



Long-term outcomes of laparoscopic versus open D2 gastrectomy for advanced gastric cancer

Zhengyan Li*, Bofei Li, Bin Bai, Pengfei Yu, Bo Lian, Qingchuan Zhao**

Department of Surgery, Xijing Hospital of Digestive Diseases, The Fourth Military Medical University, No. 127 Changle West Road, Xi'an 710032, China

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ABSTRACT

Background: Technical safety and short-term surgical outcomes of laparoscopy-assisted gastrectomy (LAG) for advanced gastric cancer (AGC) have been investigated in many clinical trials. However, studies with large sample size and sufficient follow-up comparing LAG and open gastrectomy (OG) for AGC have seldom been reported. The purpose of this study was to compare the long-term outcomes of LAG versus open OG for AGC using a propensity score matching analysis.

Methods: We retrospectively evaluated 459 and 856 patients who underwent LG or OG with D2 lymph node dissection, respectively, for AGC between June 2007 and June 2012. One-to-one propensity score matching was performed to compensate for heterogeneity between groups. We compared long-term outcomes between the two groups after propensity score matching.

Results: In the propensity score-matched cohort, no significant differences were observed in 5-year overall survival (OS) (52.0% vs. 53.4%; $P = 0.805$) and disease-free survival (DFS) (46.8% vs. 47.3%; $P = 0.963$) between the LAG group and OG group. Stratified analysis showed that the 5-year OS and DFS rates were comparable between the two groups in each tumor stage ($P > 0.05$). Multivariate analysis revealed that the operation method was not an independent prognostic factor for OS or DFS. Further analysis showed that the recurrence pattern was similar between the LAG group and the OG group ($P > 0.05$).

Conclusion: LAG is a feasible surgical procedure for AGC in terms of long-term prognosis, although the results should be confirmed by the ongoing randomized controlled trials.

1. Introduction

Gastric cancer is a worldwide health concern and is the second leading cause of cancer-related deaths in China [1]. Gastrectomy with proper perigastric lymph node dissection remains the cornerstone of radical resection of potentially curable gastric cancer. With the advantages of minimally invasive and better early postoperative outcomes, laparoscopy-assisted gastrectomy (LAG) for early gastric cancer have garnered tremendous popularity over open gastrectomy (OG) since it was first reported by Kitano et al in 1994 [2–4]. Till now, extensive research has been performed in the field of LAG for advanced gastric cancer (AGC) and demonstrated that LAG is a safe and feasible procedure with better short-term outcomes as compared with OG [5–7]. However, the long-term outcomes of LAG for AGC have not been thoroughly evaluated because of studies with large sample size and sufficient follow-up have seldom been reported. Additionally, it also remains controversial whether LAG can be performed for AGC with serous infiltration (T4a) [8,9]. We, therefore, designed this study to

evaluate and compare the long-term outcomes of LAG and OG with D2 lymph nodes dissection for AGC.

2. Materials and methods

2.1. Patients

Patients with postoperative pathological diagnoses of AGC who underwent LAG or OG were screened from the prospectively maintained gastric cancer database at the Department of Digestive Surgery, Xijing Hospital of Digestive Diseases, The Fourth Military Medical University from June 2007 to June 2012. The inclusion criteria were as follows: (1) histologically confirmed adenocarcinoma by gastroscopy and pathological biopsy; (2) depth of invasion confined to pT2, pT3 or pT4a; (3) no distant metastasis or invasion to adjacent organs; (4) curative resection (R0) was performed; (5) no combined with other malignancy; (6) no emergency operation; (7) no history of abdominal surgery; (8) no neoadjuvant chemotherapy; (9) no combined resection of other

* Corresponding author. Department of Surgery, Xijing Hospital of Digestive Diseases, The Fourth Military Medical University, No. 127 Changle West Road, Xi'an 710032, China.

** Corresponding author. Department of Surgery, Xijing Hospital of Digestive Diseases, The Fourth Military Medical University, No. 127 Changle West Road, Xi'an 710032, China.
E-mail addresses: lizhengyan01@sina.com (Z. Li), zhaoqc@fmmu.edu.cn (Q. Zhao).

organs; (10) all underwent LAG or OG with D2 lymph node dissection. Ultimately, 1315 patients were included in analysis. The entire cohort included 459 patients underwent LAG and 856 patients underwent OG.

To reduce the effect of selection bias on the surgery type and potential confounding due to the limits of respective study, we performed propensity score matching using a logistic regression model with the following variables: age, gender, comorbidities, extent of resection, histologic type, pT stage, pN stage and pTNM stage. We performed one-to-one matching using a 0.02 caliper width. Finally, the propensity score matched cohort comprised 410 patients in each group. Pathologic staging were evaluated according to the 8th Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging system of gastric cancer [10].

2.2. Surgical procedure

The operative procedures for LAG and OG with D2 dissection have been described in detail previously [11–13]. The present study was approved by the Ethics Committee of Xijing Hospital, Fourth Military Medical University and informed consents were obtained from all participants before surgery. The patients chose the surgical type (LAG or OG) by their individual decision after they were informed of the advantages and risks of each surgical type. We routinely administered postoperative adjuvant chemotherapy with 5-fluorouracil and cisplatin to each patient with stage II or more advanced cancer.

2.3. Follow-up

Patients were followed up every 3 months during the first 2 years and then every 6 months from 2 to 5 years, and then annually. The length of follow-up was defined as the time from surgery to the final follow-up date of June 2017 or time of death.

2.4. Statistical analysis

All statistical analyses were performed using SPSS, ver.22.0 (SPSS Inc., Chicago IL, USA). The chi-square test was used to compare categorical variables between the two groups, and the independent sample *t*-test or Mann-Whitney *U* test was used to compare continuous variables. Survival curves were calculated using the Kaplan–Meier method and analyzed by the log-rank test. Multivariate analyses were performed by Cox proportional hazard model with forward selection to identify independent risk factors for overall survival (OS) and disease-free survival (DFS). Variables with *P* values less than 0.10 in the univariate analysis were considered in multivariate analysis. *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Patient characteristics for the entire and propensity score-matched cohort are summarized in Table 1. A total of 1315 patients meet the inclusion criteria during the 5-year period (2007–2012). Among the entire cohort, significant differences were observed in the gender, age, tumor size, pT stage, pN stage, pTNM stage and comorbidities between the two groups (*P* < 0.05). The propensity score-matched cohort was comprised of 820 patients. Each group included 410 patients, and both groups were well balanced for all variables.

3.2. Long-term survival outcomes for the propensity score-matched cohort

After a median follow-up period of 69 months (range 3–120 months). Neither the 5-year OS rate (52.0% vs. 53.4%, *P* = 0.805, Fig. 1A) nor the 5-year DFS (46.8% vs. 47.3%, *P* = 0.963, Fig. 1B) significantly differed between the patients in the LAG and OG groups.

Stratified analysis showed that the 5-year OS rates for the patients after LAG and OG: 84.0% versus 91.3% for the patients with stage IB (*P* = 0.271, Fig. 2A), 64.7% versus 69.3% for the patients with stage II (*P* = 0.315, Figure 2C), 32.6% versus 31.8% for the patients with stage III (*P* = 0.521, Fig. 2E). Regarding DFS rate, stratified analysis showed that the 5-year DFS rates for the patients after LAG and OG: 82.0% versus 87.0% for the patients with stage IB (*P* = 0.508, Figure 2B), 56.9% versus 62.0% for the patients with stage II (*P* = 0.302, Figure 2D), 29.0% versus 26.4% for the patients with stage III (*P* = 0.374, Fig. 2F). The results demonstrate that the 5-year OS or DFS rate is comparable between the two groups in the same stage.

3.3. Long-term survival outcomes for stage T4a gastric cancer

In terms of patients in T4a stage, the 5-year OS rate was 42.4% for the LAG group and 33.8% for the OG group for the entire cohort. No significant differences was observed between the two groups (*P* = 0.074, Fig. 3A). After propensity score matching, the 5-year OS rate was also comparable between the patients in the LAG and OG groups (39.3% vs. 48.2%, *P* = 0.618, Fig. 3C).

The 5-year DFS rate of patients in the LAG group was superior to that of the patients in the OG group for the entire cohort (40.4% vs. 26.8.2%, *P* = 0.012, Fig. 3B). However, the superiority of LAG group did not exist for the propensity score-matched cohort (35.7% vs. 32.1%, *P* = 0.397, Fig. 3D).

3.4. Analyses of prognostic factors for OS and DFS

Multivariate analysis revealed that the age, tumor size, pT stage, and pN stage were independent prognostic factors whereas the operation method was not (Table 2). Multivariate analysis revealed that the large tumor (> 5 cm), advanced pT stage (T3, T4a), and lymph node metastasis (N1–N3b) were independent prognostic factors for decreased DFS (Table 3).

3.5. Recurrence patterns of LAG and OG groups

In the propensity score-matched cohort, 216 patients (115 cases in the LAG group and 101 cases in the OG group) experienced recurrence within 5 years after surgery. Our results revealed the recurrence pattern was similar between the LAG group the OG group (Table 4).

4. Discussion

Gastrectomy with proper perigastric lymph node dissection remains the cornerstone of radical resection of EGC or AGC. For EGC, comparison of between LAG and OG demonstrated that LAG was a safe and feasible procedure with better short-term outcomes and equivalent rate of tumor recurrence and long-term survival [14–16]. With regard to LAG for AGC, most studies focus on short-term outcomes and showed that LAG with D2 lymph node dissection was a safe procedure for AGC if it was performed by experienced surgeons [17–19]. The comparison of long-term survival outcomes and recurrence for patients undergoing LAG and OG for AGC are still lacking. Additionally, many studies that reported the 5-year OS rate of patients with AGC were limited by inadequate follow-up, unmatched groups, insufficient extent of lymph node dissection and small sample size. Comparing with most previous studies on this topic, our study is in relatively large sample size with sufficient follow-up. Additionally, we used the propensity score matching method to reduce the effect of selection bias and potential confounding due to the limits of respective study. Moreover, our study is valuable because it only included cases performed gastrectomy with D2 lymph node dissection which has been accepted as the standard for AGC [20].

In a retrospective study of LAG for gastric cancer from 2003 to 2009, Pak et al. [21] reported an acceptable long-term outcomes of LAG

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