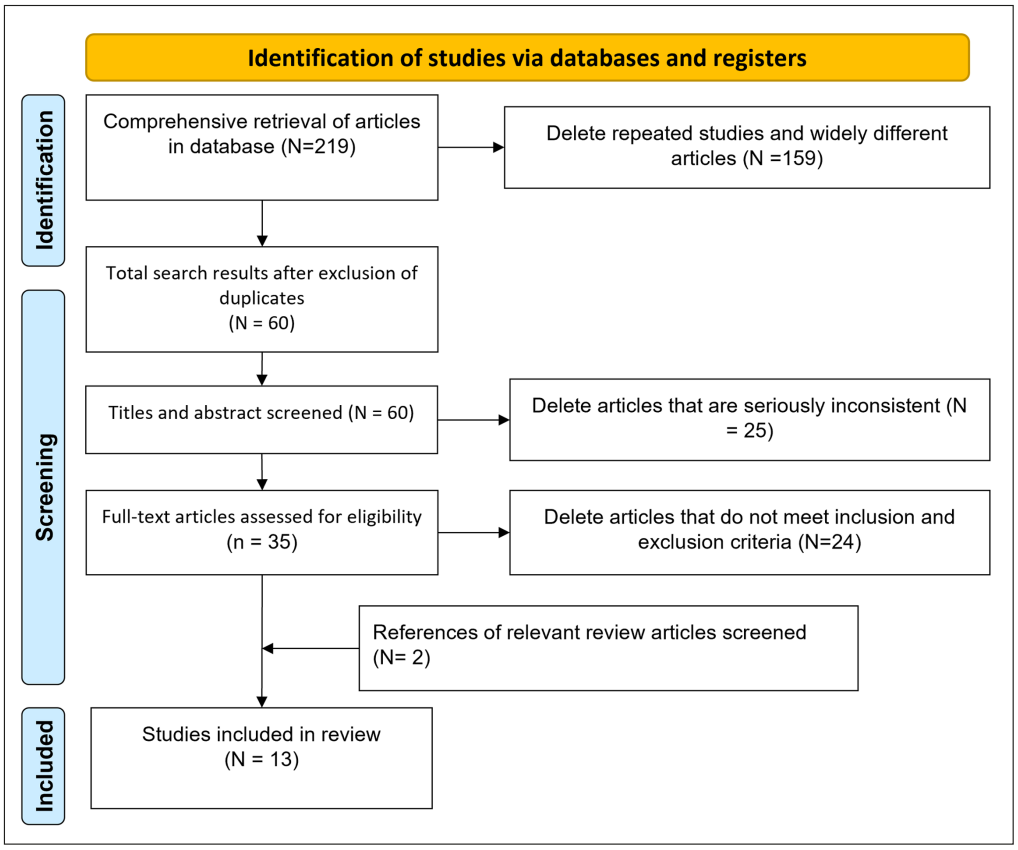


**Figure 1.** Procedure for article selection.

### General Characteristics and Quality Evaluation of the Articles

The general characteristics of all studies are shown in Table I[17-29]. Risk of bias in the included RCTs was assessed using the Cochrane bias risk evaluation tool, which is edited by the Cochrane Collaborative network and is the first choice recommended by statisticians and system reviewers for evaluating RCT[30]. The evaluation results are shown in Figures 2 and 3. According to the bias risk charts, for the random sequence generation (selection bias), 66.7% of the included RCTs had low risk of bias and 33.3% of RCTs had an unclear risk of bias. For the allocation concealment (selection bias), 33.3% of RCTs had low risk, 50% of RCTs had unclear risk, and 16.7% of RCTs had high risk of bias. For the performance bias, 66.7% of RCTs had low risk, and the risk was unclear in 33.3% of RCTs. For the detection bias, 50% of RCTs had low risk and the risk was unclear in 50% of RCTs. For the attrition bias, 100% of RCTs had low risk of bias. For the reporting bias, 83.3% of RCTs had low risk and the risk was unclear in 16.7% of RCTs. The risk of other bias was unclear in 100% of RCTs.

Risk of bias in the included nRCTs was evaluated using the NOS scale for evaluation, with the total score of 9, and higher score indicating better quality[31]. Specific ratings of the included nRCTs are shown in Table II.

### Results of Meta-Analysis

#### (I) Operation time

Seven studies[17-19,21,22,26,27] reported operation time data. The meta-analysis results showed statistically significant differences between the D2 and D2+ groups [MD=118.75 min, 95% CI (58.94, 178.56), $p<0.00001$]. Compared with the D2 group, the operation time in the D2+ group was longer with an average of 110.50 min (Figure 4).

#### (II) Intra-operative blood loss

Four studies[17,19,21,22] reported intra-operative blood loss. The meta-analysis results showed a significant difference between these two groups [MD=290.45 mL, 95% CI (198.63, 382.26), $p<0.07$]. Blood loss in the D2+ group was significantly more than that in the D2 group, and the test for heterogeneity was 0.03 (Figure 5).

#### (III) Rate of post-operative complication

Twelve studies[17-23,25-29] mentioned the incidence of post-operative complications. The meta-analysis results showed that the post-operative complication rate in the D2+ group was significantly higher than that in the D2 group [RR=1.43, 95% CI (1.07, 1.92), $p<0.0001$] (Figure 6).

#### (IV) Post-operative mortality

Twelve studies[17-25,27-29] mentioned post-operative mortality rate. The meta-analysis results showed that the differences between the two groups were not statistically significant. Compared with the D2 group, post-operative mortality of D2+ group was not increased [RR=1.53, 95% CI (0.91, 2.55), $p=0.51$] (Figure 7).

#### (V) Post-operative 5-year OS

Six studies[17,21,22,25,27,29] reported post-operative 5-year OS. The meta-analysis results showed that the differences between the two groups were not statistically significant. Compared with D2 surgery, D2+ surgery would not improve post-operative OS [HR=1.05, 95% CI (0.91, 1.21), $p=0.99$] (Figure 8).

### Publication Bias and Sensitivity Analysis

No publication bias was detected using Funnel plot analysis of studies reporting on the operation time (Figure 9A), post-operative complications (Figure 9B) and post-operative mortality (Figure 9C). Sensitivity analysis was carried out by excluding each study one by one. No significant changes in the sensitivity and specificity were observed.

## Discussion

We conducted a systematic review of current studies comparing safety and therapeutic effect of standard D2 and D2+ lymphadenectomy in patients with advanced gastric cancer. Thirteen studies involving 3,056 patients were included in our review[17-29]. The results of our meta-analysis showed that D2+ surgery is associated with the increase in post-operative complications and does not improve the long-term survival rate of patients with advanced gastric cancer.

Our results showed that despite an obvious statistical heterogeneity regarding operation time, intra-operative blood loss and post-operative complication, the sensitivity and specificity did not change significantly when each study was excluded one by one. No statistical heterogeneity was detected in terms of post-operative mortality and 5-year OS.

**Table I.** General characteristics of the selected articles.

| Author | Year | Research type | Country | D2 cases | D3 cases | D2 male/female | D3 male/female | D2 (year) age | D3 (year) age |
|---|---|---|---|---|---|---|---|---|---|
| Maeta et al[17] | 1999 | RCT | Japan | 35 | 35 | 21/14 | 20/15 | 60 ± 11 | 59 ± 9 |
| Jiang et al[18] | 2000 | RCT | China | 32 | 21 | 19/13 | 11/10 | 46-83 | 34-84 |
| Xu et al[19] | 2002 | Non-RCT | China | 50 | 36 | NA | 22/14 | 29-70 | 34-68 |
| Bostanci et al[20] | 2004 | Non-RCT | Turkey | 100 | 34 | 63/37 | 21/13 | 58.5 ± 13 | 53 ± 12.6 |
| Kunisaki et al[21] | 2006 | Non-RCT | Japan | 430 | 150 | 286/144 | 109/41 | 62.2 ± 12.5 | 59.3 ± 10.7 |
| Yonemura et al[22] | 2006 | RCT | Japan | 128 | 128 | 84/44 | 86/42 | 63.8 ± 9.7 | 62.5 ± 10.2 |
| Zhan et al[41] | 2006 | Non-RCT | China | 146 | 126 | 92/34 | 113/33 | NA | NA |
| Kulig et al[23] | 2007 | RCT | Poland | 141 | 134 | 85/56 | 83/51 | 31-81 | 34-77 |
| Sasako et al[25] | 2008 | RCT | Japan | 263 | 260 | 176/87 | 183/77 | 25-75 | 25-75 |
| Yonemura et al[25] | 2008 | RCT | Japan | 135 | 134 | 90/45 | 91/43 | 63.8 ± 9.7 | 62.5 ± 10.2 |
| Hu et al[27] | 2009 | Non-RCT | China | 55 | 62 | 42/13 | 48/14 | 58.8 ± 11.4 | 54.3 ± 11.4 |
| Huang et al[26] | 2009 | Non-RCT | China | 101 | 50 | 77/24 | 35/15 | 52.3 ± 11.2 | 52.6 ± 12.5 |
| Zheng et al[28] | 2011 | Non-RCT | China | 33 | 42 | 19/14 | 29/13 | 53.5 ± 11.2 | 55.9 ± 8.9 |
| Bostanci et al[29] | 2013 | Non-RCT | Turkey | 370 | 98 | 248/122 | 61/37 | 60.2 ± 12.4 | 56.2 ± 11.9 |

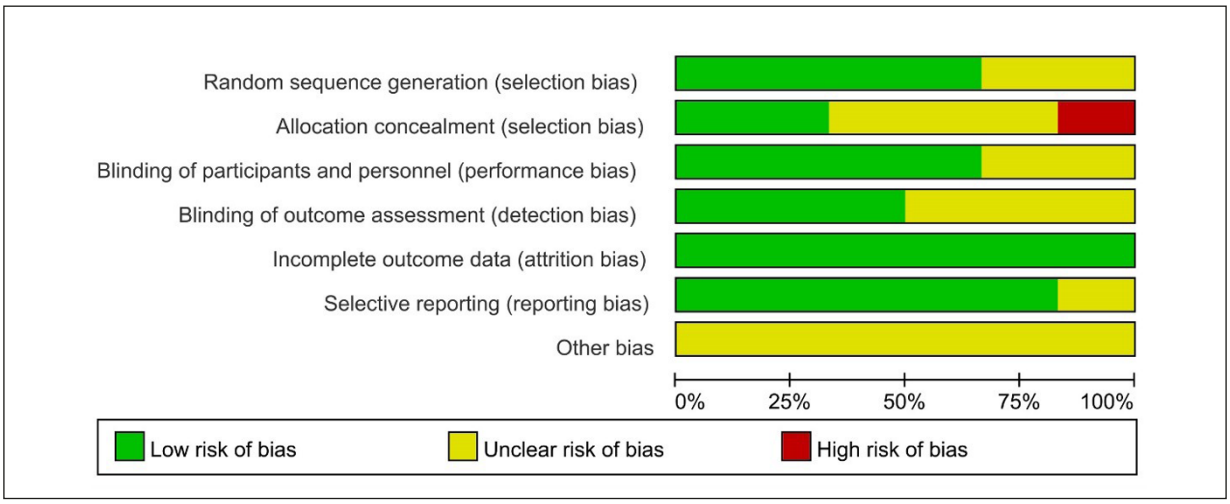


**Figure 2.** Risk of bias graph.

There was a significant difference in the rate of post-operative complications between the patients that underwent D2 and D2+ operations. However, high heterogeneity was detected, and the results of sensitivity analysis were different after excluding each study one after another. Therefore, we suggest that the reason for the difference in the post-operative complications was probably related to variability in the surgical expertise levels among the included studies. Notably, modern technology in combination with experienced surgical team allows to perform the D2+ surgery in a safe way.

The results of our meta-analysis showed that compared to D2 surgery, D2+ surgery could not

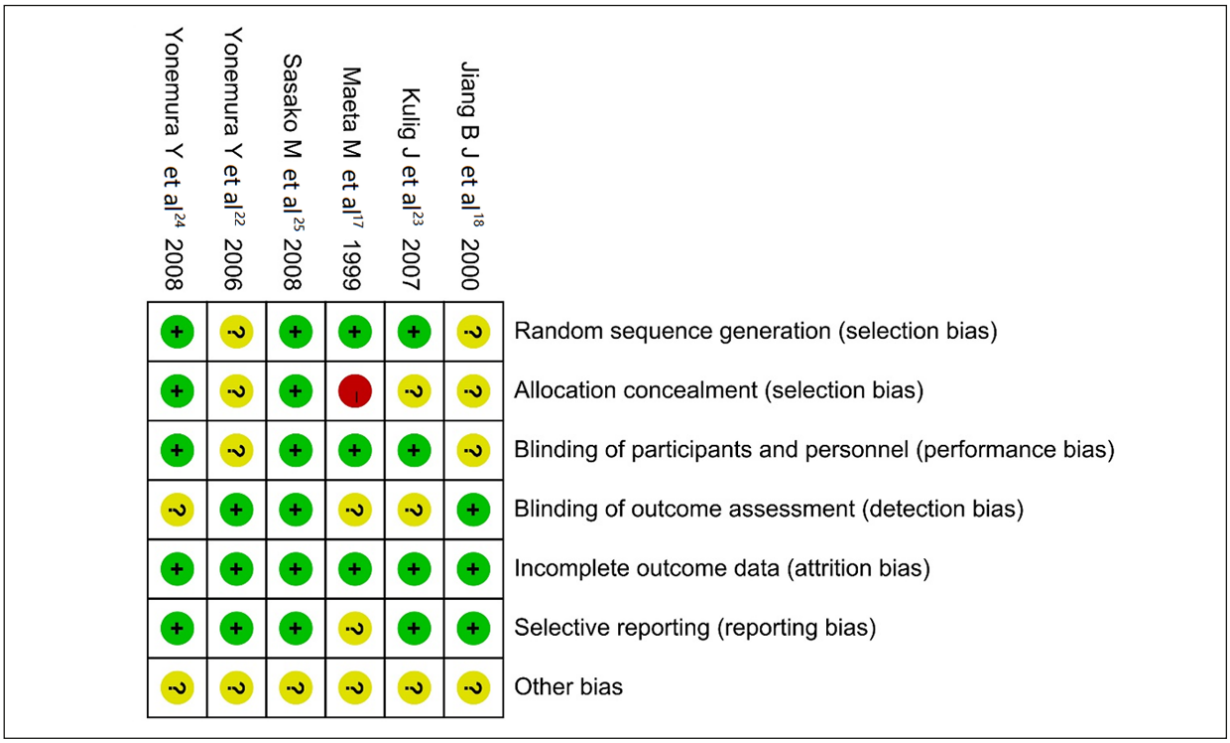


**Figure 3.** Risk of bias summary.

**Table II.** Newcastle-Ottawa Scale for assessing the quality of nRCTs.

| Study ID | | Selection | | | | Comparability | | Outcome | | | Total score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design | Comparability of cohorts on the basis of the analysis | Assessment outcome | Follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | |
| Xu et al[19] | 2002 | 1 | 1 | 1 | 1 | 1 | | | | | **5** |
| Bostanci et al[20] | 2004 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | | **7** |
| Kunisaki et al[21] | 2006 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | **9** |
| Hu et al[27] | 2009 | 1 | 1 | 1 | 1 | 1 | | 1 | 1 | 1 | **8** |
| Huang et al[26] | 2009 | 1 | 1 | 1 | 1 | 1 | | | | | **5** |
| Zheng et al[28] | 2011 | 1 | 1 | 1 | 1 | 1 | | | | | **5** |
| Bostanci et al[29] | 2013 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | **9** |

Evaluating concerns of cohort study consists of the following three aspects: selection, comparability and outcome. A study can be awarded a maximum of one star for each numbered item.

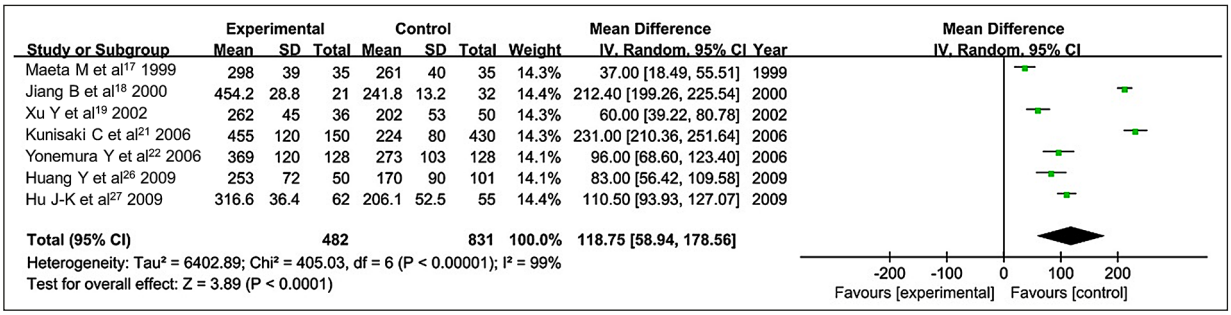


**Figure 4.** Forest plot of comparison in operation time between D2 and D3 patients. D3 patients are the experimental group, and D2 patients are the controlled group).

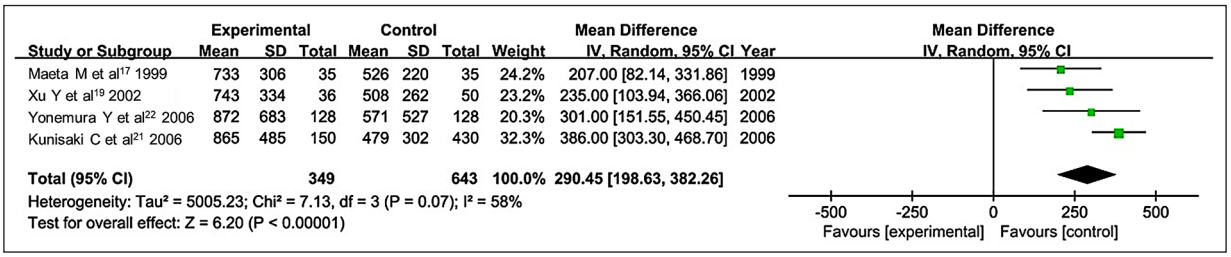


**Figure 5.** Forest plot of comparison in intra-operative blood loss between D2 and D3 patients.

improve the long-term survival of GC patients. However, significant differences were found in many subgroup studies. In 2008, a RCT published by Sasako et al[25] found that D2+ surgery does not improve the survival rate in curable gastric cancer as compared with D2 surgery. However, in subgroups with 5-10 cm tumor size and negative lymph node metastasis, D2+ surgery resulted in better 5-year OS than D2 surgery. In 2009, a study by Fujimura et al[32] reported that patients who accepted selective removal of station 16 b1 lateral group lymph nodes and station 16a2 interior group lymph nodes with positive metastasis had better prognosis. Similarly, a retrospective case-control conducted by Hu et al[27] found that in patients with T4 stage, D2+PALD was associated with the 5-year OS of 66.7%, which was significantly higher than

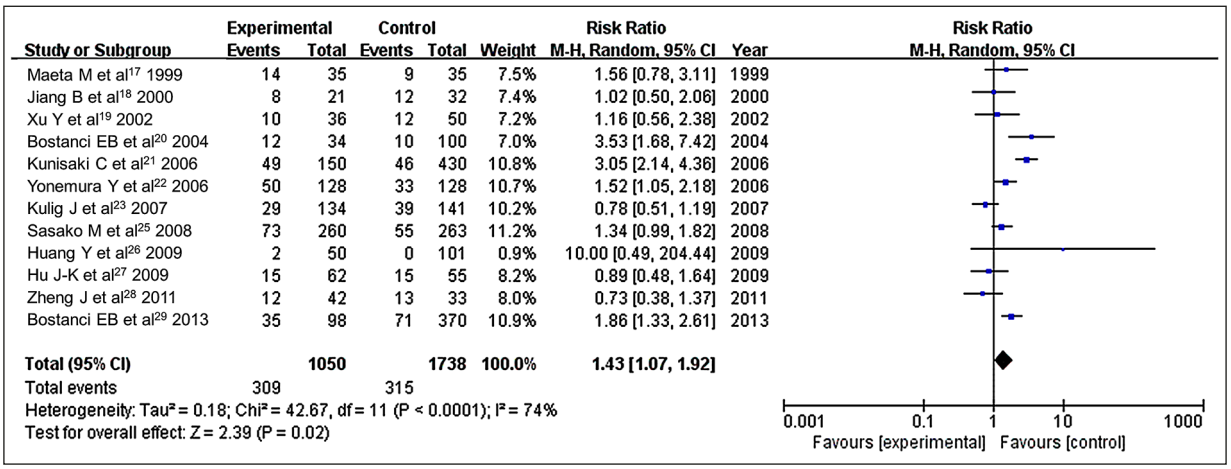


**Figure 6.** Forest plot of comparison in post-operative complication between D2 and D3 patients.

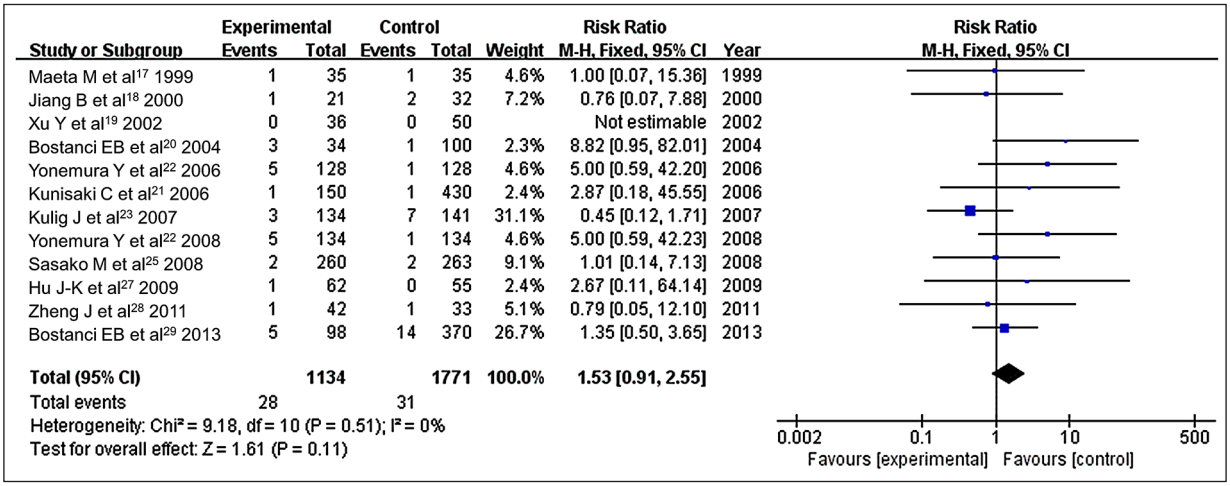


**Figure 7.** Forest plot of comparison in post-operative mortality rates between D2 and D3 patients.

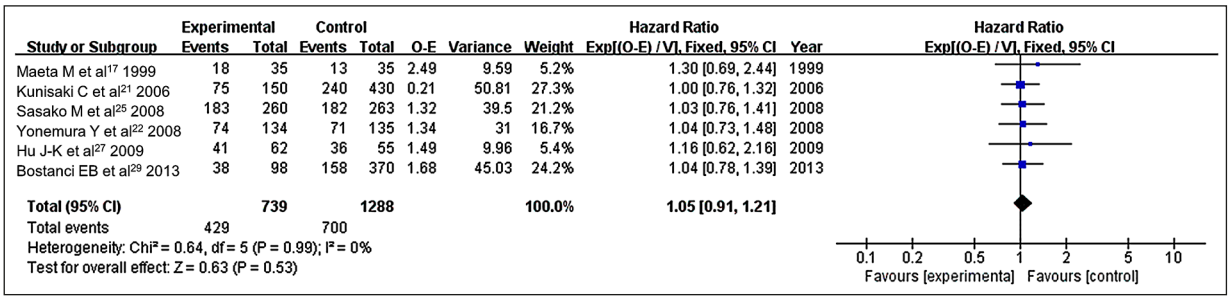


**Figure 8.** Forest plot of comparison in post-operative 5-year OS between D2 and D3 patients.

the 5-year OS of the D2 group (56.4%). In 2016, Morita et al[33] reported that D2+ surgery did not increase the long-term survival of aged patients with lymph node positive metastasis between the upper side of the left renal vein, abdominal aorta and inferior vena cava. Although all studies have demonstrated that D2+ surgery has certain survival advantages for specific populations, current guidelines do not recommend a prophylactic D2+ surgery, since the clinicians still lack accurate method of assessing lymph-node metastases before surgery. While a multi-dis-

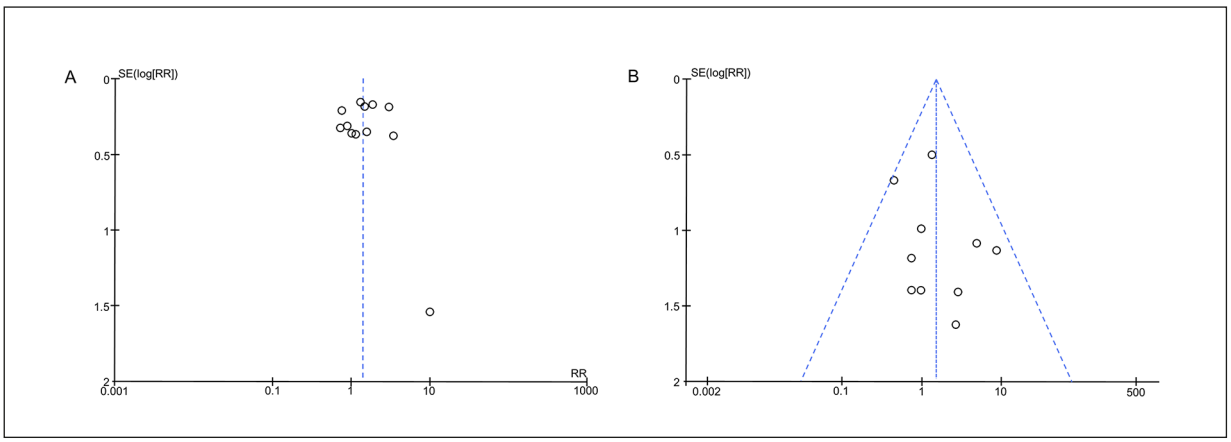


**Figure 9.** Publication bias: Funnel plot of post-operative complication (**A**), Funnel plot of post-operative mortality (**B**).

ciplinary team cooperation can improve the accuracy in lymph node metastasis evaluation, neither can provide a positive diagnosis[34].

Numerous studies[3,35-39] show that chemotherapy can be an effective adjuvant therapy for gastric cancer. Some reports[35-39] suggest that the combination of perioperative chemotherapy and D2+ surgery may increase long-term survival of GC patients. In 2009, Yoshikawa et al[35] published a study on the treatment of gastric cancer with positive 16th lymph node by combining pre-operative chemotherapy and D2+ surgery. Although the study was terminated early as the mortality rate in the tested population was higher than 5%, the results showed that preliminary multi-modal treatment improved the 3-year survival rate which was as high as 27%. In 2012, a study by Oyama et al[36] showed that, compared with D2+ surgery alone, D2+ surgery combined with chemotherapy could improve 2-year OS and recurrence-free survival. In 2014, a study by Tsuburaya et al[37] showed that the 3-year and 5-year OS of patients with gastric cancer and wide-range lymph node metastasis who were treated with D2+ surgery combined with pre-operative chemotherapy reached 59% and 53%, respectively. In 2014, a phase II clinical trial[38] in the Zhongshan Hospital showed that patients receiving D2+ surgery combined with pre-operative chemotherapy had better long-term survival and progression-free survival compared to chemotherapy alone group. Taken together, these studies demonstrate that the treatment of gastric cancer with combined pre-operative chemotherapy and D2+ surgery can achieve better long-term survival. However, further studies are needed to prove the efficacy of the combined treatment. Recent studies[37-39] of JCOG 0001 and JCOG 0405 reported S-1 plus cisplatin might be a preferred preoperative scheme for gastric cancer with extensive lymph node metastasis. A RCT on this protocol that is currently underway (clinical trial number: NCT02139605) could provide more evidence for the development of clear management guidelines for lymph node dissection in gastric cancer.

## Conclusions

D2+ surgery is safe but does not improve the long-term survival rate of patients with advanced gastric cancer. Prophylactic D2+ surgery is not recommended. However, D2+ (especially D2+PAND) surgery has certain survival advantages for specific patients, and D2+ surgery combined with chemotherapy maybe improve long-term survival rate. In patients with clinically para-aortic nodal suspected metastases, treatment model of preoperative chemotherapy combined D2+PAND surgery might be reasonable.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Funding

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### Authors' Contribution

Xiaofeng Liao collected data, designed this work and wrote the manuscript; Peng Liu, Yinan Wang and Tianxiang Lei took part in the quality evaluation of the articles and article selection; Heli Liu designed this work, revised the manuscript. All authors contributed to final approval, accountability for the manuscript. The authors are grateful to doctor Songlin Zhu from Cancer Hospital of Hunan Province for his generous help on statistical analysis.

### Ethics Approval

Not applicable.

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