

# Effect of laparoscopic gastrectomy on compliance with adjuvant chemotherapy in patients with gastric cancer

Huizheng Bao, MD\*, Na Xu, MD, Zhongkun Li, MD, Hongtao Ren, MD, Hong Xia, MD, Na Li, MD, Hao Yu, MD, Janbiao Wei, MD, Chengyi Jiang, MD, Lu Liu, MD

## Abstract

This study was designed to investigate the effect of laparoscopic gastrectomy on adjuvant chemotherapy in patients with gastric cancer.

Patients with gastric cancer who underwent radical gastrectomy at our institution from January 2008 to January 2015 with R0 resection, as determined by a pathological examination, were included in this study. According to the surgical approach, patients were divided into the laparoscopic gastrectomy (LG) group and open gastrectomy (OG) group. Short-term and long-term outcomes were compared between the 2 groups.

Of the 206 patients enrolled in the study, 114 patients were included in the LG group and 92 patients were included in the OG group. There was no significant difference in patients' general data, including age, sex, medical comorbidities, and pathological staging, between the 2 groups. However, patients in the LG group had less intraoperative blood loss, fewer postoperative complications, and a shorter hospital stay compared with patients in the OG group. There was no significant difference in the start time of adjuvant chemotherapy between the groups. However, compared with OG, LG had the following advantages: patients received more cycles of adjuvant chemotherapy, more patients received a full dose of on-schedule adjuvant chemotherapy, and more patients completed  $\geq 75\%$  of the planned dose. Long-term survival and disease-free survival rates were higher in the LG than in the OG.

In summary, LG can improve compliance with adjuvant chemotherapy and long-term outcomes in patients with gastric cancer.

**Abbreviations:** DFS = disease-free survival, ECOG = Eastern Cooperative Oncology Group, LG = laparoscopic gastrectomy, OG = open gastrectomy, OS = overall survival, PS = performance status.

**Keywords:** adjuvant chemotherapy, gastric carcinoma, laparoscopic gastrectomy, minimally invasive surgery, radical gastrectomy

## 1. Introduction

According to the recommendations of relevant clinical guidelines, if the pathological stage of the tumor is Ib with lymph node metastasis, or the stage is II or higher, adjuvant chemotherapy should be used in patients with R0 resection after undergoing surgery for gastric cancer.<sup>[1–4]</sup> Studies have shown that early and full-dose adjuvant chemotherapy can improve the long-term survival of patients.<sup>[5–7]</sup> Since open gastrectomy (OG) for gastric cancer is highly invasive and patients recover slowly postoperatively, it often leads to delayed chemotherapy and an inadequate dosage.<sup>[8]</sup> Compared with open surgery, laparoscopic gastrectomy (LG) has many advantages, including less intraoperative

blood loss, reduced postoperative pain, less postoperative release of inflammatory factors, and rapid recovery, and the long-term outcome is similar to that of open surgery.<sup>[9–22]</sup> It has been reported that LG can improve the compliance with adjuvant chemotherapy in patients with colon cancer.<sup>[23]</sup> However, to the best of knowledge, no study has evaluated the effect of LG on adjuvant chemotherapy in patients with gastric cancer. Therefore, the study herein aims to examine the effect of LG on the compliance of adjuvant chemotherapy in patients with gastric cancer.

## 2. Patients and methods

This study complied with the ethical principles of the Declaration of Helsinki. This retrospective research study was approved by the ethics committee of our institution. The requirement for informed consent from all patients was waived because of the retrospective nature of this study.

From January 2008 to January 2015, 562 patients with gastric cancer received radical gastrectomy at our hospital. Of these, 269 patients received LG and 293 received OG. The indications for LG include clinical stage T1-3N0M0 and patients who receive no neoadjuvant therapy. However, medical insurance in China does not cover the costs of various surgical instruments used in LG, and LG is not listed in the treatment guidelines for gastric cancer. Therefore, if the patient's clinical stage is T1-3N0-1M0, the surgeon presents the available treatment regimens (laparoscopic

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Jilin Cancer Hospital, Changchun, Jilin, People's Republic of China.

\* Correspondence: Huizheng Bao, Jilin Cancer Hospital, Changchun, Jilin 130012, People's Republic of China (e-mail: baohzbel@aliyun.com).

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or open gastrectomy) and then allows the patient to choose the surgical approach.

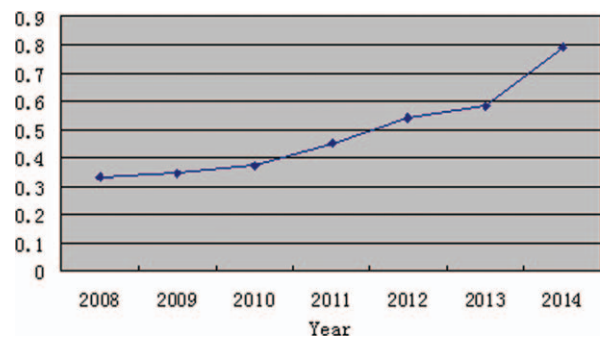
In this study, inclusion criteria were as follows: patients who met the aforementioned surgical indications, patients with R0 resection determined by a postoperative pathological examination, and patients who received at least 1 cycle of adjuvant chemotherapy after radical gastrectomy. Exclusion criteria were as follows: patients with incomplete clinical data and patients who underwent intraoperative removal of other organs. Two hundred six patients met the inclusion and exclusion criteria. Of these, 114 patients received LG and were included in the LG group, and 92 patients received OG and were included in the OG group. Staging of gastric carcinoma was based on the seventh edition of the TNM classification of gastric carcinoma, as proposed by the Union for International Cancer Control and American Joint Committee on Cancer. For patients operated on before 2010, staging was recalculated to match the seventh TNM classification. Specific surgical details have been previously described in the literature.<sup>[24]</sup>

We reviewed postoperative mortality, defined as death within 30 days after the operation, and postoperative morbidity, defined as complications occurring within 30 postoperative days. Morbidity was graded according to the Clavien–Dindo classification. Major complications were defined as grades 3, 4, and 5, and minor complications were classified as grades 1 and 2.<sup>[25]</sup>

Indications for adjuvant chemotherapy are tumors with a pathological stage Ib and lymph node metastasis or stage II and higher, and patients without contraindications to chemotherapy. The specific chemotherapy regimens were determined by medical oncologists. The chemotherapy regimens administered to patients were as follows: intravenous 5-fluorouracil combined with intravenous cisplatin, oral fluoropyrimidine and S-1, and oral S-1 and intravenous cisplatin.<sup>[26]</sup> The maximum number of cycles of chemotherapy was 6. The medical oncologists determined whether to delay chemotherapy or reduce the dosage of chemotherapy according to patients' symptoms, signs, and auxiliary examination results.

Patients were followed up with once every 3 months for the first 3 years postoperatively, once every 6 months for the fourth and fifth years, and subsequently, once every year. Follow-up examinations included brain, chest, and abdominal computed tomography examinations. If tumor recurrence was suggested based on the symptoms, timely hospital visits were provided. The last follow-up visit was in January 2016. Disease recurrence was defined as locoregional or distant metastasis confirmed by a radiology or pathology examination when appropriate.<sup>[27]</sup> Overall survival (OS) was assessed from the date of surgery until the last follow-up visit or death due to any cause. Disease-free survival (DFS) was calculated from the date of surgery until the date of cancer recurrence or death due to any cause.

SPSS software 13.0 for Windows (SPSS Inc, Chicago, IL) was used to perform the statistical analysis. Variables following a normal distribution are presented as a mean and standard deviation, and they were analyzed using the Student *t* test. Variables following a non-normal distribution are expressed as a median and range, and they were compared using the Wilcoxon test. Differences in the semiquantitative results were analyzed using the Mann–Whitney *U* test. Differences in the qualitative results were analyzed using the  $\chi^2$  test or Fisher exact test, as appropriate. Survival rates were analyzed using the Kaplan–Meier method, and differences between the 2 groups were analyzed using the log-rank test. Univariate analyses were performed to identify prognostic variables related to OS. Univariate variables with  $P < .05$  were



**Figure 1.** Proportion of patients undergoing LG among the total number of patients each year. LG = laparoscopic gastrectomy.

selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted hazard ratios with corresponding 95% confidence intervals were calculated.  $P < .05$  was considered statistically significant.

### 3. Results

As shown in Fig. 1, the proportion of patients undergoing LG among the total number of patients each year was gradually increasing.

Patients in the 2 groups showed no significant difference in age, sex, the Eastern Cooperative Oncology Group performance status (PS) score, medical comorbidities, and pathological stage (Table 1). Advantages of LG included less intraoperative blood loss ( $P = .019$ ), fewer postoperative complications ( $P = .027$ ), few major complications ( $P = .033$ ), and a shorter hospital stay ( $P = .031$ ) (Table 2). There were no significant differences in the

**Table 1**  
Comparison of baseline characteristics between the 2 groups.

	LG (n=157)	OG (n=129)	P value
Age, y	61 (42–70)	59 (40–69)	.359
Sex			.342
Male	107	81	
Female	50	48	
Comorbidities			
Hypertension	9	7	.911
Diabetes mellitus	5	6	.739
COPD	5	4	1.000
Liver cirrhosis	3	2	1.000
ECOG PS score			.805
0	121	101	
1	36	28	

COPD = chronic obstructive pulmonary disease, ECOG = Eastern Cooperative Oncology Group, LG = laparoscopic gastrectomy, OG = open gastrectomy, PS = performance status.

**Table 2**  
Comparison of postoperative data between the 2 groups.

	LG (n=157)	OG (n=129)	P value
Operative time, min	200 (150–320)	150 (120–340)	.025
Blood loss, mL	210 (160–480)	280 (200–560)	.019
Length of postoperative stay	8 (6–22)	10 (8–38)	.031
Overall complications	16	25	.027
Major complications	3	9	.033
Minor complications	13	16	

LG = laparoscopic gastrectomy, OG = open gastrectomy.

**Table 3**  
Comparison of pathological results between the 2 groups.

	LG (n=157)	OG (n=129)	P value
Retrieved lymph nodes	18 (16–26)	20 (16–26)	.225
Pathological TNM stage (7th AJCC-UICC)			.800
IIB	45	38	
IIIA	61	50	
IIIB	38	33	
IIIC	13	8	
Histological type			.757
Differentiated	97	82	
Undifferentiated	60	47	

LG=laparoscopic gastrectomy, OG=open gastrectomy.

pathologic results such as the number of lymph nodes dissected and tumor differentiation between the 2 groups (Table 3). Compared with patients in the OG group, patients in the LG group had better compliance with adjuvant chemotherapy; specifically, patients received more cycles of adjuvant chemotherapy ( $P=.044$ ), more patients received a full dose of on-schedule adjuvant chemotherapy (delayed chemotherapy doses and reduced chemotherapy doses:  $P=.027$  and  $.014$ , respectively), and more patients completed  $\geq 75\%$  of the planned dose ( $P=.000$ ) (Table 4). No significant difference in the time of the first adjuvant chemotherapy and the incidence of grade 3 or 4 chemotherapy toxicity was found between the 2 groups. The pathological TNM staging had no effect on compliance with adjuvant chemotherapy (Table 5).

The median follow-up duration was 30 months. The 5-year OS rates of patients in the LG group and OG group were 56% and 42%, respectively, and the difference was statistically significant (Fig. 2,  $P=.030$ ). The 5-year DFS rates in the LG and OG groups were 42% and 18%, respectively, and the difference was statistically significant (Fig. 3,  $P=.005$ ). Results of multivariate analysis showed that a higher T stage, higher N stage, less than 75% of total planned regimen without delay or dose reduction, reduced chemotherapy doses, and OG were independent predictors of a poor prognosis (Tables 6 and 7).

**Table 4**  
Comparison of chemotherapy compliance between the 2 groups.

	LG (n=157)	OG (n=129)	P value
Cisplatin + 5-FU	59	45	
Fluoropyrimidine + S1	50	48	
Cisplatin + S1	48	36	
Time interval to initiate chemotherapy, d	38 (32–68)	42 (35–85)	.192
Percentage of planned regimen received	78 (54–94)	67 (46–85)	.044
Patients with delayed chemotherapy doses	16	25	.027
Patients with reduced chemotherapy doses	22	33	.014
More than 75% of total planned regimen without delay or dose reduction	114	68	.000
Toxicity grade 3	31	25	.938
Toxicity grade 4	16	11	.632

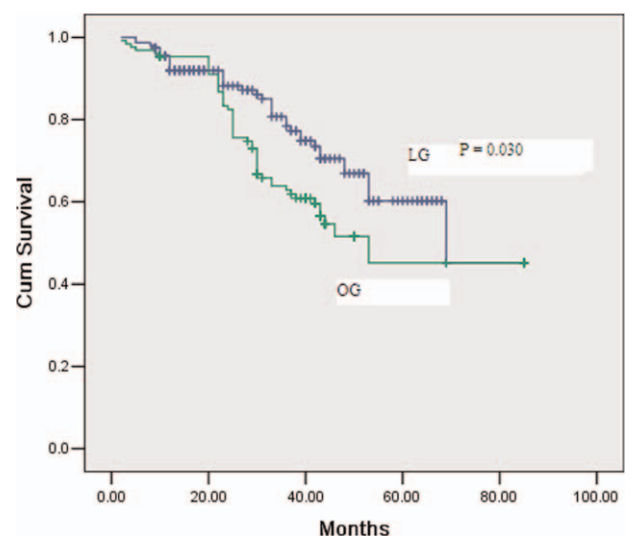
5-FU=fluorouracil, LG=laparoscopic gastrectomy, OG=open gastrectomy.

**Table 5**  
Comparison of chemotherapy compliance stratified by pathologic stage.

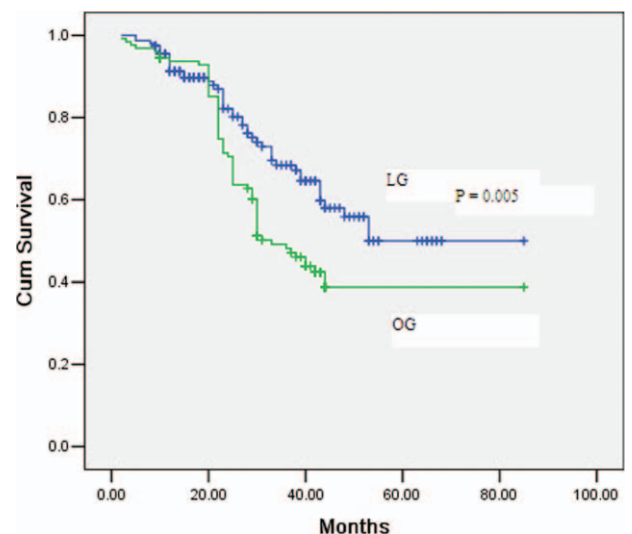
	Stage II (n=83)	Stage III (n=203)	P value
Percentage of planned regimen received	71 (48–94)	74 (46–82)	.249
Patients with delayed chemotherapy doses	11	30	.738
Patients with reduced chemotherapy doses	13	42	.328
More than 75% of total planned regimen without delay or dose reduction	52	130	.825

#### 4. Discussion

Adjuvant chemotherapy plays an important role in the treatment of gastric cancer because of its effect on improving prognosis.<sup>[1–4]</sup> Good compliance can enhance the efficacy of adjuvant



**Figure 2.** Kaplan-Meier overall survival curve following laparoscopic gastrectomy (LG) or open gastrectomy (OG) ( $P=.030$ ).



**Figure 3.** Kaplan-Meier disease-free survival curve following laparoscopic gastrectomy (LG) or open gastrectomy (OG) ( $P=.005$ ).

**Table 6**  
**Multivariate Cox regression analyses of overall survival.**

Regression variables	Adjusted hazard ratio	95% CI	P value
Pathological T stage			
T <sub>1</sub> /T <sub>2</sub>	1.00		
T <sub>3</sub> /T <sub>4</sub>	1.93	1.59–3.54	.032
Pathological N stage			
N <sub>0</sub> /N <sub>1</sub>	1.00		
N <sub>2</sub> /N <sub>3</sub>	2.90	2.03–5.19	.008
Surgical approach			
LG	1.00		
OG	1.26	1.12–1.80	.040
More than 75% of total planned regimen without delay or dose reduction			
Yes	1.00		
No	1.98	1.58–2.30	.025
Reduced chemotherapy doses			
No	1.00		
Yes	1.49	1.24–1.74	.030

LG=laparoscopic gastrectomy, OG=open gastrectomy.

chemotherapy and ultimately improve patients' long-term survival outcomes.<sup>[5–7]</sup> LG for gastric cancer has seen a rapid advancement in the past 10 years.<sup>[9–13]</sup> LG has the advantages of minimally invasive surgeries such as less blood loss, reduced postoperative pain, and a faster recovery.<sup>[9–18]</sup> However, whether the advantages of the minimally invasive nature of LG can be translated into better compliance with adjuvant chemotherapy has not been reported. To our knowledge, the present study is the first report on compliance with adjuvant chemotherapy in patients with gastric cancer by LG, and we found that compliance can improve long-term survival outcomes.

The cycles of chemotherapy, dosage of chemotherapy, and presence of delayed chemotherapy are important indicators of compliance to chemotherapy.<sup>[28]</sup> The current study showed that compared with patients in the OG group, patients in the LG group were more compliant with chemotherapy. LG has many advantages in patients with gastric cancer such as less invasion and a rapid postoperative recovery.<sup>[29–31]</sup> In theory, patients in the LG group should start the first adjuvant chemotherapy earlier. However, in the present study, there was no significant difference in the start time of the first adjuvant chemotherapy

**Table 7**  
**Multivariate Cox regression analyses of disease-free survival.**

Regression variables	Adjusted hazard ratio	95% CI	P value
Pathological T stage			
T <sub>1</sub> /T <sub>2</sub>	1.00		
T <sub>3</sub> /T <sub>4</sub>	2.54	1.45–3.22	.020
Pathological N stage			
N <sub>1</sub> /N <sub>2</sub>	1.00		
N <sub>3</sub>	2.06	1.45–4.06	.010
Surgical approach			
LG	1.00		
OG	1.39	1.10–2.06	.037
More than 75% of total planned regimen without delay or dose reduction			
Yes	1.00		
No	1.71	1.38–1.99	.021
Reduced chemotherapy doses			
No	1.00		
Yes	1.59	1.28–1.70	.035

LG=laparoscopic gastrectomy, OG=open gastrectomy.

between the 2 groups. The reason for this finding is that LG has been widely used in clinical practice for only more than 10 years,<sup>[5–10]</sup> and the start time of adjuvant chemotherapy is still traditionally determined by the surgeons' experience during OG. The early initiation of adjuvant chemotherapy can improve patients' long-term survival; thus, the next step is to study whether adjuvant chemotherapy can be started earlier for patients undergoing LG.

Previous studies have shown that compliance with adjuvant chemotherapy is affected by many factors such as the type of resection, patients' age, PS score, and comorbidities.<sup>[32,33]</sup> In the current study, the aforementioned factors in the 2 groups were not significantly different; therefore, the difference in compliance with adjuvant chemotherapy between the 2 groups can be attributed to the different surgical approaches.

The ultimate goal of adjuvant chemotherapy in patients with gastric cancer undergoing radical gastrectomy is to improve their long-term survival outcomes. In the present study, long-term OS and DFS rates were higher in the LG group than in the OG group. In addition, results of multivariate analysis indicated that the surgical approach is an independent predictor of prognosis. Therefore, the survival advantage for patients in the LG group can be attributed to the effect of LG on chemotherapy compliance.

There are certain differences in the therapeutic models for respectable gastric cancer between eastern and western countries. In eastern countries, surgical resection is performed first, followed by adjuvant therapy.<sup>[11]</sup> In western countries, patients with pathological stage  $\geq$ Ib receive neoadjuvant therapy first, followed by surgical resection; whereas patients with pathological stage  $\geq$ Ib who do not receive neoadjuvant therapy are given adjuvant therapy.<sup>[34]</sup> This study did not include patients who had undergone neoadjuvant therapy, as patients' treatment course for gastric cancer in this study followed the guidelines of eastern countries. Therefore, the conclusions reached in this study are only applicable to eastern countries, not to western countries.

The limitations of this study include its single-center, retrospective design, and other factors affecting patients' compliance with chemotherapy and prognosis that were not analyzed. Moreover, the median follow-up duration in this study was only 30 months, and the late recurrence of tumors and death of patients were not observed.

## 5. Conclusion

In summary, LG can improve the compliance of patients with gastric cancer with adjuvant chemotherapy, and this compliance can be translated into a survival advantage. We look forward to conducting prospective, multicenter, large-sample, randomized controlled trials to clarify this advantage as soon as possible.

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## References

- [1] Japanese Gastric Cancer Association Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;14:113–23.
- [2] Abu Arab W. Video-assisted thoracoscopic surgery for non-small cell lung cancer. *Minim Invasive Surg Oncol* 2017;1:1–1.
- [3] Cocolini F, Montori G, Ceresoli M, et al. Advanced gastric cancer: what we know and what we still have to learn. *World J Gastroenterol* 2016;22:1139–59.

- [4] Isobe Y, Nashimoto A, Akazawa K, et al. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. *Gastric Cancer* 2011;14:301–16.
- [5] Cao J, Qi F, Liu T. Adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis. *Scand J Gastroenterol* 2014;49:690–704.
- [6] Takahashi Y. Real-time intraoperative diagnosis of lung adenocarcinoma high risk histological features: a necessity for minimally invasive sublobar resection. *Minim Invasive Surg Oncol* 2017;1:12–9.
- [7] Miceli R, Tomasello G, Bregni G, et al. Adjuvant chemotherapy for gastric cancer: current evidence and future challenges. *World J Gastroenterol* 2014;20:4516–25.
- [8] Greenleaf EK, Kulaylat AN, Hollenbeak CS, et al. Timing of adjuvant chemotherapy and impact on survival for resected gastric cancer. *Ann Surg Oncol* 2016;23:4203–13.
- [9] Lu Y, Jiang B, Liu T. Laparoscopic versus open total gastrectomy for advanced proximal gastric carcinoma: a matched pair analysis. *J BUON* 2016;21:903–8.
- [10] Gu J, Zhao E. Laparoscopic gastrectomy for locally advanced gastric carcinoma: long-term survival outcomes and prognostic factors. *Int J Clin Exp Med* 2015;9:11485–93.
- [11] Wu H, Li W, Chen G, et al. Outcome of laparoscopic total gastrectomy for gastric carcinoma. *J BUON* 2016;21:603–8.
- [12] Shu B, Lei S, Li F, et al. Laparoscopic total gastrectomy compared with open resection for gastric carcinoma: a case-matched study with long-term follow-up. *J BUON* 2016;21:101–7.
- [13] Zhang X, Sun F, Li S, et al. A propensity score-matched case-control comparative study of laparoscopic and open gastrectomy for locally advanced gastric carcinoma. *J BUON* 2016;21:118–24.
- [14] Zhang Y, Qi F, Jiang Y, et al. Long-term follow-up after laparoscopic versus open distal gastrectomy for advanced gastric cancer. *Int J Clin Exp Med* 2015;8:13564–70.
- [15] Najmeh S, Cools-Lartigue J, Mueller C, et al. Comparing laparoscopic to endoscopic resections for early gastric cancer in a high volume North American center. *J Gastrointest Surg* 2016;20:1547–53.
- [16] Hao Y, Y Yu P. Comparison of laparoscopy-assisted and open radical gastrectomy for advanced gastric cancer: a retrospective study in a single minimally invasive surgery center. *Medicine (Baltimore)* 2016;95:e3936.
- [17] Zheng L, Lu L, Jiang X, et al. Laparoscopy-assisted versus open distal gastrectomy for gastric cancer in elderly patients: a retrospective comparative study. *Surg Endosc* 2016;30:4069–77.
- [18] He W, Tu J, Huo Z, et al. Surgical interventions for gastric cancer: a review of systematic reviews. *Int J Clin Exp Med* 2015;8:13657–69.
- [19] Li B, Liu HY, Guo SH, et al. Detection of microsatellite instability in gastric cancer and dysplasia tissues. *Int J Clin Exp Med* 2015;8:21442–7.
- [20] Huang ZN, Huang CM, Zheng CH, et al. Learning curve of the application of Huang three-step maneuver in a laparoscopic spleen-preserving splenic hilar lymphadenectomy for advanced gastric cancer. *Medicine (Baltimore)* 2016;95:e3252.
- [21] Luo GD, Chen BH, Cao YK, et al. Hand-assisted laparoscopic versus open radical resection of gastric remnant cancer: a clinical comparison. *Int J Clin Exp Med* 2015;8:21152–8.
- [22] Shu B, Lei S, Li F, et al. Short and long-term outcomes after gastrectomy for gastric carcinoma in elderly patients. *Int J Clin Exp Med* 2015;8:13578–84.
- [23] Jung YB, Kang J, Park EJ, et al. Time to initiation of adjuvant chemotherapy in colon cancer: comparison of open, laparoscopic, and robotic surgery. *J Laparoendosc Adv Surg Tech A* 2016;26:799–805.
- [24] Lin JX, Huang CM, Zheng CH, et al. Laparoscopy-assisted gastrectomy with D2 lymph node dissection for advanced gastric cancer without serosa invasion: a matched cohort study from South China. *World J Surg Oncol* 2013;11:4.
- [25] Xiao H, Xie P, Zhou K, et al. Clavien-Dindo classification and risk factors of gastrectomy-related complications: an analysis of 1049 patients. *Int J Clin Exp Med* 2015;8:8262–8.
- [26] Fujitani K. Overview of adjuvant and neoadjuvant therapy for resectable gastric cancer in the East. *Dig Surg* 2013;30:119–29.
- [27] Rausei S, Ruspi L, Galli F, et al. Seventh tumor-node-metastasis staging of gastric cancer: five-year follow-up. *World J Gastroenterol* 2016;22:7748–53.
- [28] Park HS, Jung M, Kim HS, et al. Proper timing of adjuvant chemotherapy affects survival in patients with stage 2 and 3 gastric cancer. *Ann Surg Oncol* 2015;22:224–31.
- [29] Son T, Hyung WJ. Laparoscopic gastric cancer surgery: current evidence and future perspectives. *World J Gastroenterol* 2016;22:727–35.
- [30] Lee HJ, Yang HK. Laparoscopic gastrectomy for gastric cancer. *Dig Surg* 2013;30:132–41.
- [31] Lianos GD, Rausei S, Ruspi L, et al. Laparoscopic gastrectomy for gastric cancer: current evidences. *Int J Surg* 2014;12:1369–73.
- [32] Landrum MB, Keating NL, Lamont EB, et al. Reasons for underuse of recommended therapies for colorectal and lung cancer in the Veterans Health Administration. *Cancer* 2012;118:3345–55.
- [33] El Shayeb M, Scarfe A, Yasui Y, et al. Reasons physicians do not recommend and patients refuse adjuvant chemotherapy for stage III colon cancer: a population based chart review. *BMC Res Notes* 2012;5:269.
- [34] Okines A, Verheij M, Allum W, et al. ESMO Guidelines Working Group Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(suppl 5):v50–4.