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ORIGINAL ARTICLE

Comparisons of perioperative and survival outcomes of laparoscopic versus open gastrectomy for serosa-positive (pT4a) gastric cancer patients: a propensity score matched analysis

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Abstract

Background Data about whether laparoscopic gastrectomy (LG) is applicable in serosa-positive (pT4a) gastric cancer patients remain rare. The purpose of this study is to compare the perioperative and long-term outcomes between the laparoscopic and open gastrectomy (OG) in pT4a gastric cancer patients who underwent curative resection.

Methods A total of 1086 consecutive pT4a patients (101 patients with LG and 985 with OG) who underwent curative gastrectomy in a high-volume center between 2006 and 2016 were evaluated. Demographics, surgical, and oncologic outcomes were analyzed. Propensity score matching (PSM) analysis was performed to balance baseline confounders, and COX regression analysis was performed to identify independent prognostic factors.

Results After PSM adjustment, a well-balanced cohort comprising 101 patients who underwent LG and 201 who underwent OG was analyzed. Operative time (288.7 vs. 234.2 min; $P<0.001$) was significantly longer, while estimated blood loss (172.8 vs. 220.7 ml; $P<0.001$) was significantly less in the LG group compared with the OG group. There were no significant differences between groups in total number of harvested lymph nodes, postoperative stays, readmission rate, and postoperative complication rate. The 3-year overall survival (OS) rate was not significant different in the LG and OG groups (66.7% vs. 62.8%, $P=0.668$), and the subsequent multivariate analysis revealed that the surgical approach was not an independent prognostic factor for OS (HR = 1.123; 95%CI: 0.803–1.570; $P=0.499$). In sensitivity analysis including 78 pairs well-matched patients operated by an experienced surgeon, the results were similar to these for the matched entire cohort.

Conclusion LG can be a safe and feasible approach for pT4a gastric cancer treatment. However, well-designed high-quality RCTs are expected to draw a definitive conclusion on this topic.

Keywords Gastric cancer · Serosa invasion · Laparoscopic gastrectomy · Surgical outcomes · Overall survival

Introduction

Currently, gastric cancer (GC) still remains a commonly diagnosed cancer and a leading cause of cancer death worldwide [1]. Due to the advances in surgical equipment and the enhanced expertise of surgeons, the recorded 5-year survival rate has exceeded 95% for early gastric cancer (EGC) [2, 3], and laparoscopic gastrectomy (LG) with limited lymphadenectomy is recommended for patients with EGC considering its minimally invasive nature and the accepted oncologic outcomes compared with open gastrectomy (OG). In contrast to EGC, LG for advanced gastric cancer (AGC) is more technically challenging for curative resection owing

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to a relatively larger tumor size and more extensive lymph node metastasis. Despite accumulated studies have found its safety and feasibility in AGC [4–6], whether LG can be safely extended to AGC patients remains inconclusive, especially, for patients with serosal invasion (pT4a). To date, there are few studies [7, 8] reported the surgical and oncologic outcomes of LG for this specific subgroup of AGC patients. Therefore, the aim of this study was to compare the surgical and oncologic results of LG and OG for GC patients with pathologically confirmed serosal invasion (pT4a).

Methods

Patients and ethical issues

A total of 1493 consecutive patients with pathologically confirmed T4a gastric cancer were selected from the database of Surgical Gastric Cancer Patient Registry in West China Hospital (WCH-SGCPR) from January 2006 to December 2016, with registration number WCH-SGCPR-2020–06, and the establishment of this database was approved by the Research Ethics Committee of West China Hospital (No.2014–215). The inclusion criteria were as follows: (1) histologically proven adenocarcinoma, (2) pathological examination confirmed in T4a stage, and (3) underwent curative resection. The exclusion criteria were patients with: (1) distant metastasis; (2) other synchronous or metachronous malignancies; (3) other types of gastric neoplasms, such as neuroendocrine neoplasm; (4) stump cancer; (5) any preoperative oncologic treatment; (6) conversion to open surgery; and (7) incomplete baseline data. Additionally, patients who underwent proximal gastrectomy were excluded due to the unstandardized surgical procedure [9]. Ultimately, 1086 patients were included in the present study. The flow diagram is shown in Fig. 1.

Surgery procedure

The procedures for both laparoscopic gastrectomy (LG) and open gastrectomy (OG) have been previously described in detail [10, 11]. Patients in this study were operated by eight skilled surgeons (having performed at least 50 gastrectomies for gastric cancer) according to the Japanese gastric cancer treatment guidelines [12], and patients in the LG group were operated by five of these surgeons. The resection pattern of distal or total gastrectomy was based on the site of the primary tumor. The methods of anastomosis were determined by surgeon's preference and patient's anatomy. Finally, the resected specimens were pathologically classified according to the JGCA classification [13] and staged with the AJCC 8th TNM system [14].

Follow-up

The follow-up was mainly performed through out-patient visits. All patients were recommended to undergo follow-up every 3 to 6 months in the first 3 years and at least once yearly during the subsequent years [15]. Follow-up information was also collected from the database and updated to Jan 1, 2020. In the 1086 patients, 113 of them lost contact during follow-up (8 in the LG group and 105 in the OG group), the

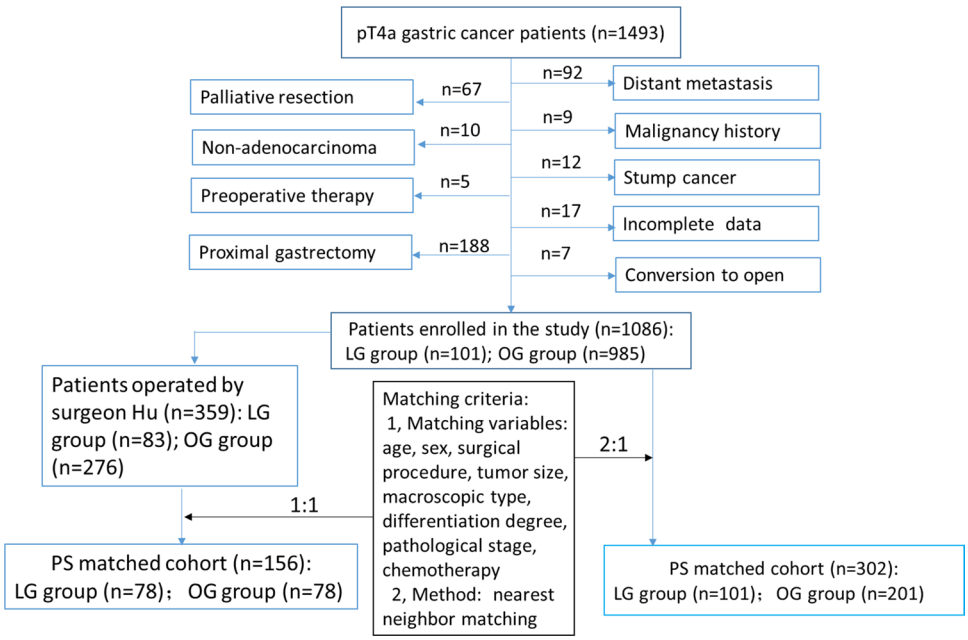

Fig. 1 Flowchart of patient selection and matching

overall follow-up rate was 89.6% (92.1% and 89.3% in the LG and OG group, respectively). The main reasons for lost follow-up are because of the change of telephone number and address and refusal to attend to out-patient interview of our hospital.

Outcomes measurement

The primary outcome was overall survival (OS). The secondary outcomes were perioperative parameters, including operative time, estimated blood loss, total number of harvested lymph nodes, postoperative hospital stays, readmission, and postoperative complications. The OS was defined as the time duration from the date of operation to the date of death for any cause. Postoperative complications which occurred within 30 days after surgery or during hospital stay were recorded using Clavien-Dindo classification system[16].

Statistical analysis

For intergroup comparison, the Chi-square test and Fisher exact test were used to compare nominal data. The Student's *t* test and Mann–Whitney *U* test were used to compare normal distribution and nonparametric distributions, respectively. The log-rank test and Kaplan–Meier method were utilized to calculate cumulative survival rates. Risk factors for OS were evaluated by univariate and multivariate Cox regression analyses. Factors with a P value < 0.05 in the univariate analysis as well as surgical procedure (LG vs. OG) were entered into the multivariate model using an "Enter" method. The analyses were all performed with software IBM SPSS Statistics version 23.0 (International Business Machines Corporation, Armonk, NY, USA).

To balance the potential confounders between the LG and OG group, propensity score matching (PSM) analyses were performed in the entire cohort and a subset cohort operated by surgeon Hu, with the same following variables: age, sex, surgical procedure, tumor size, macroscopic type, tumor differentiation degree, pathological stage, and adjuvant chemotherapy. A 0.2-width caliper of the standard deviation of the logit and the nearest neighbor matching method was used to match across the two groups [17]. Balance of baseline parameters between the two groups was assessed by standardized mean difference (SMD) before and after PSM, and a SMD ≤ 0.1 indicated that a well-balanced covariate was achieved [18]. The PSM analysis was performed using R version 3.6.0 with MatchIt package.

P values less than 0.05 (two-sided) were considered to be statistically significant.

Results

Participant characteristics

The demographic and pathologic characteristics of the entire cohort are presented in Table 1. A total of 1086 pT4a patients were included in the analysis, of which, 101 patients received laparoscopic gastrectomy (LG) and 985 underwent open gastrectomy (OG). Compared with patients in the LG group, patients in the OG group had an older age ($P < 0.001$), larger tumor size ($P < 0.001$), higher proportion of multiple tumor location ($P = 0.012$), higher grade of macroscopic type ($P = 0.009$), and more advanced tumor stage ($P = 0.038$). No significant differences were detected in other clinicopathological variables between the LG and OG groups. To reduce the baseline bias, a 2:1

Table 1 The clinicopathological characteristics of gastric cancer patients in the whole cohort before and after PSM

		Before matching			After matching		
	LG ($n = 101$)	OG ($n = 985$)	P value	SMD	OG ($n = 201$)	P value	SMD
Age, years (≥65/<65)	9/92	267/718	<0.001	0.382	18/183	0.990	0.002
Sex (male/female)	73/28	658/327	0.264	0.119	145/56	0.980	0.003
Comorbidities (yes/no)	31/70	323/662	0.668	0.045	57/144	0.674	0.051
Gastrectomy extent (distal/total)	59/42	595/390	0.697	0.040	118/83	0.961	0.006
Lymph node dissection (<D2/≥D2)	7/94	67/918	0.961	0.005	17/184	0.643	0.057
Tumor size, cm (≥5/<5)	54/47	700/285	<0.001	0.368	109/92	0.900	0.015
Tumor location (upper/middle/lower/multiple)	22/16/59/4	141/125/584/135	0.012	0.318	40/25/116/20	0.292	0.146
Macroscopic type (type1-2/type3-4)	57/44	423/562	0.009	0.336	114/87	0.963	0.006
Tumor differentiation (G1 + G2/G3 + G4)	19/82	229/756	0.312	0.109	34/167	0.683	0.049
Nodal involvement (N0/1/2/3a/3b)	21/16/24/30/10	164/146/199/294/182	0.048	0.201	41/27/55/51/27	0.746	0.045
TNM stage (IIB/IIIA/IIIB/IIIC)	21/40/30/10	164/345/294/182	0.038	0.228	41/82/51/27	0.809	0.044
Adjuvant chemotherapy (yes/no or unknown)	53/48	488/497	0.575	0.059	103/98	0.840	0.025

Table 2 Comparison of short-term surgical outcomes between LG and OG groups in the whole cohort after PSM

	PSM cohort ($n=302$)		P value
	LG ($n=101$)	OG ($n=201$)	
Operation time, min	288.7 ± 50.2	234.2 ± 49.5	< 0.001
Estimated blood loss, ml	172.8 ± 133.1	220.7 ± 131.8	< 0.001
No. of retrieved lymph nodes	32.8 ± 14.1	29.6 ± 12.2	0.055
Postoperative hospital stays, day	10.8 ± 4.6	11.2 ± 4.3	0.063
Readmission (%)	2(1.0)	1(1.0)	1.000
Postoperative complication (%)			
Pulmonary complication	9(8.9)	15(7.5)	0.686
Gastroparesis	5(5.0)	6(3.0)	0.615
Intra-abdominal abscess	2(2.0)	4(2.0)	1.000
Wound infection	1(1.0)	1(0.5)	1.000
Anastomotic leak	0(0.0)	1(0.5)	1.000
Abdominal hemorrhage	0(0.0)	1(0.5)	1.000
Chylous leakage	2(2.0)	1(0.5)	0.260
Cholecystitis	1(1.0)	2(1.0)	1.000
Intestinal necrosis	0(0.0)	1(0.5)	1.000
Overall complications (%)	20(19.8)	32(15.9)	0.481
Clavien–Dindo classification			0.646
Grade I (%)	7(6.9)	10(5.0)	
Grade II (%)	12(11.9)	20(10.0)	
Grade III (%)	1(1.0)	1(0.5)	
Grade IV (%)	0(0.0)	0(0.0)	
Grade V (%)	0(0.0)	1(0.5)	
Clavien-Dindo grade ≥ III (%)	1(1.0)	2(1.0)	1.000

PSM was performed, which yielded 201 patients in the OG group and 101 patients in the LG group. After matching, there were no longer significant differences in the baseline variables between patients in the LG and OG group (almost all SMD values ≤ 0.1 and all P values > 0.05).

Surgical outcomes

The short-term outcomes between the LG and OG groups are shown in Table 2. After PSM, patients who underwent LG had a significantly longer surgery time (288.7 vs. 234.2 min; $P < 0.001$) and less estimated blood loss (172.8 vs. 220.7 ml, $P < 0.001$). However, the number of retrieved lymph nodes ($P = 0.055$), postoperative hospital stays ($P = 0.063$), and readmission rate ($P = 1.000$) was not significantly different between the two groups. With respect to postoperative complications, there was no significant difference in overall postoperative complication rate between the LG and OG groups (19.8% vs. 15.9%, $P = 0.481$). No significant difference in the severe complication (C-D ≥ IIIa) rate was observed between the two groups (1.0% vs. 1.0%, P = 1.000).

Survival analysis

As shown in Fig. 2a, after PSM, patients in the LG group had a similar overall survival compared with these in the OG group (3-year OS rate: 66.7% vs. 62.8%, $P = 0.668$). When stratified by different surgical procedures, comparing the LG and OG group, the difference in OS is insignificant in patients who underwent distal or total gastrectomy (Fig. 2b, c). In addition, the stage-stratified analysis shows that there were no significant differences between the two groups (Fig. 3a–d). Multivariate analysis identifies that the surgical approach (HR = 1.123; 95%CI: 0.803–1.570; $P = 0.499$) was not an independent prognostic factor for OS (Table 3).

Sensitivity analysis

Considering the factor of "surgeons" may have an important effect on the short-term and even long-term outcomes to some extent, we selected patients (359 patients comprising 83 in the LG group and 276 in the OG group) operated by an

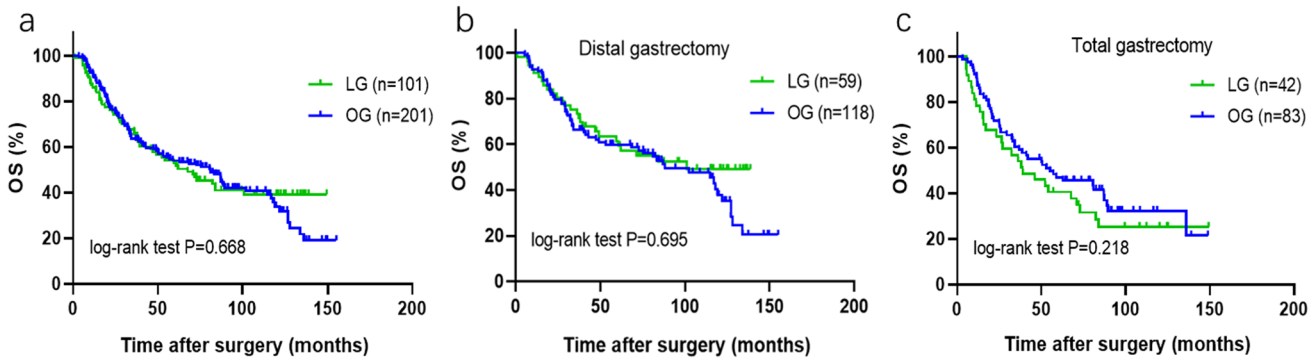

Fig. 2 Kaplan–Meier survival analysis of overall survival for LG vs. OG in the matched whole cohort. **a** Total patients; **b** patients with distal gastrectomy; **c** patients with total gastrectomy

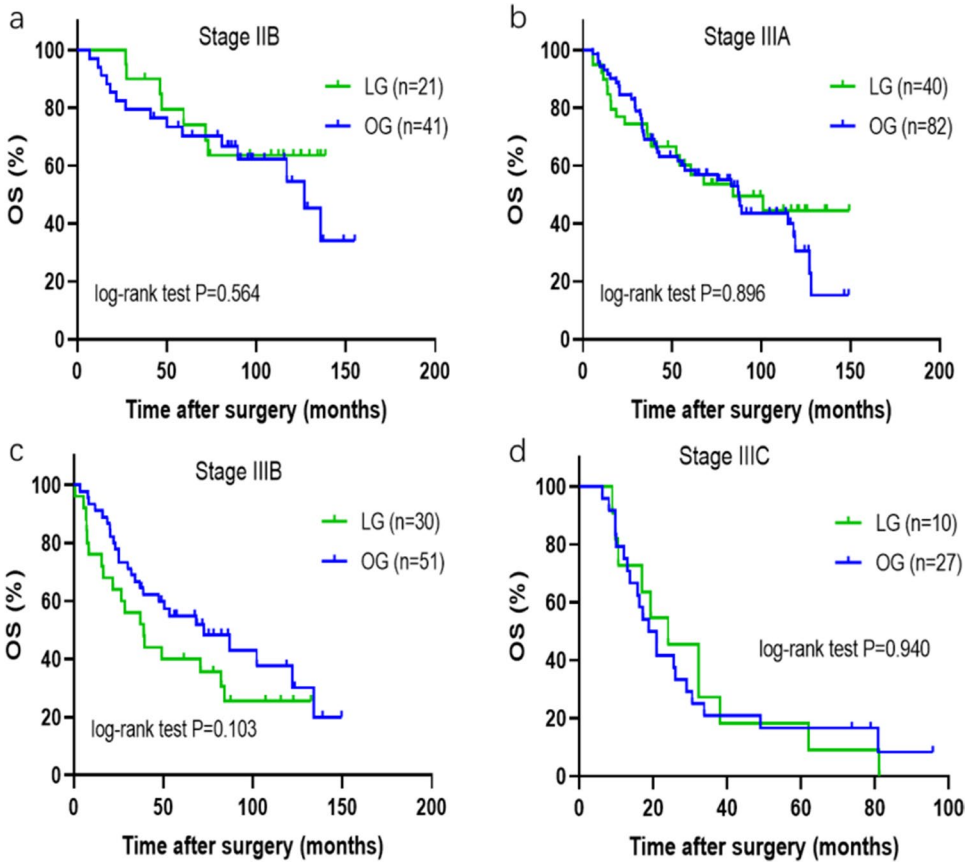

Fig. 3 Kaplan–Meier survival analysis of overall survival for LG vs. OG in matched whole cohort. **a** Stage IIB; **b** stage IIIA; **c** stage IIIB; **d** stage IIIC

experienced surgeon (Prof. Hu) as an inner validation cohort to evaluate the safety and feasibility of LG.

The baseline features are summarized in Table 4. After PSM, 78 pairs of patients were selected for analysis and the baseline variables were all comparable between the two groups. In terms of the short-term outcomes (Table 5), we found similar results that the LG group had a longer operative time (299.6 vs. 247.9 min; $P<0.001$) and less blood loss (161.9 vs. 212.5 ml; $P=0.005$) when compared with the OG group. Other surgical outcomes show no significant

Table 3 Univariate and multivariate analysis of risk factors of overall survival in the whole cohort after PSM

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≥65 vs. <65)	1.072(0.639–1.799)	0.791		
Gender (male vs. female)	0.974(0.686–1.383)	0.885		
Comorbidities (yes vs. no)	0.901(0.635–1.276)	0.556		
Surgery approach (laparoscopic vs. open)	0.948(0.681–1.318)	0.688	1.123(0.803–1.570)	0.499
Lymphadenectomy (≥D2vs. <D2)	0.615(0.384–0.983)	0.040	0.588(0.358–0.965)	0.036
Surgery procedure (total vs. distal)	1.536(1.124–2.101)	0.007	1.310(0.934–1.838)	0.117
Tumor size (≥5 vs. <5 cm)	2.083(1.500–2.894)	<0.001	1.440(0.995–2.083)	0.053
Macroscopic type (Bormann 3–4 vs. 0–2)	1.282(0.936–1.756)	0.121		
Tumor differentiation (G3/4 vs. G1/2)	1.007(0.669–1.515)	0.973		
TNM stage				
IIIA vs. IIB	1.723(1.055–2.815)	0.025	1.637(0.998–2.686)	0.051
IIIB vs. IIB	2.345(1.403–3.917)	0.001	2.154(1.266–3.666)	0.005
IIIC vs. IIB	6.164(3.520–10.797)	<0.001	5.958(3.331–10.659)	<0.001
Adjuvant chemotherapy (yes vs. no/unknown)	0.673(0.492–0.922)	0.013	0.686(0.494–0.953)	0.025

Table 4 The clinicopathological characteristics of LG and OG gastric cancer patients in the subset cohort before and after PSM

	Before matching ($n=359$)				After matching ($n=156$)			
	LG ($n=83$)	OG ($n=276$)	P value	SMD	LG ($n=78$)	OG ($n=78$)	P value	SMD
Age, years (≥65 vs. <65)	7/76	79/197	<0.001	0.542	7/71	8/70	0.786	0.043
Sex (male/female)	59/24	193/83	0.840	0.025	56/22	55/23	0.860	0.028
Comorbidities (yes/no)	27/56	87/189	0.863	0.022	26/52	20/58	0.292	0.168
Gastrectomy extent (distal/total)	47/36	133/143	0.178	0.169	43/35	47/31	0.517	0.103
Lymph node dissection (<D2/≥D2)	6/77	4/272	0.015	0.285	6/72	2/76	0.276	0.129
Tumor size, cm (≥5/<5)	46/37	199/77	0.004	0.351	44/34	40/38	0.521	0.102
Tumor location (upper/middle/lower/multiple)	18/15/47/3	88/26/141/21	0.040	0.282	18/14/43/3	19/9/46/4	0.715	0.057
Macroscopic type (type1-2/type3-4)	48/35	115/161	0.010	0.424	43/35	46/32	0.628	0.077
Tumor differentiation (G1 + G2/G3 + G4)	15/68	65/211	0.293	0.135	15/63	19/59	0.438	0.124
Nodal involvement (N0/1/2/3a/3b)	19/14/20/22/8	48/34/54/78/62	0.010	0.317	14/14/20/22/8	18/8/18/25/9	0.779	0.029
TNM stage (IIB/IIIA/IIIB/IIIC)	19/34/22/8	48/88/78/62	0.010	0.339	14/34/22/8	18/26/25/9	0.908	0.014
Adjuvant chemotherapy (yes/no or unknown)	47/36	187/89	0.062	0.230	47/31	46/32	0.870	0.026

differences between the two groups (all P values > 0.05). In terms of the long-term outcome, the OS rate is also comparable between the LG group and OG group (3-year OS rate: 71.2% vs. 68.5%; $P=0.654$) (Fig. 4a). Subgroup analyses based on surgical procedure and pathological stage indicate that there were no significant differences between the two groups (all P values > 0.05) (Figs. 4b, c and 5a–d). Meanwhile, the multivariate analyses for this matched cohort demonstrate that the surgery approach was not an independent prognostic factor for OS (HR = 1.077; 95%CI: 0.675–1.719; $P=0.754$) (Table 6).

Table 5 Comparison of short-term surgical outcomes between the LG and OG group in the subset cohort after PSM

	LG ($n=78$)	OG ($n=78$)	P value
Operation time, min	299.6 ± 47.6	247.9 ± 44.5	<0.001
Estimated blood loss, ml	161.9 ± 107.1	212.5 ± 110.4	0.005
No. of retrieved lymph nodes	34.4 ± 14.7	38.1 ± 16.9	0.162
Postoperative hospital stays, day	10.8 ± 4.9	11.1 ± 5.8	0.745
Readmission (%)	1(1.3)	0(0.0)	1.000
Postoperative complication (%)			
Pulmonary complication	8(10.3)	5(6.4)	0.385
Gastroparesis	2(2.6)	3(3.9)	1.000
Intra-abdominal abscess	3(3.9)	1(1.3)	0.620
Cholecystitis	1(1.3)	0(0.0)	1.000
Wound infection	0(0.0)	1(1.3)	1.000
Anastomotic leak	0(0.0)	1(1.3)	1.000
Overall complications (%)	14(17.9)	11(14.1)	0.577
Clavien–Dindo classification			0.512
Grade I (%)	4 (5.1)	3 (3.8)	
Grade II (%)	9(10.3)	6(7.7)	
Grade III (%)	1(1.3)	1(1.3)	
Grade IV (%)	0(0.0)	1(1.3)	
Grade V (%)	0(0.0)	0(0.0)	
Clavien-Dindo grade ≥ III (%)	1(1.3)	2(2.6)	1.000

Discussion

Laparoscopic gastrectomy (LG) for advanced gastric cancer has recently grown in popularity in both eastern and western countries [19]. However, LG has still not gained widespread in serosa-invasive gastric cancer because of the uncertainty of surgical and oncological efficacy [20]. In this study, we demonstrated that, in pT4a gastric cancer patients, LG was as safe as open gastrectomy (OG) with comparable short-term and long-term outcomes in both the matched entire cohort and inner subset cohort.

Since the first LG for gastric cancer was reported in 1994 [21], numerous studies have noted the merits of LG over OG in gastric cancer patients, including reduction of surgical pain, earlier recovery of intestinal function, and cosmetic effect [22–24]. Meanwhile, LG has been performed at our center since 2006 [25], and an earlier study demonstrated the advantage in decreasing hospital stay and the disadvantage in consuming longer surgery time of LG relative to OG [11], which was in accordance with the results reported by other studies. To date, LG with D1 + α or D1 + β lymphadenectomy has been regarded as a stipulated option for EGC considering its advantages in quality of life in early postoperative period and acceptable long-term survival rate [26, 27]. However, compared with EGC, LG for AGC is relatively more challenging due to the technical complexity in performing D2 lymph node dissection [28].

With the improvement of proficiency of surgeons and surgical devices, more and more studies have confirmed the

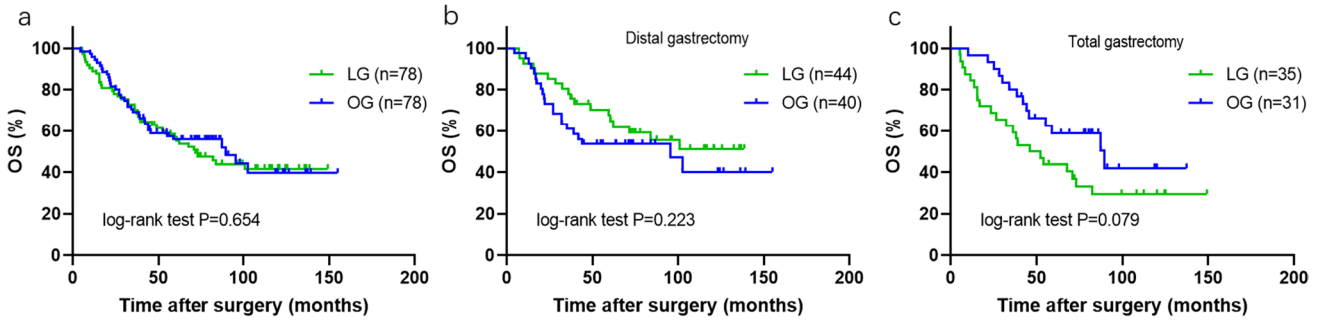

Fig. 4 Kaplan–Meier survival analysis of overall survival for LG vs. OG in the matched subset cohort. **a** Total patients; **b** patients with distal gastrectomy; **c** patients with total gastrectomy

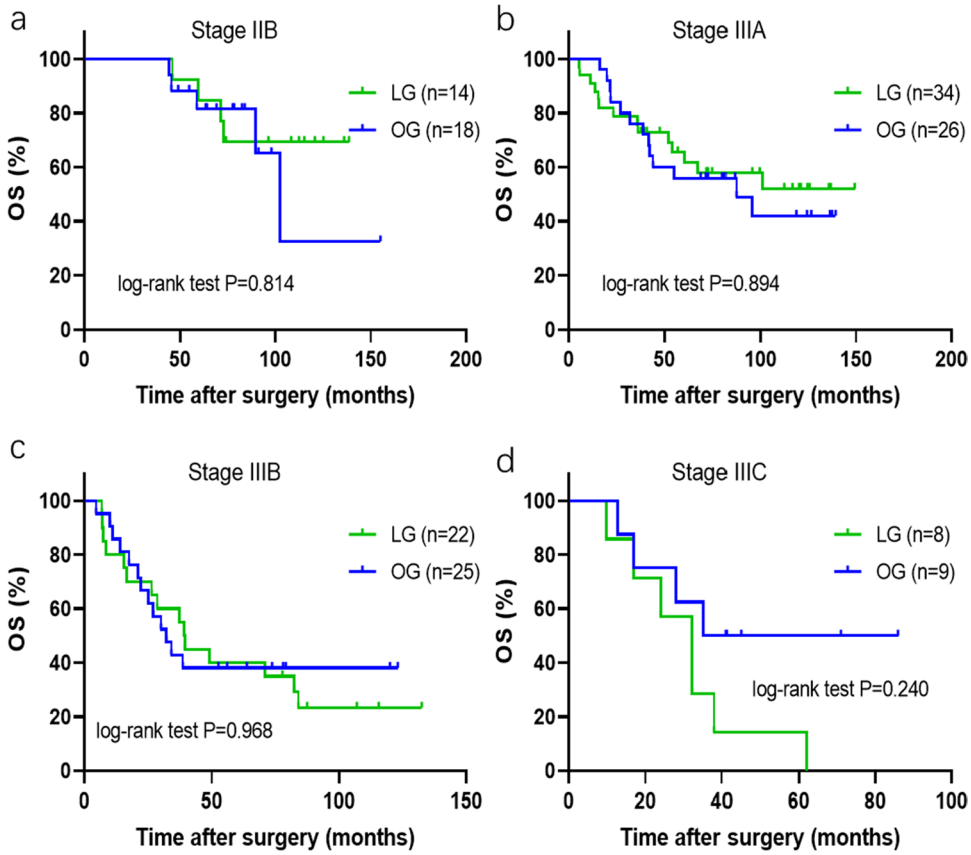

Fig. 5 Kaplan–Meier survival analysis of overall survival for LG vs. OG in the matched subset cohort. **a** Stage IIB; **b** stage IIIA; **c** stage IIIB; **d** stage IIIC

efficacy of LG in lymph nodes dissection for AGC [29–31]. At present, two large multicenter randomized clinical trials (CLASS-01 [29] and KLASS-02 [30] trial) have reported that the compliance rates of D2 lymphadenectomy were similar between the two groups and the number of harvested lymph nodes in the LG group was not inferior to that in the OG group. In our study, D2/D2 + lymphadenectomy for AGC was performed in principle, and the number of harvested lymph nodes tended to be higher in the LG group (LG vs. OG: 32.8 vs. 29.6; $P = 0.055$) in the matched whole cohort. Considering the discrepancy of proficiency of multiple surgeons involved, we selected patients who were operated by an experienced surgeon (Prof. Hu) to make a further sensitivity analysis. We found that the number of harvested lymph nodes was comparable in both the groups (LG vs. OG: 34.4 vs. 38.1; $P = 0.162$). Therefore, LG with D2 lymphadenectomy could be performed by experienced surgeons to obtain relatively sufficient lymph nodes in pT4a patients.

On the other hand, whether LG with D2 lymphadenectomy could be performed as safely as OG for AGC patients is also a major concern in clinical practice. Park et al. [32] reported that the postoperative morbidity was similar in AGC patients between the LG and OG groups (17.0% and

Table 6 Univariate and multivariate analysis of risk factors of overall survival in the subset cohort after PSM

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≥65 vs. <65)	1.233(0.633–2.400)	0.537		
Gender (male vs. female)	1.059(0.648–1.731)	0.818		
Comorbidities (yes vs. no)	0.978(0.590–1.621)	0.931		
Surgery approach (laparoscopic vs. open)	1.078(0.684–1.699)	0.654	1.077(0.675–1.719)	0.754
Lymphadenectomy (≥D2vs. <D2)	0.445(0.204–0.968)	0.036	0.370(0.164–0.839)	0.017
Surgery procedure (total vs. distal)	1.272(0.808–2.002)	0.297		
Tumor size (≥5 vs. <5 cm)	1.610(1.006–2.576)	0.045	0.982(0.585–1.647)	0.944
Macroscopic type (Bormann 3–4 vs. 0–2)	1.368(0.868–2.157)	0.176		
Tumor differentiation (G3/4 vs. G1/2)	0.657(0.402–1.073)	0.091		
TNM stage				
IIIA vs. IIB	1.971(0.926–4.193)	0.065	2.081(0.965–4.486)	0.061
IIIB vs. IIB	4.028(1.894–8.564)	<0.001	4.537(2.063–9.978)	<0.001
IIIC vs. IIB	5.278(2.158–12.907)	<0.001	5.947(2.297–15.398)	<0.001
Adjuvant chemotherapy (yes vs. no/unknown)	0.566(0.360–0.892)	0.013	0.535(0.332–0.862)	0.010

18.8%; $P=0.749$) in COACT 1001 trial. Additionally, a recent systematic review and meta-analysis conducted by Yao et al. [33] drew a same conclusion in AGC patients. Moreover, for pT4a patients, Zhang et al. [8] reported that the overall complication rates in the LG and OG group were 7.2% and 15.1% ($P<0.05$), while Li et al. [7] reported a comparable complication rate in the LG and OG groups (14.4% and 16.3%, respectively; $P=0.581$). In our study, in different matched cohorts, the complication rates were all similar between the two groups, and there were also no differences between the two groups in terms of major and minor complications. Based on these results, our study indicated that LG is a safe treatment with no inferior postoperative outcomes compared with OG.

The last but most important, the oncologic outcome is the most important indicator for deciding the applicability of LG in AGC patients. Currently, the CLASS-01 trail has disclosed that the 3-year disease-free survival (DFS) rate and OS rate were similar between the LG and OG groups for advanced gastric cancer [20]. Meanwhile, the recently published KLASS-02 trial also reported comparable long-term survival rates between the two groups [34]. These high-quality studies indicated that LG was oncologically equivalent to OG for AGC. Nevertheless, there were few studies reported the stage-specific survival outcomes of patients in pT4a stage. A retrospective study by Zhang et al. [8] showed that there were no significant differences in 5-year DFS rate (37.8% vs. 35.3%, $P>0.05$) and OS rate (47.7% vs. 40.3%, $P>0.05$) between the LG and OG groups in pT4a patients. Besides, Li et al. [7] showed similar results and found that there was no significant difference in recurrence pattern including local, peritoneum, and hematogenous recurrence in patients with pT4a gastric cancer. In the present study, the 3-year OS rate of all patients who underwent LG was comparable to those who underwent OG after PSM was performed, and the results remained consistent in the subgroup analyses based on the surgery procedure and pathological stage (all *P* values > 0.05). Meanwhile, these findings were further confirmed in the inner matched validation cohort. However, it is worth noting that, in the inner matched validation set, patients undergoing laparoscopic total gastrectomy tended to have lower OS rate than those in the open total gastrectomy group ($P=0.079$). This outcome may indicate that laparoscopic procedure needs to be performed with caution in this particular subgroup of patients. Nevertheless, considering the relatively small sample size of this study, the oncological safety of laparoscopic total gastrectomy for pT4a patients still needs to be further evaluated by large-scale prospective studies. This study has several limitations. First, this is a single center retrospective study with several confounding factors. Even though we tried our best to offset available biases with PSM analysis, some residual confounding unmeasured factors may exist. Second, the precise data about recurrence time and pattern are not available in the present study because the time when patients had suffered recurrence was often ambiguous or unknown from their relatives. Thus, whether laparoscopic procedure would increase the risk of recurrence or metastasis in patients with pT4a gastric

cancer remains unclear, even though the OS outcome was not significantly different between the groups.

In conclusion, our study suggests that LG can be a safe and feasible technique for pT4a gastric cancer patients in terms of short-term and long-term oncologic outcomes. However, well-designed high-quality RCTs are expected to draw a definitive conclusion on this topic.

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Authors' contributions Study conception and design: Jian-Kun Hu, Hua-Yang Pang, Lin-Yong Zhao, and Zi-Qi Zhang. Acquisition of data: Hua-Yang Pang, Lin-Yong Zhao and Zi-Qi Zhang, Danil Galiullin, Kai-Liu, Xiao-Long Chen, Wei-Han Zhang, Xin-Zu Chen, and Kun Yang. Analysis and interpretation of data: Hua-Yang Pang, Lin-Yong Zhao, Zi-Qi Zhang, Zhang, Danil Galiullin, and Wei-Han Zhang. Drafting of manuscript: Hua-Yang Pang and Lin-Yong Zhao. Critical revision of manuscript: Hua-Yang Pang, Lin-Yong Zhao and Zi-Qi Zhang, Wei-Han Zhang, Xiao-long Chen, and Kun Yang. Final approval of the version to be published: Jian-Kun Hu.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethical approval This study was based on the information gathered from the database of the Surgical Gastric Cancer Patient Registry of West China Hospital (WCH-SGCPR) under registration number: WCH-SGCPR-2020–06. The establishment of this database was approved by the Research Ethics Committee of West China Hospital. Informed consent individual patients were waived because of the retrospective nature of the analysis.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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