The effectiveness and safety of D2 plus para-aortic lymphadenectomy for resectable gastric cancer: a systematic review and meta-analysis

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Abstract

Background: Gastric cancer (GC) is among the malignant tumors of highest morbidity and mortality in the world, and has a profile of high lymph node metastasis rate. Lymph node clearance is a critical part of gastric cancer surgery, however, the extent of lymph node clearance, for example, whether to perform abdominal aortic lymph node dissection, remains considerably controversial. In this study, we performed a systematic review and meta-analysis to assess the effects of D2 plus para-aortic lymphadenectomy (PALD) on survival and postoperative complications in patients with GC.

Methods: An electronic search was conducted through PubMed, Embase and Cochrane Library. The Q test and $I^2$ were used to assess heterogeneity. The publication bias was evaluated via funnel plots. All statistical analyses were performed using STATA 14.0 (STATA, College Station, TX).

Results: 908 studies were retrieved via literature search and eight studies were finally included. There was no significant difference between D2 and D2+PALD in the 5-year survival rate after surgery (HR: 1.00, 95% CI: 0.97-1.03, $P = 0.897$; $I^2 = 64.9$). Besides, the 30-day mortality (RR: 1.17, 95% CI: 0.66-2.10, $P = 0.590$; $I^2 = 0.0$) and the overall risk of postoperative complications (RR: 1.15, 95% CI: 0.83-1.59, $P = 0.411$; $I^2 = 35.5$) were comparable between D2 and D2+PALD.

Conclusion: Based on current literature body, compared with D2, D2+PALD does not prevail in terms of long-term survival or perioperative outcomes.

Background

Gastric cancer (GC) is among the malignant tumors of highest morbidity and mortality in the world. More than 1 million new cases along with an estimated 783,000 deaths (equivalent to one twelfth of all-cause death worldwide) were reported in 2018, making GC the fifth leading cause of cancer incidence and third of cancer-related death. The high-risk regions of gastric cancer are mainly in East Asia, namely China, South Korea and Japan. Due to mild and atypical clinical manifestations and signs in earlier stage, GC patients are usually diagnosed in advanced stage, leading to poor prognosis. The therapeutic strategies of GC mainly including surgery, radiotherapy, chemotherapy, etc., among which surgical treatment is especially important. Gastrectomy plus second-stage lymph node dissection (D2) has become a standard curative procedure for advanced GC in East Asian countries, especially in Japan.

Five-year survival rates and postoperative complications are well-recognized indicators that are robust to assess the efficacy and safety of surgery. Lymph node metastasis can occur in the early stage of GC, for advanced GC patients, the risk is even higher, so lymph node dissection is particularly critical in GC surgery. However, the extent of lymph node clearance, for example, whether to perform abdominal aortic lymph node dissection, remains considerably controversial. According to the 4th edition of Japanese Gastric Cancer Treatment Guidelines, for the tumor not invading esophagus, the removal of lymph nodes in the D2 lymphadenectomy for total gastrectomy includes No. 1-7, 8a, 9, 11p, 11d and 12a lymph nodes. The removal of lymph nodes in the D2 plus para-aortic lymphadenectomy (PALD) including D2 lymphadenectomy plus No. 16 lymph node. Studies have shown that more than 20% of patients with advanced gastric cancer have No. 16 lymph node metastasis. Some researchers believe that D2+PALD can extract more lymph nodes than traditional D2, achieving better therapeutic effects and improving patient survival. On the contrary, some researchers believe that D2+PALD can lead to greater trauma, higher blood transfusion rates, longer operative time and hospital stay, etc., without increasing the patient's five-year survival rate. In this study, we evaluated existing literature and conducted a systematic review meta-analysis to compare the clinical effects of the two procedures.

Materials And Methods

Literature and search strategy

Databases such as PubMed, Embase, and Cochrane library database were independently searched by two authors to identify original articles published until the end of June, 2019, using the following terms: "gastric", "stomach", "cancer", "tumor", "malignancy", "neoplasm", "para-aortic", "D3", "D4", and "lymphadenectomy". Manual screening of references was also conducted. No language restriction was performed.

Study selection

This meta-analysis is performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The inclusion and exclusion criteria for this meta-analysis were as follows: (1) All patients underwent radical gastrectomy with pathological diagnosis of primary GC. (2) Patients with distant metastasis, residual GC, severe cardiovascular, respiratory, liver or renal function diseases were excluded. (3) There should be sufficient data, including survival rate, postoperative complications, etc., and studies with inadequate data were excluded. (4) Data and related results can be extracted directly or indirectly from the original study. Conference abstracts and reports were excluded due to incomplete information. (5) Only comparable original articles were included, excluding reviews, systematic reviews and meta-analyses, letter to editor, case reports, and single-arm studies. The study selection process was conducted by two independent reviewers in accordance with the following procedure: the retrieved literature were firstly reviewed via title and abstract screening, the remaining were then scrutinized by full-text.

Data extraction and quality assessment

The following data were independently extracted by two authors: first author, year of publication, country, study period, sample size, age, TNM stage, abdominal aortic lymph node condition, type of surgery, time of surgery, intraoperative blood loss, blood transfusion, postoperative complications, postoperative mortality and survival data. The Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the methodological quality of the included studies. According to the evaluation criteria of the NOS scale, studies with more than 5 points were judged as moderate quality studies, while studies with 7 or more points were considered high quality studies.
**Statistical analysis**

Continuous data were processed using weighted mean difference (WMD) and 95% Confidence interval (CI), and postoperative complications and survival relative risk (RR) or risk ratio (HR) and 95% CI. Quantitative syntheses were conducted using random effects model to provide more conservative results, considering the inevitable heterogeneity. Cochran Q test and \( I^2 \) statistic were used to quantify and evaluate study heterogeneity. \( P < 0.1 \) and/or \( P < 0.05 \) were considered significant statistical heterogeneity. Heterogeneity was detected by sensitivity analysis. Publication bias was evaluated via funnel plots. Since the number of studies included in each meta-analysis is less than 10, funnel plots, instead of Egger's test, were used to assess publication bias, considering the lack of statistical power. All statistical analyses were performed using Stata 14.0 software (Stata Corporation, College Station, TX USA). \( P < 0.05 \) was considered to be statistically significant.

**Results**

**Search results and study characteristics**

The flow chart of the literature search is shown in Figure 1. Based on a predefined search strategy, 908 studies were initially identified through database and manual search. After excluding duplicates, screening title and abstracts, 879 unrelated studies were excluded and the remaining 29 studies were further evaluated by full-text view. Among these 29 studies, 21 articles were excluded due to incomplete information or other reasons. In the end, the meta-analysis included eight eligible studies, all of which were retrospective observational cohort studies. All included studies were published between 2003 and 2014, with sample sizes ranging from 117 to 1792. Among these studies, three were from Japan, four from China, and one from Poland. According to the results of NOS assessment, among the eight studies, two with eight and three with seven were considered of high-quality, the remaining three scored six points and were deemed moderate-quality. The detailed baseline characteristics of all included studies are summarized in Table 1.

**Impact of D2+PALD on long-term survival of GC patients**

We first evaluated the effect of D2+PALD on 5-year survival. A total of seven studies were pooled. The results showed no significant difference between the two groups (HR: 1.00, 95% CI: 0.97-1.03, \( P = 0.897; I^2 = 64.9\% \)) (Fig. 2). No significant asymmetry was observed in funnel plot.

**Impact of D2+PALD on perioperative outcomes of GC patients**

Mortality analysis within 30 days after surgery revealed no significant difference between the mortality of the two groups. D2+PALD did not dramatically increase postoperative mortality within 30 days (RR: 1.17, 95% CI: 0.66-2.10, \( P = 0.590; I^2 = 0.0 \)) (Table 2). In addition, a summary of complications showed that D2+PALD did not significantly increase the overall risk of postoperative complications (RR: 1.15, 95% CI: 0.83-1.59, \( P = 0.411; I^2 = 35.5\% \)) (Figure 3), including abdominal infection, anastomotic leakage, pancreatic fistula, and pulmonary infection, no significant difference between the two groups (Table 2). No significant asymmetry was observed in funnel plots of each quantitative syntheses.

**Publication bias**

According to the results of the funnel plot observation, there is no significant publication bias in this study.

**Discussion**

Surgical treatment is the only way to achieve radical cure for resectable GC, and has been significantly improved through decades of development. The Japan Gastric Cancer Association was the first to define the three stations of GC in 1998, and defined the terminology of the operations as D1, D2, and D3 according to the range of lymph nodes in the operation, and updated the lymph node dissection range of GC according to the extent of gastric resection in 2011. Wu et al published a study comparing D1 and D2 in 2006, and the results showed that the 5-year survival rates of patients with advanced GC after D1 and D2 were 53.6% and 59.5%, respectively (95% CI: 0.53-0.62, \( P = 0.231 \)). Compared with D1 surgery, patients with advanced GC undergoing D2 surgery achieved better survival outcome. Plenty of retrospective studies have shown that D2 resection can improve survival in patients with higher T &N-staged tumors, and in this regard, D2 surgery has been widely used to treat advanced GC in Asia. Controversy lies in whether to perform D2 or D2+ PALD surgery on patients with advanced GC. According to relevant studies, once gastric tumors invade the subserosal (T3 phase), serosal (T4a phase) or adjacent structures (T4b phase), the metastatic risk of para-aortic lymph nodes (PANs) increases to 10% to 30%. PALD may help to remove potential metastases, and in the meantime, surely help to collect more lymph nodes, which is critical to staging and prognosis prediction. Maeta et al reported that a patient with pathological PAN metastases survived more than 80 months after systemic PALD. Park et al found that the median overall survival of patients with isolated PAN metastases was significantly longer than that of patients with single organ metastases other than PAN or multiple organ metastases. Tokunaga et al retrospectively analyzed 178 patients with pathologically positive PAN who underwent radical resection and observed a 5-year survival rate of 13.0%. Fujiwara et al performed preoperative chemotherapy on 20 patients who had no other non-cure factors other than PALN metastasis and had a good clinical response to induction chemotherapy. After D2+PALD treatment, the 3-year and 5-year survival rates were increased to 72% and 65%, respectively. Fushida et al studied 24 patients with GC who were diagnosed with PAN metastasis, all patients underwent D2+PALD and the prognosis was good. Tokunaga et al retrospectively studied the role of D3 lymphadenectomy in 173 patients, suggesting that D3 resection may be beneficial for selected PAN-positive patients without other incurable factors. However, Hu et al showed that D2 plus PALD was not...
significantly superior, survival-wise, to D2 in patients with T3-4, N2 staging. Besides, Sasako et al showed that D2 lymphadenectomy plus prophylactic PALD did not improve the survival rate of curable GC compared with D2 lymphadenectomy, even though D2+PALD did not increase the risk of anastomotic leakage, pancreatic fistula, and abdominal infection. In line with the conclusion of the work by Sasako et al, the results of our comprehensive analysis on prophylactic and therapeutic D2+PALD showed that, compared with D2, D2+PALD did not improve the patients’ long-term survival, but nonetheless, did not increase the risk of postoperative complications.

It is well known that D2+PALD is more difficult to perform than D2, with longer operative time, more bleeding, and longer hospital stays, requiring experienced surgeons. However, with the development of modern technology, the extensive use of advanced medical equipment has reduced the operation time, operative mortality and surgery-related morbidity. D2+PALD can also perform as safely as D2 in professional medical centers with well-trained surgeons.

Several limitations reside in our work. First, all the included studies are retrospective, which affects the level of evidence of this study to some extent. Second, we only focused on overall survival as efficacy outcome in this study, other outcomes like recurrence free survival and rate of recurrence were not covered due to lack of data. Third, we were unable to access the personalized data of included studies to perform any further analyses to adjust for confounding factors. Fourth, the surgical results are closely related to the surgeon's experience. The expertise and approach of surgeons differs and matters, in which resides heterogeneity. Fifth, the postoperative intervention, such as postoperative radiotherapy and chemotherapy, on the patients also has a great impact on the outcome, however, due to the lack of relevant data, we did not account for this confounding factor. Sixth, the number of studies included is relatively small, especially for the studies concerning therapeutic D2+PALD, which might affect the credibility of the results of the analyses concerning long-term survival and perioperative complications. Besides, the lack of comparable studies on therapeutic D2+PALD makes it impossible to draw a conclusion, in this regard, more elaborately designed multi-center studies with larger sample size are needed in the future to illuminate the advantages and disadvantages of D2+PALD more comprehensively.

Conclusion

In summary, D2 + PALD can be as safe as standard D2, but requires experienced surgeons to operate. Prophylactic D2 + PALD did not increase postoperative complications compared to standard D2, but no long-term survival benefit was achieved. The role of therapeutic D2 + PALD requires more researches to further confirm. More well-designed multi-center studies of larger scale are needed in the future to explore D2 + PALD.

Declarations

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Not applicable.

Authors’ contributions

Shi-Hui Zou contributed to acquisition and analysis of data, the design and concept of the work, and drafted the manuscript. Jin-Xin Liu contributed to the conception, analysis and revisions of the work. Hui-Mian Xu and Bao-Jun Huang contributed to analysis, interpretation and revisions of the work. Jia-Le Zhang contributed to the conception, acquisition, analysis and interpretation of data and revisions of the work. All authors approve of the final version of the manuscript.

Disclosure of interest

The authors report no conflict of interest.

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Data availability statement

The authors confirm that the data supporting the finding of this this study are available within the article.

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**Tables**
| Author     | Country | Year | Sample size | TNM stage | Involvement of Para-aortic lymph node | Post-operative mortality (P/S) | Survival data (5-year OS, P vs S) | Anastomotic leakage (P/S) | Pancreatic fistula (P/S) | Pu disco |
|------------|---------|------|-------------|-----------|--------------------------------------|-----------------------------|---------------------------------|--------------------------|--------------------------|---------|
| Sasako et al. | Japan  | 2008 | 523/260/263 | T2b, T3, T4 | N                                    | 0.8%/0.8%                   | 70.3%/69.2%                    | 1.9%/2.3%                  | 6.2%/5.3%                | T.1     |
| Hu et al.   | China   | 2009 | 117/62/550  | T1, T2, T3, T4 | NR                                  | 0%/1.8%                      | 65.8%/66.1%                    | NR                       | NR                       | 3.2     |
| Zhang et al. | China   | 2013 | 1792/448/1344 | T1, T2, T3, T4 | NR                                  | 2%/2%                        | 31.2%/26.6%                    | 2%/2%                     | NR                       | 1       |
| Zhang et al. | China   | 2014 | 157/69/885  | pT3, pT4 | Y                                   | 0/0                          | 43.7%/31.8%                    | 1.4%/1.1%                  | 2.9%/2.3%                |         |
| Zhan et al.  | China   | 2003 | 153/73/850  | I, II, III/IV | NR                                  | 0/0                          | 46%/27%                        | 0/0                       | 0/0                      |         |
| Kulig et al. | Poland  | 2007 | 275/134/141 | T1, T2, T3 | N                                   | 2.2%/4.9%                    | 3.7%/6.4%                      | 0.7%/1.4%                  |                     |         |
| Yonemura et al. | Japan | 2007 | 269/134/135 | T2, T3, T4 | N                                   | 3.7%/0%                      | 55%/52.6%                      | NR                       | NR                       |         |
| Kunisaki et al. | Japan | 2006 | 580/150/430 | T2, T3, T4 | NR                                  | 0.67%/0.23%                  | 50.4%/56%                      | 6%/2.8%                    | 10.8%/8.7%               | 12      |

Abbreviations: P: D2+PALD; PALD: Para-aortic lymph node dissection; S: Stand D2; OS: Overall survival; NR: Not reported; N: No; Y: Yes.

**Figures**

**Flow diagram**

The flow diagram of study selection.
Figure 2
Forest plots evaluating the impact of D2+PALD on long-term survival.

Figure 3
Forest plots evaluating the impact of D2+PALD on postoperative complications.
Figure 4

Funnel plot for the analysis of long-term survival.