Surgical and long-term oncologic outcomes of laparoscopic and open gastrectomy for serosa-positive (pT4a) gastric cancer: A propensity score-matched analysis

Zhengyan Li[**], Yezhou Liu, Yiming Hao, Bin Bai, Deliang Yu, Qingchuan Zhao[*]

Xijing Hospital of Digestive Diseases, The Fourth Military Medical University, Xi'an, 710032, China

A B S T R A C T

Background: To date, it has been unclear whether laparoscopic gastrectomy (LG) is suitable for patients with serosa-positive (pT4a) gastric cancer. The purpose of this study was to compare the surgical and long-term oncologic outcomes of LG and open gastrectomy for pT4a gastric cancer.
Methods: We prospectively collected data from 987 patients with pathological confirmed pT4a gastric cancer who underwent LG or OG at our institution between June 2009 and May 2015. A 1:1 matched propensity score matching (PSM) analysis was performed to reduce confounding bias. The primary outcome was 5-year overall survival (OS).
Results: After PSM, a well-balanced cohort of 202 pairs patients was analyzed. The LG group showed a longer operation time (261.42 vs. 171.00 min, $P = 0.001$), less blood loss (185.47 vs. 217.84 ml, $P = 0.000$), and shorter postoperative hospital stay (7.56 vs. 8.22 days, $P = 0.007$). The overall complication rate was 14.4% in the LG group and 16.3% in the OG group ($P = 0.581$). The minor (grade II) and severe (grade $\geq$ IIIa) complication rates were similar (LG, 6.9% vs. OG, 9.9%, P = 0.282; LG, 7.4% vs. OG, 6.4%, P = 0.695, respectively). The LG and OG groups showed similar survival 5-year OS and 5-year Disease-free survival (DFS) rates (44.6% vs. 42.1%, $P = 0.403$; 40.1 vs. 37.6%, $P = 0.321$, respectively). The recurrence rate and pattern did not differ between the two groups during the follow-up stage ($P > 0.05$).
Conclusions: For patients with pT4a gastric cancer, LG with D2 lymph node dissection can be a safe and feasible procedure in terms of surgical and long-term oncologic outcomes.

1. Introduction

Laparoscopic gastrectomy (LG) has been increasingly performed since it was first reported in 1994 by Kitano et al. [1]. Based on the experience accumulation of LG for EGC, some experienced surgeons in high-volume centers have applied the laparoscopic procedure for patients with locally advanced gastric cancer (AGC). Recently, several multicenter RCTs have reported LG is a safe and feasible surgical procedure for AGC in terms of short-term outcomes [2–4]. In china, more than 80% of the gastric patients are diagnosed at advanced stages and cases with serosa-positive (pT4a) gastric cancer account a large proportion. To date, it is still remains unclear whether the LG is applicable for pT4a gastric cancer under the consideration of increased peritoneal and port-site recurrences resulting from malignant cell dissemination [5–7]. In addition, pT4a gastric cancer patients are always associated

with large tumor size and lymph nodes metastasis, and radical surgery requires gastrectomy with extended lymphadenectomy [8]. For these cases, LG with D2 lymph dissection still remains a challenging procedure because of its technical difficulties and possible complications. To date, the surgical and long-term oncologic outcomes of LG for pT4a gastric cancer have been seldom reported.

Therefore, in this study, we compare the surgical and long-term oncologic outcomes of LG and OG with D2 lymph node dissection for pT4a gastric cancer.

2. Materials and methods

2.1. Patients

We selected patients who underwent LG and OG at our center from

June 2009 to May 2015 in prospectively maintained gastric cancer database. Pathologic staging were updated according to the 8th Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging system of gastric cancer [9]. The inclusion criteria were as follows: histologically proven adenocarcinoma; pathological examination confirmed in T4a stage; age between 18 and 70 years; no distant metastasis or invasion to adjacent organs; no combined with other malignancy; no emergency operation; and no previous chemotherapy or surgery for gastric cancer.

We performed 1:1 matching using a logistic regression model with the following variables: age, sex, body mass index (BMI), extent of resection, ASA grade, tumor size, histologic type, pN stage and pTNM stage. The present study was approved by the Ethics Committee of Xijing Hospital, Fourth Military Medical University.

2.2. Surgical procedure

The procedures for laparoscopic and open with D2 dissection have been previously described in detail [10–12]. All surgeries were performed by surgeons experienced in laparoscopic and open gastrectomy. Patients chose the surgical types individually after they were informed of the risks of surgical, complication, and oncological. We routinely administered postoperative adjuvant chemotherapy with 5-fluorouracil and cisplatin to each patient with stage II or more advanced cancer.

2.3. Postoperative evaluation and follow-up

The primary outcome was 5-year overall survival (OS). The secondary outcomes were 5-year disease-free survival (DFS), surgical outcomes, and postoperative complications. The OS were defined as the interval between surgery and death. The DFS were defined as the interval between surgery and first recurrence or death. Postoperative complications occurred within 30 days after surgery were recorded and

classified according to the Clavien–Dindo classification system [13,14]. 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 May 2018 or 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 analysis was performed by Cox proportional hazard model to identify independent risk factors for survival. All values were two-tailed, and P values < 0.05 were considered significant.

3. Results

After propensity score matching, 202 pairs of LG and OG patients were selected for final analysis. The characteristics of patients were well balanced between the two groups (Table 1).

3.1. Short-term surgical outcomes

Table 2 shows details of the surgical outcomes and postoperative complications of the two groups. The LG group was associated with longer operating time (236.63 vs. 176.52 min, $P = 0.000$), less estimated blood loss (164.64 vs. 203.22 ml, $P = 0.000$). The time to first flatus (3.29 vs. 3.92 days, $P = 0.000$), time to start liquid diet (3.37 vs. 3.98 days, $P = 0.000$), and postoperative hospital stay (7.39 vs. 8.03 days, $P = 0.023$) were shorter in the LG group than those in the OG

Table 1
Characteristics of patients.

Variables	Entire cohort			Propensity score-matched cohort		
	LTG (n = 211)	OTG (n = 776)	P value	LTG (n = 202)	OTG (n = 202)	P value
Age, years			0.564			1.000
≤60	141(66.8)	502(64.7)		135(66.8)	135(66.8)	
>60	70(33.2)	274(35.3)		67(33.2)	67(33.2)	
Sex			0.801			0.435
Male	156(73.9)	567(73.1)		150(74.3)	143(70.8)	
Female	55(26.1)	209(26.9)		52(25.7)	59(29.2)	
BMI, kg/m²	22.23 ± 3.30	22.01 ± 3.20	0.376	22.04 ± 3.10	21.66 ± 2.62	0.182
ASA grade			0.716			0.863
1-2	190(90.0)	692(84.6)		183(90.6)	184(91.1)	
3	21(10.0)	84(15.4)		19(9.4)	18(8.9)	
Tumor size, cm			0.081			1.000
≤5.0	138(65.4)	456(58.8)		130(64.4)	130(64.4)	
>5.0	73(34.6)	320(41.2)		72(35.6)	72(35.6)	
Histological type			0.071			1.000
Differentiated	39(18.5)	105 (13.5)		30(14.9)	30(14.9)	
Undifferentiated	172(81.5)	671(86.5)		172(85.1)	172(85.1)	
Extent of resection			0.991			1.000
DG	63(29.9)	232(29.9)		58(28.7)	58(28.7)	
TG	148(70.1)	544(70.1)		144(71.3)	144(71.3)	
pN stage			0.376			1.000
pN0	29(13.7)	102(13.1)		27(13.4)	27(13.4)	
pN1	32(15.2)	94(12.1)		27(13.4)	27(13.4)	
pN2	48(22.7)	171(22.0)		47(23.3)	47(23.3)	
pN3a	68(32.2)	238(30.7)		68(33.7)	68(33.7)	
pN3b	34(16.1)	171(22.0)		33(16.3)	33(16.3)	
pTNM stage			0.302			1.000
IIB	29(13.7)	102(13.1)		27(13.4)	27(13.4)	
IIIA	80(37.9)	265(34.1)		74(36.6)	74(36.6)	
IIIB	68(32.2)	238(30.7)		68(33.7)	68(33.7)	
IIIC	34(16.1)	171(22.0)		33(16.3)	33(16.3)	

Table 2
Surgical outcomes and postoperative complications.

Characteristics	LG (n = 202)	OG (n = 202)	*P* value
Operation time (min)	236.63 ± 71.54	176.52 ± 43.47	**0.000**
Estimated blood loss (ml)	164.64 ± 80.24	203.22 ± 95.54	**0.000**
No. of retrieved lymph nodes	28.86 ± 5.31	27.94 ± 8.09	0.177
Time to first flatus (d)	3.29 ± 1.31	3.92 ± 1.23	**0.000**
Time to start liquid diet (d)	3.37 ± 1.28	3.98 ± 1.46	**0.000**
Postoperative hospital stay (d)	7.39 ± 2.53	8.03 ± 3.16	**0.023**
Conversion to open	12(5.9)		
Postoperative complication			
Wound infection	3(1.5)	6(3.0)	0.500
Pancreatitis	0(0.0)	1(0.5)	1.000
Pulmonary	5(2.5)	7(3.5)	0.558
Pancreatic fistula	1(0.5)	0(0.0)	1.000
Intra-abdominal abscess	3(1.5)	5(2.5)	0.721
Intra-abdominal bleeding	4(2.0)	2(1.0)	0.681
Duodenal stump leakage	2(1.0)	2(1.0)	1.000
Anastomotic bleeding	2(1.0)	1(0.5)	1.000
Anastomotic leakage	4(2.0)	3(1.5)	1.000
Bowel obstruction	2(1.0)	5(2.5)	0.446
Hepatic	2(1.0)	1(0.5)	1.000
Cardiac	1(0.5)	0(0.0)	1.000
Overall complications (%)	29(14.4)	33(16.3)	0.581
Clavien–Dindo classification			
Grade II (%)	14(6.9%)	20(9.9%)	0.282
Grade IIIa (%)	8(4.0%)	6(3.0%)	0.586
Grade IIIb (%)	4(2.0%)	5(2.5%)	1.000
Grade IV (%)	3(1.5%)	2(1.0%)	1.000
Grade V (%)	0(0.0%)	0(0.0%)	—
Clavien-Dindo grade ≥ IIIa (%)	15(7.4%)	13(6.4%)	0.695

P < 0.05 are in bold.

group. The overall postoperative complication rate did not differ significantly between the LG group and the OG group (14.4% vs. 16.3%, *P* = 0.581). No significant differences were observed in the minor (Clavien–Dindo grade II) and severe complication (Clavien–Dindo grade ≥ IIIa) rates between the two groups (LG, 6.9% vs. OG, 9.9%, *P* = 0.282; LG, 7.4% vs. OG, 6.4%, *P* = 0.695, respectively).

3.2. Long-term survival and subgroup analyses

With a median follow-up of 57 months (range 36–107 months), The LG and OG groups showed similar 5-year overall survival (OS) and

Disease-free survival rates (DFS) rates (44.6% vs. 42.1%, *P* = 0.403; 40.1 vs. 37.6%, *P* = 0.321, respectively) (Fig. 1). Stage-specific analysis showed that the 5-year OS rate for patients in stage IIB was 63.0% in the LG group and 66.7% in the OG group; in stage IIIA, 55.4% and 50.0%; in stage IIIB, 36.8% and 32.4%; in stage IIIC, 21.2% and 24.2%, respectively. The 5-year OS rates were comparable between the two groups (Fig. 2, *P* > 0.05). In the subgroup analyses of OS, no significant difference was observed between the two groups (Fig. 3). Multivariate analysis showed that the surgical type was also not an independent prognostic factor for OS (Table 3).

### 3.3. Recurrence pattern of LG and OG groups

During the follow-up period, 150 patients (76 cases in the LG group and 101 cases in the OG group) experienced recurrence. Comparisons of the recurrence rate and patterns did not show statistical significances between the two groups (*P* > 0.05). Table 4 summarizes the details of recurrence pattern of the two groups.

4. Discussion

In the past ten years, LG with D2 lymphadenectomy has been increasing used for the treatment of patients with locally AGC based on the experience of EGC [15–19]. The results of randomized controlled trials (RCTs) have demonstrated that LG with D2 lymphadenectomy can be performed safely by experienced surgeons [2–4]. In China, about 80% patients are diagnosed at advanced stages, and serosa-positive (pT4a) gastric cancer account for a significant proportion of these cases. To date, the surgical and long-term oncologic outcomes of LG for pT4a gastric have been rarely reported. In current study, we used the propensity score matching method to reduce the effect of selection and potential confounding biases due to the retrospective nature of this study.

Regarding surgical outcomes, our results showed that LG was associated with less blood loss, earlier time to first flatus, earlier time to start diet and shorter postoperative hospital stay days. It means that the benefits of the laparoscopic approach demonstrated in large-scale RCTs can also be offered to patients with pT4a gastric cancer.

Postoperative complication is one of the major concerns in clinical practice. Our previous study demonstrated that the occurrence of
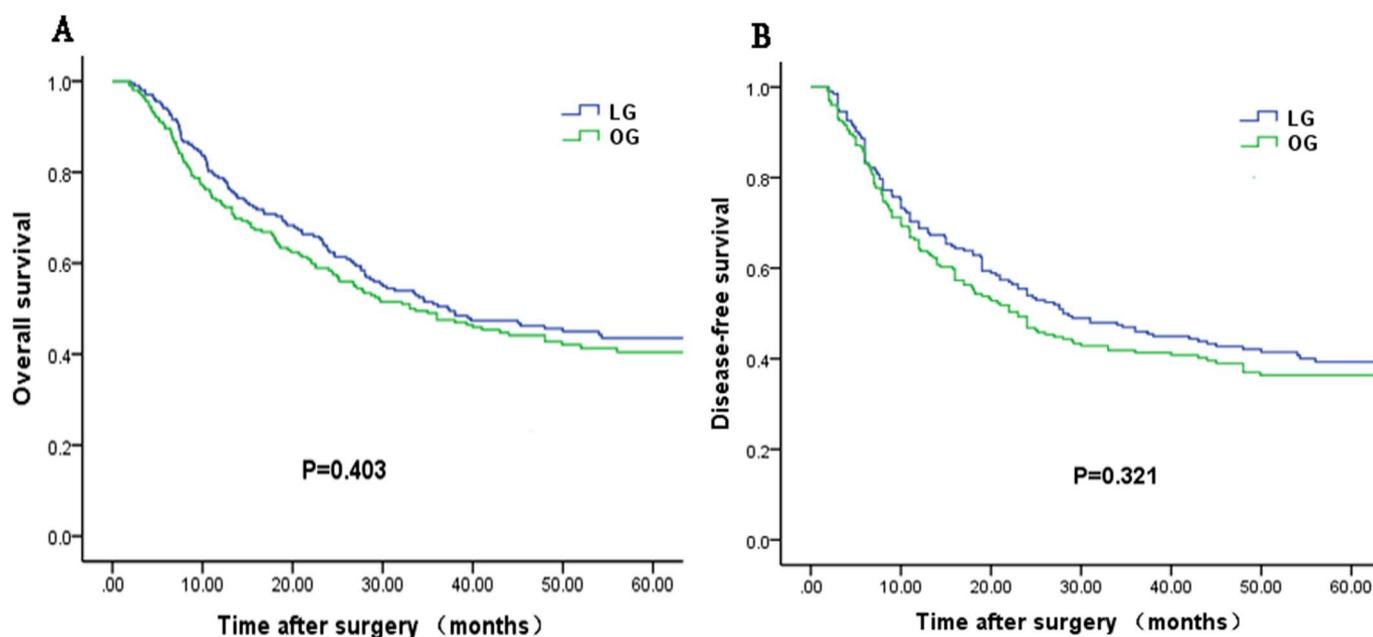
Fig. 1. Kaplan–Meier curves of OS and DFS in LG and OG groups. **A** OS of propensity score-matched cohort; **B** DFS of propensity score-matched cohort.
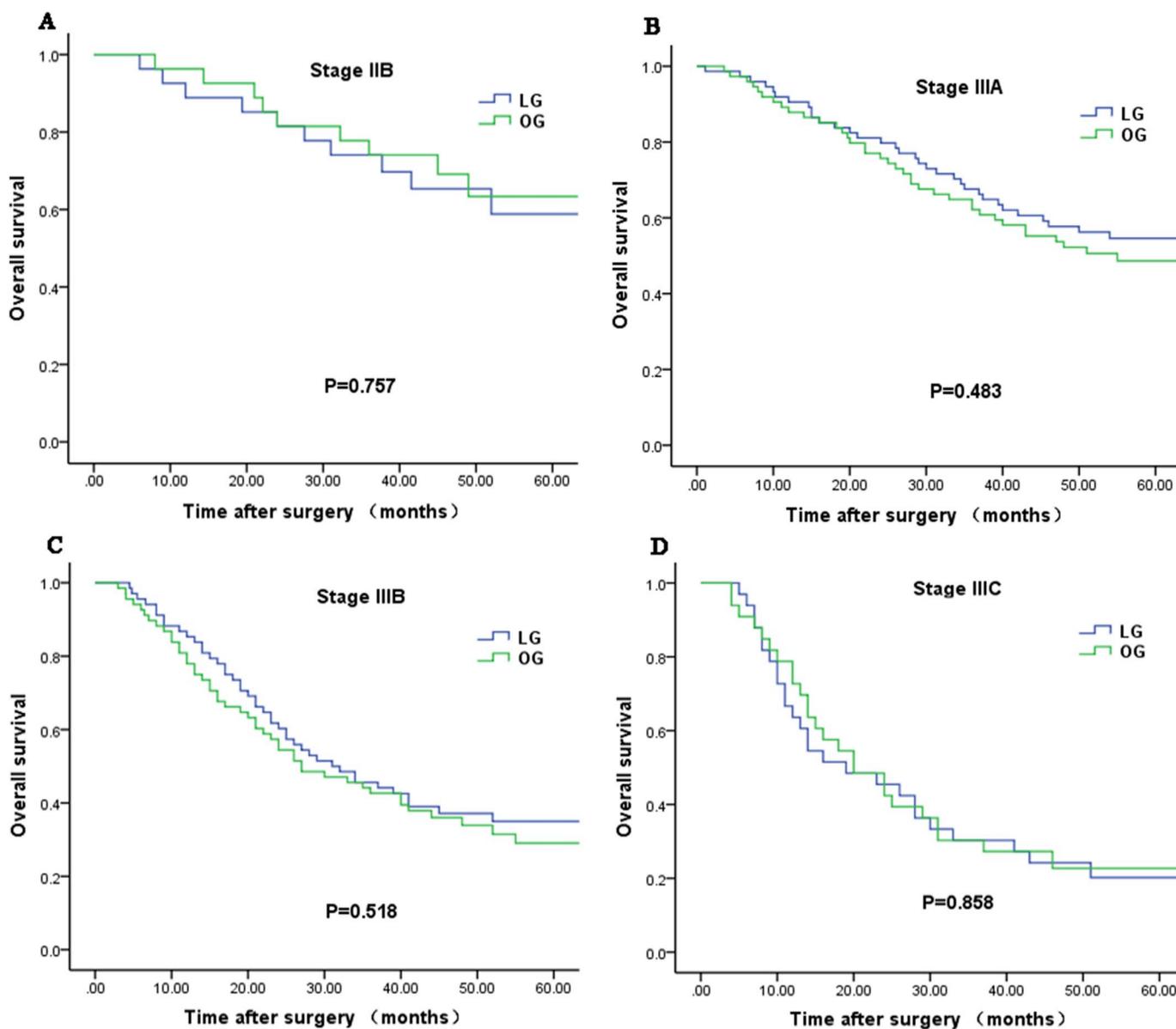
Fig. 2. Kaplan-Meier curve of OS of LG and OG groups classified by pathological stage. **A** Stage IIB; **B** Stage IIIA; **C** Stage IIIB; **D** Stage IIIC.

complications adversely affected long-term survival outcomes after LG with D2 lymph node dissection for AGC [20]. Extensive researches reported that the postoperative complication rate in patients who underwent LG were comparable to those of patients who underwent OG [2,3,16,21]. However, patients in the above-mentioned studies were in stage pT1 to pT4. They did not perform stage-specific analysis for pT4a. A retrospective study reported that postoperative complication rate did not differ between the LG and OG groups, even for patients with confirmed pT4a gastric cancer [5]. Recently, Zhang et al. [6] reported that the postoperative complication rate was 7.2% for patients with pT4a gastric cancer, which is lower than those in the OG group. In this study, our results revealed that there was no significant difference between LG and OG groups (14.4% vs. 16.3%, $P = 0.581$). Further analysis also showed no significant differences between the two groups in terms of minor and severe complications. In terms of major individual complications, we found no significant differences in the frequencies of anastomotic-related complications (leakage, stricture, and bleeding), abdominal abscess, and pulmonary complications between the two groups. Based on these results, our study suggests that LG is a technical feasible procedure with comparable or even better short-term outcomes

as compared with OG.

Long-term survival and recurrence are two key indicators for assessing oncological safety. Currently, although LG for locally AGC still remains controversial due to the lack of long-term results from RCTs. Some retrospective studies have reported that the long-term survival outcomes of patients underwent LG are similar with those treated with OG [22–26]. However, few of them reported the stage-specific survival outcomes of patients in pT4a stage. Son et al. [5] reported the survival and recurrence patterns were comparable between the LG and OG groups in a small retrospective study. Additionally, they also demonstrated that the LG did not increase peritoneal recurrences of patients with pT4a gastric cancer when compared to OG. A recent retrospective study of LG versus OG for pT4a gastric cancer also showed no significant differences in 5-year DFS rate (37.8% vs. 35.3%, $P > 0.05$) and OS rate (47.7% vs. 40.3%, $P > 0.05$) with an average follow-up of 37 month [6]. In this study, the 5-year OS and DFS rate of all patients underwent LG were also comparable to those underwent OG after propensity score matching was performed. In our study, the surgical type was not a prognostic factor for OS; however, age, tumor size, histologic type, No. of retrieved lymph nodes (RLNs), and pN2-N3 stage

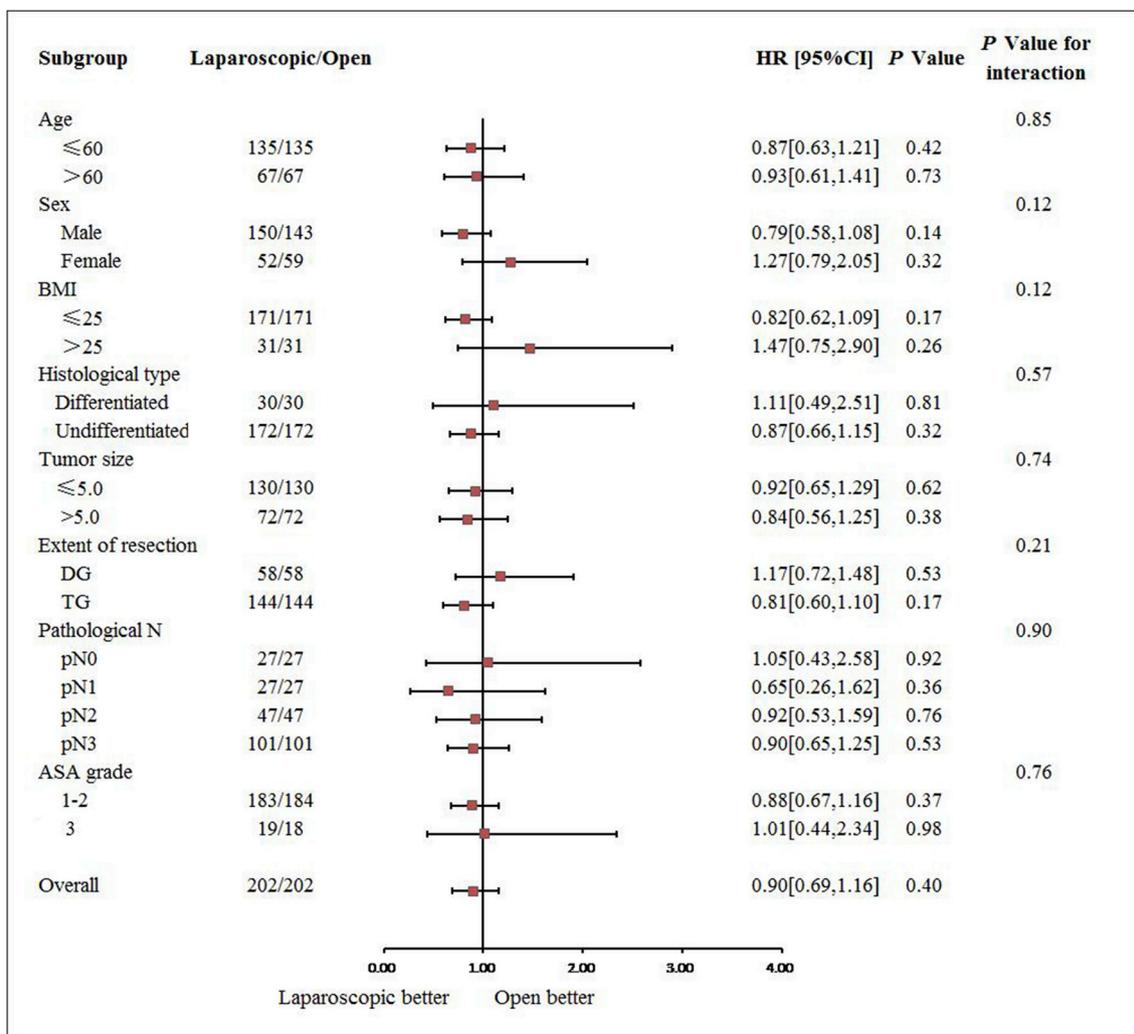| Subgroup	Laparoscopic/Open	HR [95%CI]	P Value	P Value for interaction
Age				0.85
⩽60	135/135	0.87[0.63,1.21]	0.42	
>60	67/67	0.93[0.61,1.41]	0.73	
Sex				0.12
Male	150/143	0.79[0.58,1.08]	0.14	
Female	52/59	1.27[0.79,2.05]	0.32	
BMI				0.12
⩽25	171/171	0.82[0.62,1.09]	0.17	
>25	31/31	1.47[0.75,2.90]	0.26	
Histological type				0.57
Differentiated	30/30	1.11[0.49,2.51]	0.81	
Undifferentiated	172/172	0.87[0.66,1.15]	0.32	
Tumor size				0.74
⩽5.0	130/130	0.92[0.65,1.29]	0.62	
>5.0	72/72	0.84[0.56,1.25]	0.38	
Extent of resection				0.21
DG	58/58	1.17[0.72,1.48]	0.53	
TG	144/144	0.81[0.60,1.10]	0.17	
Pathological N				0.90
pN0	27/27	1.05[0.43,2.58]	0.92	
pN1	27/27	0.65[0.26,1.62]	0.36	
pN2	47/47	0.92[0.53,1.59]	0.76	
pN3	101/101	0.90[0.65,1.25]	0.53	
ASA grade				0.76
1-2	183/184	0.88[0.67,1.16]	0.37	
3	19/18	1.01[0.44,2.34]	0.98	
Overall	202/202	0.90[0.69,1.16]	0.40	

Laparoscopic better   Open better

Fig. 3. Subgroup analyses of OS in LG and OG groups.

were identified as independent prognostic factors by multivariate analysis.

Regarding the tumor recurrence, a study of 1417 patients after LG from multicenter stated that the recurrence rate is 3.5% (50/1417), and the most common recurrence pattern after LG was hematogenous, followed by peritoneal and locoregional [27]. However, majority of patients were in early stage, and cases in stage II or more only account for 9.2% (130/1417). Another study of 1304 gastric cancer patients reported the recurrence rate was 60.8% (793/1304), and the distant metastasis is the most common recurrence pattern, followed by local-regional recurrence and peritoneum implanting [28]. The patients in stage II or more account for 87.9% (1147/1304), which therefore associated with higher recurrence rate and different common recurrence patterns as compared with the result reported by Song et al. [27]. In the present study, patients in stage III account for 86.6% in the propensity score-matched cohort, indicating poor prognosis of these cases. The recurrence rate was 37.6% after LG, and peritoneal were the most common recurrence pattern, followed by locoregional recurrence and hematogenous recurrence. Our results showed that the recurrence rate and pattern did not differ between the two groups during the follow-up stage. These indicated that LG did not increase peritoneal recurrence rate as compared with OG. Port site metastasis associated with pneumoperitoneum and laparoscopic tumor handling has also been regard as one of the major concern in clinical practice, although it is actually quite rare based on current evidence [29,30]. Several reports stated that laparoscopic surgery does not promote peritoneal recurrence or

port site metastasis of gastric cancer [5,17,23]. In our study, two patients experienced port site metastasis in the LG group during the follow-up period. However, it was not a unique event to LG, because 1 cases of wound metastasis were also found in the OG group. These demonstrated that LG do not increase port site metastasis of patients with pT4a gastric cancer.

Tumor size has been shown to be correlated with prognosis of gastric cancer [31–33], and it still kept prognostic value in our study. In previous study, LG was not generally performed in patients with larger tumors because of the potential risk of increased conversion rate, thus having a negative effect on clinical outcomes [34,35]. In this study, patients with tumor size larger than 5 cm account for 35.6% in the propensity score-matched cohort, and the conversion rate is comparable with previous studies. Additionally, survival outcomes of patents after LG were also comparable to those treated by open procedure in the subgroup analysis for cases with tumor size larger than 5 cm.

Serosa-positive gastric cancer was always associated with a higher risk of lymph node metastasis. In the present study, patients with N1-N3 gastric cancer account for 86.6% of all cases. Researches have reported that inadequate RLNs were significantly associated with the unfavorable survival outcome of gastric cancer patients. AJCC recommended that a necessity of at least 15 RLNs for radical gastrectomy to ensure N-stage reliability [36]. Recently, several studies have stated that sufficient number of RLNs was associated with better prognosis of gastric patients with lymph node metastasis. Therefore, the harvest of at least 15 lymph nodes may not be applicable for all gastric cancer patients

Table 3
Univariate and multivariate analyses of prognostic factors for OS.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age(years)			**0.005**			**0.001**
≤60	1	1		1	1	
> 60	1.471	1.127–1.921		1.584	1.210–2.073	
Sex			0.300			
Male	1	1				
Female	1.162	0.875–1.543				
BMI (kg/m^2)			0.619			
≤25	1	1				
> 25	0.912	0.633–1.312				
Tumor size (cm)			**0.001**			**0.028**
≤5.0	1	1		1	1	
> 5.0	1.566	1.205–2.036		1.350	1.032–1.766	
Histological type			**0.001**			**0.033**
Differentiated	1	1		1	1	
Undifferentiated	2.140	1.390–3.294		1.657	1.042–2.633	
Extent of resection			**0.598**			
DG	1	1				
TG	1.081	0.810–1.443				
No. of retrieved lymph nodes			**0.008**			**0.007**
> 25	1	1		1	1	
≤25	1.423	1.096–1.846		1.429	1.101–1.855	
ASA grade			**0.508**			
1-2	1	1				
3	1.160	0.747–1.800				
Surgical type			0.403			
OG	1	1				
LG	0.895	0.691–1.160				
pN stage			**0.000**			
N0	1			1		
N1	1.007	0.533–1.902	0.983	–	–	–
N2	1.858	1.097–3.147	**0.021**	1.778	1.045–3.026	0.034
N3	3.113	1.926–5.033	**0.000**	2.586	1.563–4.277	0.000

P < 0.05 are in bold.

Table 4
Recurrence pattern of LG and OG groups.

Recurrence pattern	LAG(n = 202)	OG(n = 202)	*P* value
Patients with recurrence	76(37.6)	74(36.6)	0.837
Local	11(5.4)	10(5.0)	0.823
Remnant stomach	8(4.0)	7(3.5)	0.792
Anastomosis	3(1.5)	3(1.5)	1.000
Peritoneum	27(13.4)	22(10.9)	0.446
Hematogenous	21(10.4)	19(9.4)	0.739
Liver	13(6.4)	7(3.5)	0.169
Lung	1(0.5)	1(0.5)	1.000
Bone	2(1.0)	3(1.5)	1.000
Brain	0(0.0)	2(1.0)	0.478
Other	5(2.5)	6(3.0)	0.760
Distant lymph node	1(0.5)	3(1.5)	0.315
Mix types	16(7.9)	20(9.9)	0.485

[37–39]. Chen et al. [40] stated that the harvest of least 25 lymph nodes could yield better survival outcomes in stage N2 to N3 gastric cancer. Zhao et al. [41] also demonstrated a necessity of at least 25 RLNs for AGC patients with lymph node metastasis. In the present study, multivariate analysis also confirmed that retrieved less than 25 lymph nodes is an independent prognostic factor for decreased OS. Based on current evidence, we recommended that a necessity of 25 RLNs for patients with pT4a gastric cancer.

There are several limitations in the present study. First, this is a single-center retrospective study. Additionally, propensity-score matched method could not offset all biases. Third, some patients were not followed up to 5 years which may lead to a higher survival rate. Therefore, Well-designed multicenter RCTs are warranted to reach more definitive conclusions on this topic.

In conclusion, our study suggests that LG can be a safe and feasible procedure for patients with pT4a gastric cancer in terms of surgical and long-term oncologic outcomes.

Compliance with ethical standards

Disclosures

Zhengyan Li, Yezhou Liu, Yiming Hao, Bin Bai, Deliang Yu, and Qingchuan Zhao have no conflicts of interest or financial ties to disclose.

Funding

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.01.003.

References

[1] S.I.Y. Kitano, M. Moriyama, K. Sugimachi, Laparoscopy-assisted billroth I gastrectomy, Surg. Laparosc. Endosc. 4 (1994) 146–148.

[2] Y.K. Park, H.M. Yoon, Y.W. Kim, J.Y. Park, K.W. Ryu, Y.J. Lee, O. Jeong, K.Y. Yoon, J.H. Lee, S.E. Lee, W. Yu, S.H. Jeong, T. Kim, S. Kim, B.H. Nam, C. group, Laparoscopy-Assisted versus open D2 distal gastrectomy for advanced gastric cancer: results from a randomized phase II multicenter clinical trial (COACT 1001), Ann. Surg. 42 (2017) S98–S99.

[3] Y. Hu, C. Huang, Y. Sun, X. Su, H. Cao, J. Hu, Y. Xue, J. Suo, K. Tao, X. He, H. Wei, M. Ying, W. Hu, X. Du, P. Chen, H. Liu, C. Zheng, F. Liu, J. Yu, Z. Li, G. Zhao, X. Chen, K. Wang, P. Li, J. Xing, G. Li, Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: a randomized controlled trial, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 34 (2016) 1350–1357.

[4] N. Inaki, T. Etoh, T. Ohyama, K. Uchiyama, N. Katada, K. Koeda, K. Yoshida, A. Takagane, K. Kojima, S. Sakuramoto, N. Shiraishi, S. Kitano, A multi-institutional, prospective, phase II feasibility study of laparoscopy-assisted distal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer (JLSSG0901), World J. Surg. 39 (2015) 2734–2741.

[5] T. Son, W.J. Hyung, J.H. Lee, Y.M. Kim, S.H. Noh, Minimally invasive surgery for serosa-positive gastric cancer (pT4a) in patients with preoperative diagnosis of cancer without serosal invasion, Surg. Endosc. 28 (2014) 866–874.

[6] F. Zhang, Y. Lan, B. Tang, Y. Hao, Y. Shi, P. Yu, Comparative study of laparoscopy-assisted and open radical gastrectomy for stage T4a gastric cancer, Int. J. Surg. 41 (2017) 23–27.

[7] Y. Xu, J. Hua, J. Li, L. Shi, J. Yuan, J. Du, Laparoscopic versus open gastrectomy for gastric cancer with serous invasion: long-term outcomes, J. Surg. Res. 215 (2017) 190–195.

[8] C.M. Huang, M. Xu, J.B. Wang, C.H. Zheng, P. Li, J.W. Xie, J.X. Lin, J. Lu, Is tumor size a predictor of preoperative N staging in T2-T4a stage advanced gastric cancer? Surgical oncology 23 (2014) 5–10.

[9] T. Sano, D.G. Coit, H.H. Kim, F. Roviello, P. Kassab, C. Wittekind, Y. Yamamoto, Y. Ohashi, Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project, Gastric Canc. Off. J. Int. Gastric Cancer Assoc. Jpn. Gastric Cancer Assoc. 20 (2017) 217–225.

[10] J.Z.J. Du, Y. Li, J. Li, G. Ji, G. Dong, Z. Yang, W. Wang, Z. Gao, Laparoscopy-assisted total gastrectomy with extended lymph node resection for advanced gastric cancer–reports of 82 cases, Hepatogastroenterology 57 (2010) 1589–1594.

[11] C. Fang, J. Hua, J. Li, J. Zhen, F. Wang, Q. Zhao, J. Shuang, J. Du, Comparison of long-term results between laparoscopy-assisted gastrectomy and open gastrectomy with D2 lymphadenectomy for advanced gastric cancer, Am. J. Surg. 208 (2014) 391–396.

[12] J. Shuang, S. Qi, J. Zheng, Q. Zhao, J. Li, Z. Kang, J. Hua, J. Du, A case-control study of laparoscopy-assisted and open distal gastrectomy for advanced gastric cancer, J. Gastrointest. Surg. 15 (2011) 57–62.

[13] P.A. Clavien, J. Barkun, M.L. de Oliveira, J.N. Vauthey, D. Dindo, R.D. Schulick, E. de Santibanes, J. Pekolj, K. Slankamenac, C. Bassi, R. Graf, R. Vonlanthen, R. Padbury, J.L. Cameron, M. Makuuchi, The Clavien-Dindo classification of surgical complications: five-year experience, Ann. Surg. 250 (2009) 187–196.

[14] D. Dindo, N. Demartines, P.-A. Clavien, Classification of surgical complications, Ann. Surg. 240 (2004) 205–213.

[15] Z. Li, G. Ji, B. Bai, D. Yu, Y. Liu, B. Lian, Q. Zhao, Laparoscopy-assisted distal gastrectomy versus laparoscopy-assisted total gastrectomy with D2 lymph node dissection for middle-third advanced gastric cancer, Surg. Endosc. 32 (2018) 2255–2262.

[16] Y. Shi, X. Xu, Y. Zhao, F. Qian, B. Tang, Y. Hao, H. Luo, J. Chen, P. Yu, Short-term surgical outcomes of a randomized controlled trial comparing laparoscopic versus open D2 lymph node dissection for advanced gastric cancer, Surg. Endosc. 32 (2018) 2427–2433.

[17] T. Shinohara, S. Satoh, S. Kanaya, Y. Ishida, K. Taniguchi, J. Isogaki, K. Inaba, K. Yanaga, I. Uyama, Laparoscopic versus open D2 gastrectomy for advanced gastric cancer: a retrospective cohort study, Surg. Endosc. 27 (2013) 286–294.

[18] J.H. Lee, S.H. Ahn, D.J. Park, H.H. Kim, H.J. Lee, H.K. Yang, Laparoscopic total gastrectomy with D2 lymphadenectomy for advanced gastric cancer, World J. Surg. 36 (2012) 2394–2399.

[19] A. Hamabe, T. Omori, K. Tanaka, T. Nishida, Comparison of long-term results between laparoscopy-assisted gastrectomy and open gastrectomy with D2 lymph node dissection for advanced gastric cancer, Surg. Endosc. 26 (2012) 1702–1709.

[20] Z. Li, B. Bai, Y. Zhao, D. Yu, B. Lian, Y. Liu, Q. Zhao, Severity of complications and long-term survival after laparoscopic total gastrectomy with D2 lymph node dissection for advanced gastric cancer: a propensity score-matched, case–control study, Int. J. Surg. 54 (2018) 62–69.

[21] B.W. Eom, Y.W. Kim, S.E. Lee, K.W. Ryu, J.H. Lee, H.M. Yoon, S.J. Cho, M.C. Kook, S.J. Kim, Survival and surgical outcomes after laparoscopy-assisted total gastrectomy for gastric cancer: case-control study, Surg. Endosc. 26 (2012) 3273–3281.

[22] T. Bo, Y. Peiwu, Q. Feng, Z. Yongliang, S. Yan, H. Yingxue, L. Huaxing, Laparoscopy-Assisted vs. Open total gastrectomy for advanced gastric cancer: long-term outcomes and technical aspects of a case–control study, J. Gastrointest. Surg. 17 (2013) 1202–1208.

[23] Y. Zhao, P. Yu, Y. Hao, F. Qian, B. Tang, Y. Shi, H. Luo, Y. Zhang, Comparison of outcomes for laparoscopically assisted and open radical distal gastrectomy with lymphadenectomy for advanced gastric cancer, Surg. Endosc. 25 (2011) 2960–2966.

[24] M. Inokuchi, M. Nakagawa, T. Tanioka, K. Okuno, K. Gokita, K. Kojima, Long- and short-term outcomes of laparoscopic gastrectomy versus open gastrectomy in patients with clinically and pathological locally advanced gastric cancer: a propensity-score matching analysis, Surg. Endosc. 32 (2018) 735–742.

[25] Y. Quan, A. Huang, M. Ye, M. Xu, B. Zhuang, P. Zhang, B. Yu, Z. Min, Comparison of laparoscopic versus open gastrectomy for advanced gastric cancer: an updated meta-analysis, Gastric Cancer : Off. J. Int. Gastric Cancer Assoc. Jpn. Gastric Cancer Assoc. 19 (2016) 939–950.

[26] J.X. Lin, C.M. Huang, C.H. Zheng, P. Li, J.W. Xie, J.B. Wang, L. Jun, Q.Y. Chen, L.L. Cao, M. Lin, Is all advanced gastric cancer suitable for laparoscopy-assisted gastrectomy with extended lymphadenectomy? A case-control study using a propensity score method, Ann. Surg. Oncol. 23 (2016) 1252–1260.

[27] J. Song, H.J. Lee, G.S. Cho, S.U. Han, M.C. Kim, S.W. Ryu, W. Kim, K.Y. Song, H.H. Kim, W.J. Hyung, Korean Laparoscopic Gastrointestinal Surgery Study G, Recurrence following laparoscopy-assisted gastrectomy for gastric cancer: a multicenter retrospective analysis of 1,417 patients, Ann. Surg. Oncol. 17 (2010) 1777–1786.

[28] D. Liu, M. Lu, J. Li, Z. Yang, Q. Feng, M. Zhou, Z. Zhang, L. Shen, The patterns and timing of recurrence after curative resection for gastric cancer in China, World J. Surg. Oncol. 14 (2016) 305.

[29] K.X.X. Chen, Y.P. Mou, Y. Pan, Y.C. Zhou, R.C. Zhang, D. Wu, Systematic review and meta-analysis of laparoscopic and open gastrectomy for advanced gastric cancer, World J. Surg. Oncol. 11 (2013) 182.

[30] M. Shoup, M.F. Brennan, M.S. Karpeh, S.M. Gillern, R.L. McMahon, K.C. Conlon, Port site metastasis after diagnostic laparoscopy for upper gastrointestinal tract malignancies: an uncommon entity, Ann. Surg. Oncol. 9 (2002) 632–636.

[31] X. Liu, Y. Xu, Z. Long, H. Zhu, Y. Wang, Prognostic significance of tumor size in T3 gastric cancer, Ann. Surg. Oncol. 16 (2009) 1875–1882.

[32] J. Lu, C.M. Huang, C.H. Zheng, P. Li, J.W. Xie, J.B. Wang, J.X. Lin, Consideration of tumor size improves the accuracy of TNM predictions in patients with gastric cancer after curative gastrectomy, Surgical oncology 22 (2013) 167–171.

[33] J. Deng, R. Zhang, Y. Pan, X. Ding, M. Cai, Y. Liu, H. Liu, T. Bao, X. Jiao, X. Hao, H. Liang, Tumor size as a recommendable variable for accuracy of the prognostic prediction of gastric cancer: a retrospective analysis of 1,521 patients, Ann. Surg. Oncol. 22 (2015) 565–572.

[34] F.G.X. Yue, Impact of conversion during laparoscopic gastrectomy on outcomes of patients with gastric cancer, J Buon 22 (2017) 926–931.

[35] M.J.K. Ye, G. Xu, F. Lin, Q. Zhou, K. Tao, F. Tao, Short- and long-term outcomes after conversion of laparoscopic total gastrectomy for gastric cancer: a single-center study, J BUON 22 (2017) 126–133.

[36] K. Washington, 7th edition of the AJCC cancer staging manual: stomach, Ann. Surg. Oncol. 17 (2010) 3077–3079.

[37] G. Zheng, F. Feng, M. Guo, G. Xu, S. Liu, Z. Liu, L. Sun, L. Hong, J. Yang, X. Lian, D. Fan, H. Zhang, Harvest of at least 23 lymph nodes is indispensable for stage N3 gastric cancer patients, Ann. Surg. Oncol. 24 (2017) 998–1002.

[38] Z. Shen, Y. Ye, Q. Xie, B. Liang, K. Jiang, S. Wang, Effect of the number of lymph nodes harvested on the long-term survival of gastric cancer patients according to tumor stage and location: a 12-year study of 1,637 cases, Am. J. Surg. 210 (2015) 431–440 e433.

[39] R.E. Schwarz, D.D. Smith, Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage, Ann. Surg. Oncol. 14 (2006) 317–328.

[40] H.N. Chen, X.Z. Chen, W.H. Zhang, X.L. Chen, K. Yang, J.P. Liu, B. Zhang, Z.X. Chen, J.P. Chen, Z.G. Zhou, J.K. Hu, Necessity of harvesting at least 25 lymph nodes in patients with stage N2-N3 resectable gastric cancer: a 10-year, single-institution cohort study, Medicine 94 (2015) e620.

[41] B. Zhao, J. Zhang, X. Chen, T. Sun, Z. Wang, H. Xu, B. Huang, The retrieval of at least 25 lymph nodes should be essential for advanced gastric cancer patients with lymph node metastasis: a retrospective analysis of single-institution database study design: cohort study, Int. J. Surg. 48 (2017) 291–299.