

# Surgical and Long-Term Survival Outcomes After Laparoscopic and Open Total Gastrectomy for Locally Advanced Gastric Cancer: A Propensity Score-Matched Analysis

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## Abstract

**Background** To compare the surgical and long-term survival outcomes of laparoscopic and open total gastrectomy (OTG) for locally advanced gastric cancer (AGC).

**Methods** We retrospectively evaluated 308 and 900 patients in pathological locally AGC who underwent laparoscopic total gastrectomy (LTG) or OTG between June 2008 and December 2014. We compared surgical and long-term outcomes between the two groups using propensity score matching method.

**Results** The LTG group showed a longer operation time (261.42 vs. 171.00 min,  $P = 0.001$ ), less blood loss (185.47 vs. 217.84 ml,  $P = 0.000$ ), earlier time to first flatus (3.47 vs. 4.12 days,  $P = 0.000$ ), earlier time to start liquid diet (3.76 vs. 4.27 days,  $P = 0.000$ ), and shorter postoperative hospital stay (7.56 vs. 8.22 days,  $P = 0.007$ ). The overall complication rate was 15.2% in the LTG group and 17.2% in the OTG ( $P = 0.503$ ). No significant difference was observed in overall survival (OS) and disease-free survival (DFS) between LTG and OTG (60.5% vs. 57.1%,  $P = 0.337$ ; 57.4% vs. 54.4%,  $P = 0.341$ ).

**Conclusions** Compared to OTG, LTG provides surgical benefits and comparable survival outcomes for patients with locally AGC.

## Introduction

Laparoscopic gastrectomy (LG) has been increasingly performed since it was first reported in 1994 by Kitano et al. [1]. Compared to open distal gastrectomy (ODG), randomized controlled trials (RCTs) have demonstrated that laparoscopic distal gastrectomy (LDG) was a safe and feasible surgical procedure for early gastric cancer (EGC) [2–5]. In the following years, some experienced surgeons

in high-volume centers have applied the laparoscopic gastrectomy for patients with locally advanced gastric cancer (AGC) with the experience accumulation of LDG for EGC. Currently, large RCTs have demonstrated that LDG is a feasible alternative procedure for AGC [6, 7]. According to the Japanese gastric cancer treatment guidelines, total gastrectomy with D2 lymphadenectomy is recommended for proximal AGC [8]. However, compared with LDG, laparoscopic total gastrectomy (LTG) remains a challenging procedure because of its technical difficulties and higher complication rate [9–11]. To date, only a few studies directed at the comparison of the surgical and long-term survival outcomes between LTG and OTG with D2 lymphadenectomy for AGC. We, therefore, designed this study to compare the outcomes followed by LTG and OTG for AGC.

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## Materials and methods

### Patients

We retrospectively reviewed data from a prospectively maintained gastric cancer database in our center from June 2008 to December 2014. Pathologic staging was updated according to the 8th Union for International Cancer Control/American Joint Committee on Cancer staging system

of gastric cancer [12]. Patients should meet the following criteria: patients with histologically confirmed gastric cancer; depth of invasion confined to pT2- pT4a; patients combined with no other malignancy; patients with no distant metastasis or invasion to adjacent organs; no emergency operation; no neoadjuvant chemotherapy; D2 lymphadenectomy was performed; and with complete clinical and follow-up data. Propensity score matching (PSM) was used to match the two groups on a 1:1 basis.

**Table 1** Characteristics of patients

Variables	Entire cohort			Propensity score-matched cohort		
	LTG ( <i>n</i> = 308)	OTG ( <i>n</i> = 900)	<i>P</i>	LTG ( <i>n</i> = 296)	OTG ( <i>n</i> = 296)	<i>P</i>
Age (years)			<b>0.000</b>			1.000
≤60	226 (73.4)	561 (62.3)		217 (73.3)	217 (73.3)	
>60	82 (26.6)	339 (37.7)		79 (26.7)	79 (26.7)	
Sex			<b>0.513</b>			0.210
Male	221 (71.8)	628 (69.8)		214 (72.3)	200 (67.6)	
Female	87 (28.2)	272 (30.2)		82 (27.7)	96 (32.4)	
BMI (kg/m <sup>2</sup> )	22.53 ± 3.43	21.99 ± 3.39	<b>0.016</b>	22.84 ± 3.19	22.48 ± 2.90	0.154
ASA score			0.443			0.550
1–2	266 (86.4)	761 (84.6)		258 (87.2)	253 (85.5)	
3	42 (13.6)	139 (15.4)		38 (12.8)	43 (14.5)	
Tumor size (cm)			<b>0.001</b>			1.000
≤5.0	260 (84.4)	677 (75.2)		254 (85.8)	254 (85.8)	
>5.0	48 (15.6)	223 (24.8)		42 (14.2)	42 (14.2)	
Histological type			<b>0.030</b>			1.000
Differentiated	102 (33.1)	240 (26.7)		90 (30.4)	90 (30.4)	
Undifferentiated	206 (66.9)	660 (73.3)		206 (69.6)	206 (69.6)	
pT stage			0.058			1.000
pT2	94 (30.5)	224 (24.9)		91 (30.7)	91 (30.7)	
pT3	129 (41.9)	370 (41.1)		125 (42.2)	125 (42.2)	
pT4a	85 (27.6)	306 (34.0)		80 (27.0)	80 (27.0)	
pN stage			<b>0.121</b>			0.940
pN0	103 (33.4)	262 (29.1)		101 (34.1)	101 (34.1)	
pN1	67 (21.8)	166 (18.4)		64 (21.6)	57 (19.3)	
pN2	63 (20.5)	189 (21.0)		60 (20.3)	67 (22.6)	
pN3a	58 (18.8)	205 (22.8)		56 (18.9)	56 (18.9)	
pN3b	17 (5.5)	78 (8.7)		15 (5.1)	15 (5.1)	
pTNM stage			0.093			1.000
IB	47 (15.3)	96 (10.7)		47 (15.9)	47 (15.9)	
IIA	56 (18.2)	153 (17.0)		54 (18.2)	54 (18.2)	
IIB	68 (22.1)	178 (19.8)		65 (22.0)	65 (22.0)	
IIIA	69 (22.4)	223 (24.8)		66 (22.3)	66 (22.3)	
IIIB	54 (17.5)	181 (20.1)		51 (17.2)	51 (17.2)	
IIIC	14 (4.5)	69 (7.7)		13 (4.4)	13 (4.4)	
Postoperative chemotherapy			0.326			0.851
Yes	227 (73.7)	637 (70.8)		221 (74.7)	219 (74.0)	
No	81 (26.3)	263 (29.2)		75 (25.3)	77 (26.0)	

Bold values are statistically significant ( $P < 0.05$ )

## Surgical procedure

The operative procedures of LTG and OTG were described in detail previously [13, 14]. All surgeries were performed by surgeons experienced in laparoscopic and open gastrectomy. The patients chose the surgical types individually after they were well informed of advantages and potential risks of LTG and OTG before surgery.

## Statistical analysis

The data were analyzed using SPSS ver. 22 (IBM SPSS, Chicago, USA). Continuous variables are expressed as the medians and ranges. The  $\chi^2$  test was used to compare the categorical variables. The Mann–Whitney *U* test was used to compare the continuous variables. Multivariate analysis

was conducted with the binary logistic regression model to identify independent risk factors for complications. Survival curves were calculated using the Kaplan–Meier method and analyzed by the log-rank test. Statistical significance was set at  $P < 0.05$ .

## Results

### Characteristics of patients

Table 1 summarizes the characteristics of patients in entire ( $n = 1208$ ) and PSM cohort ( $n = 592$ ). After PSM, 296 matched pairs were selected during the same time period. The baseline characteristics were closely balanced between the matched pairs.

**Table 2** Surgical outcomes and postoperative complications

Characteristics	LTG ( $n = 296$ )	OTG ( $n = 296$ )	<i>P</i>
Operation time (min)	261.42 ± 65.79	171.00 ± 44.27	<b>0.000</b>
Estimated blood loss (ml)	185.47 ± 98.38	217.84 ± 88.95	<b>0.000</b>
No. of retrieved lymph nodes	31.35 ± 6.09	30.64 ± 5.25	0.128
Time to first flatus (d)	3.47 ± 1.26	4.12 ± 0.98	<b>0.000</b>
Time to start liquid diet (d)	3.76 ± 1.19	4.27 ± 1.51	<b>0.000</b>
Postoperative hospital stay (d)	7.56 ± 2.78	8.22 ± 3.12	<b>0.007</b>
Re-admission	11(3.7)	9(3.0)	0.649
Postoperative complication			
Wound infection	4	10	0.105
Pancreatitis	0	1	1.000
Pulmonary	8	10	0.632
Stasis syndrome	2	1	1.000
Pancreatic fistula	1	0	1.000
Intra-abdominal abscess	2	4	0.682
Intra-abdominal bleeding	3	3	1.000
Duodenal stump leakage	4	6	0.524
Anastomotic bleeding	2	1	1.000
Anastomotic stricture	3	2	1.000
Anastomotic leakage	6	4	0.524
Bowel obstruction	4	5	1.000
Hepatic	4	2	0.682
Cardiac	2	1	1.000
Overall complications (%)	45 (15.2%)	51 (17.2%)	0.503
Clavien–Dindo classification			
Grade II (%)	22 (7.4%)	26 (8.8%)	0.491
Grade IIIa (%)	11 (3.7%)	15 (5.1%)	0.422
Grade IIIb (%)	9 (3.0%)	8 (2.7%)	1.000
Grade IV (%)	3 (1.0%)	2 (0.7%)	1.000
Grade V (%)	0 (0.0%)	0 (0.0%)	–
Clavien–Dindo grade ≥ IIIa (%)	23 (7.8%)	25 (8.4%)	0.763

Bold values are statistically significant ( $P < 0.05$ )

### Surgical outcomes and complications

Table 2 shows surgical outcomes and postoperative complications in PSM cohort. The LTG group was associated with longer operative time (261.42 vs. 171.00 min,  $P = 0.000$ ) and less blood loss (185.47 vs. 217.84 ml,  $P = 0.000$ ). The number of retrieved lymph nodes in the LTG group was similar with those in the OTG groups (31.35

vs.30.64,  $P = 0.128$ ). The time to first flatus (3.47 vs. 4.12 d,  $P = 0.000$ ), time to start liquid diet (3.76 vs. 4.27,  $P = 0.000$ ), and postoperative hospital stay (7.56 vs. 8.22,  $P = 0.007$ ) were shorter in the LTG group than those in the OTG group. The re-admission rate was similar between the LTG and OTG groups (3.7% vs. 3.0%,  $P = 0.649$ ). No intraoperative or 30-day postoperative mortality had occurred in PSM cohort. The overall complication rate was

**Table 3** Univariate analysis of risk factors for overall and severe complications

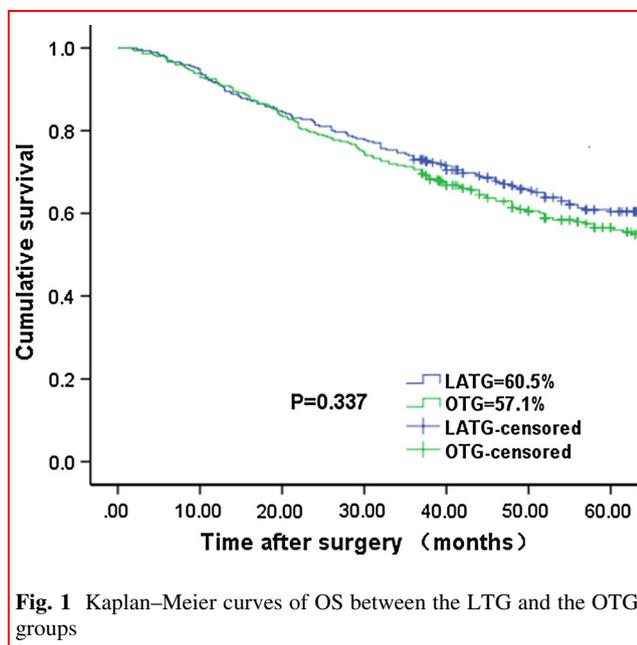
Variables	Patients ( $n = 592$ )	Overall complications		Severe complications	
		No. of complication (%)	$P$	No. of complication (%)	$P$
Sex			0.446		0.887
Male	414	64 (15.5)		34 (8.2)	
Female	178	32 (18.0)		14 (7.9)	
Age			<b>0.018</b>		<b>0.035</b>
$\leq 60$	434	61 (14.1)		29 (6.7)	
$> 60$	158	35 (22.2)		19 (12.0)	
Body mass index (kg/m <sup>2</sup> )			0.122		0.051
$\leq 25$	461	69 (15.0)		32 (6.9)	
$> 25$	131	27 (20.6)		16 (12.2)	
ASA score			0.353		0.530
1–2	511	80 (15.7)		40 (7.8)	
3	81	16 (19.8)		8 (9.9)	
Tumor stage			0.147		0.327
IB	94	20 (21.3)		10 (10.6)	
II–III	498	76 (15.3)		38 (7.6)	
Surgical method			0.503		0.763
LTG	296	45 (15.2)		23 (7.8)	
OTG	296	51 (17.2)		25 (8.4)	
Lymph node metastasis			0.142		0.607
Absent	202	39 (19.3)		39 (8.9)	
Present	390	57 (14.6)		57 (7.7)	
Operation time (min)			<b>0.049</b>		0.183
$\leq 240$	385	54 (14.0)		27 (7.0)	
$> 240$	207	42 (20.3)		21 (10.1)	
Estimated blood loss (ml)			0.717		0.468
$\leq 200$	404	64 (15.8)		35 (8.7)	
$> 200$	188	32 (17.0)		13 (6.9)	
Retrieved lymph nodes			0.320		0.502
$\leq 30$	368	64 (17.4)		32 (8.7)	
$> 30$	224	32 (14.3)		16 (7.1)	
Tumor size (cm)			0.402		0.435
$\leq 5$	508	85 (16.7)		43 (8.5)	
$> 5$	84	11 (13.1)		5 (6.0)	
Combined with splenectomy			<b>0.000</b>		<b>0.012</b>
Absent	576	88 (15.3)		44 (7.6)	
Present	16	8 (50.0)		4 (25.0)	

Bold values are statistically significant ( $P < 0.05$ )

**Table 4** Multivariate analysis of risk factors for overall and severe complications

Variables	Overall complications		Severe complications	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Age		<b>0.028</b>		<b>0.044</b>
≤60	1		1	
>60	1.700 (1.060–2.726)		1.831 (1.090–3.388)	
Combined with splenectomy		<b>0.002</b>		<b>0.032</b>
Absent	1		1	
Present	5.175 (1.867–14.344)		3.659 (1.118–11.973)	
Operation time (min)		<b>0.143</b>		
≤240	1			
>240	1.596 (0.915–2.509)			

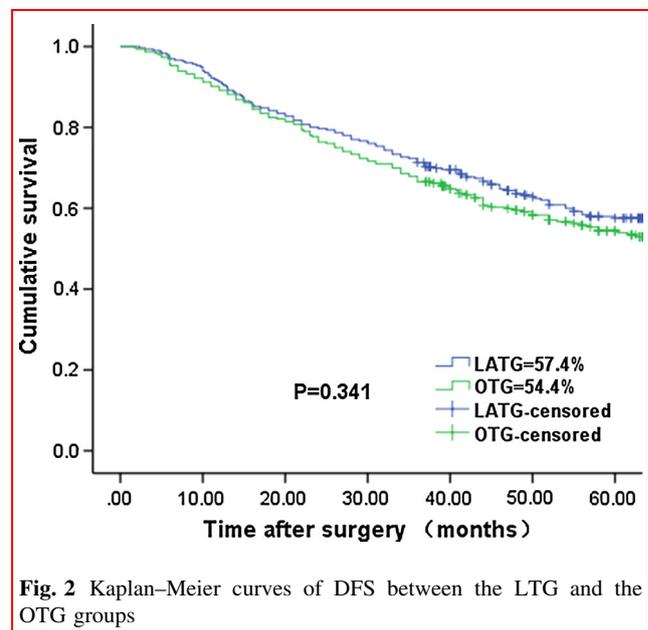
Bold values are statistically significant ( $P < 0.05$ )



comparable between the LATG group and the OTG group (15.2% vs. 17.2%,  $P = 0.503$ ).

### Risk factors for postoperative overall and severe complications

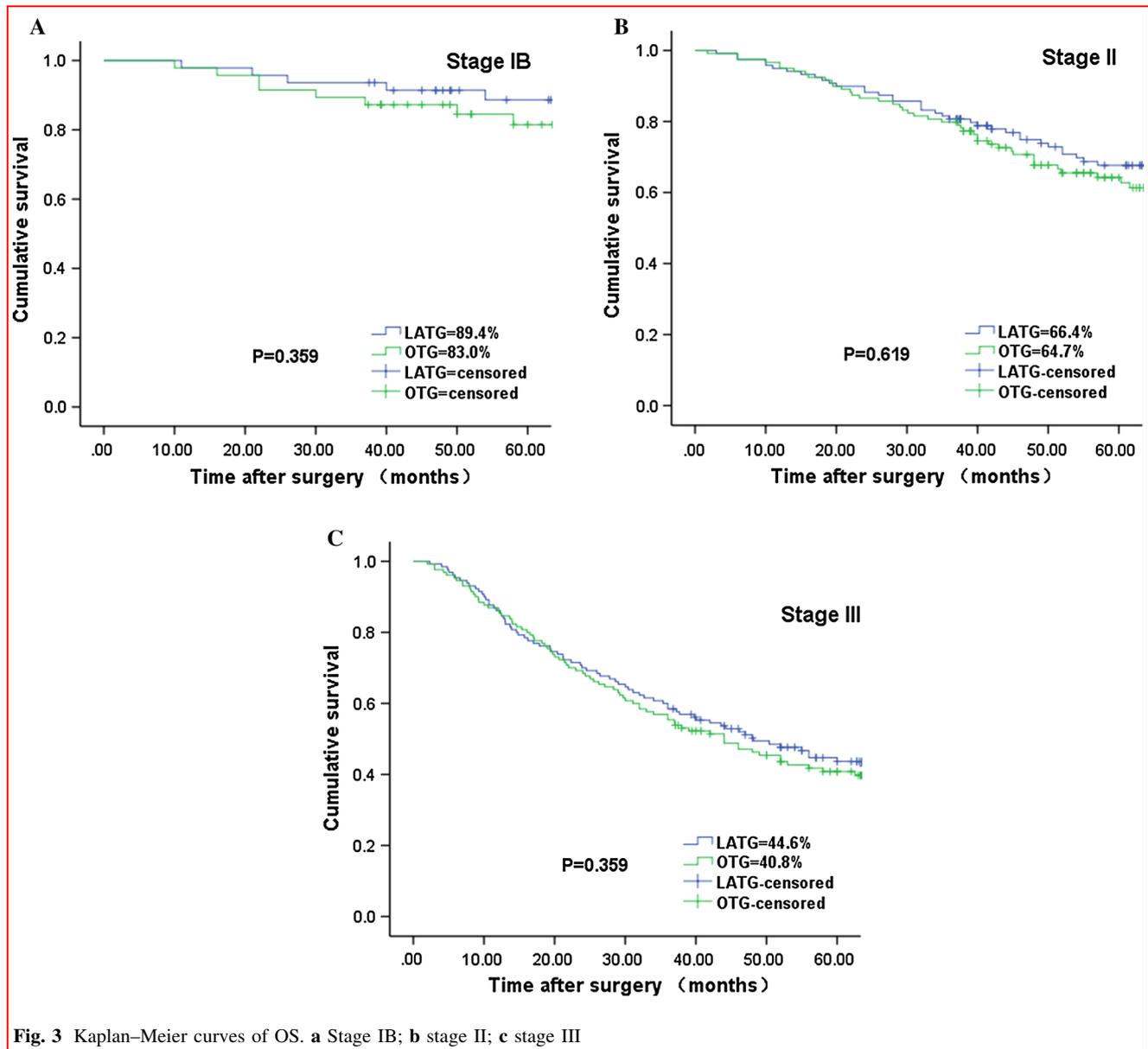
The age ( $P = 0.018$ ), operation time ( $P = 0.049$ ), and combined resection ( $P = 0.000$ ) were significantly related to the occurrence of overall complications in univariate analysis (Table 3). Multivariate analysis showed that old age (OR, 1.700; 95%CI, 1.060–2.726,  $P = 0.016$ ) and combined with splenectomy (OR, 5.175; 95%CI, 1.867–14.344,  $P = 0.002$ ) were independent risk factors of overall complication (Table 4). The age ( $P = 0.035$ ) and combined with splenectomy ( $P = 0.012$ ) were closely



related to severe complications (Table 3). In the multivariate analysis, the old age (OR, 1.831; 95%CI, 1.090–3.388,  $P = 0.044$ ) and combined with splenectomy (OR, 3.659; 95%CI, 1.118–11.973,  $P = 0.032$ ) were also identified as independent risk factors of severe complications (Table 4).

### Survival and subgroup analyses of the propensity score-matched cohort

No significant difference was observed in overall survival (OS) and disease-free survival (DFS) between LATG and OTG (60.5% vs. 57.1%,  $P = 0.337$ , Fig. 1; 57.4 vs. 54.4%,  $P = 0.341$ , Fig. 2). Stage-specific analysis revealed that the 5-year OS and DFS rates were also comparable between the LATG and OTG groups for patients in stage IB (89.4%



**Fig. 3** Kaplan–Meier curves of OS. **a** Stage IB; **b** stage II; **c** stage III

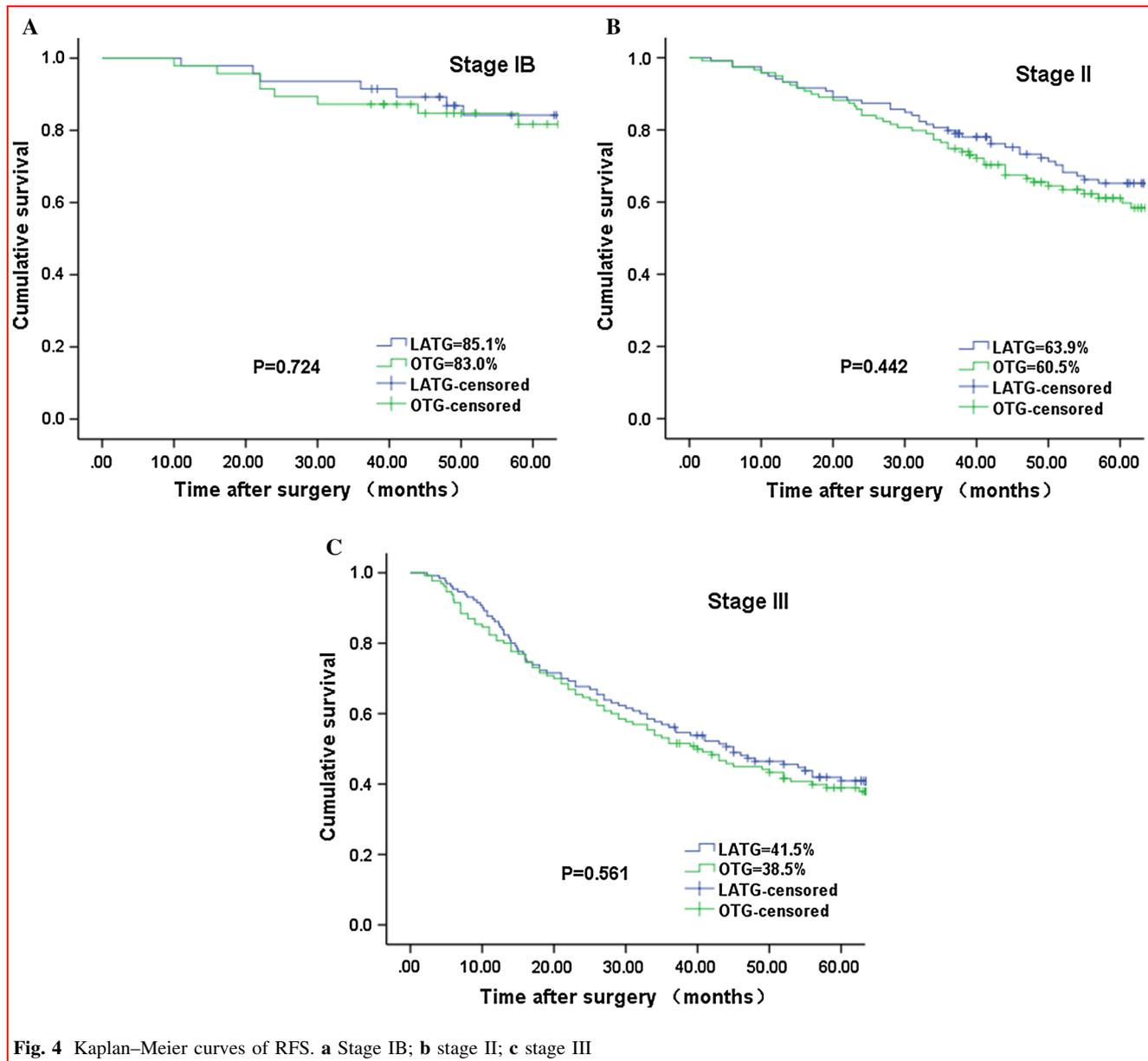
vs. 83.0%,  $P = 0.359$ , Fig. 3a; 85.1% vs. 83.0%,  $P = 0.724$ , Fig. 4a; respectively), patients in stage II (66.4% vs. 64.7%,  $P = 0.619$ , Fig. 3b; 63.9% vs. 60.5%,  $P = 0.442$ , Fig. 4b; respectively), and patients in stage III (44.6% vs. 40.8%,  $P = 0.359$ , Fig. 3c; 41.5% vs. 38.5%,  $P = 0.561$ , Fig. 4c; respectively). In the subgroup analyses of OS, the LG group was also comparable to the OG group (Fig. 5).

## Discussion

The present study showed that patients undergoing LTG experienced longer operation time. This may be attributed to the fact that LTG is more technically demanding in

lymphadenectomy, anastomosis, and digestive reconstruction as compared with OTG. Regarding other short-term outcomes, LTG for AGC had the benefits of less intraoperative blood loss and earlier postoperative recovery. This study demonstrated less invasiveness and favorable postoperative recovery from laparoscopic surgery.

Postoperative complication is a major concern in clinical practice. Studies have suggested that LTG for gastric cancer was associated with a lower overall complication rate as compared with OTG [15–17]. However, our results revealed that there was no significant difference between LTG and OTG (14.5% vs. 17.7%) and this result was consistent with several previous retrospective studies [18–21]. With respect to individual complications, no



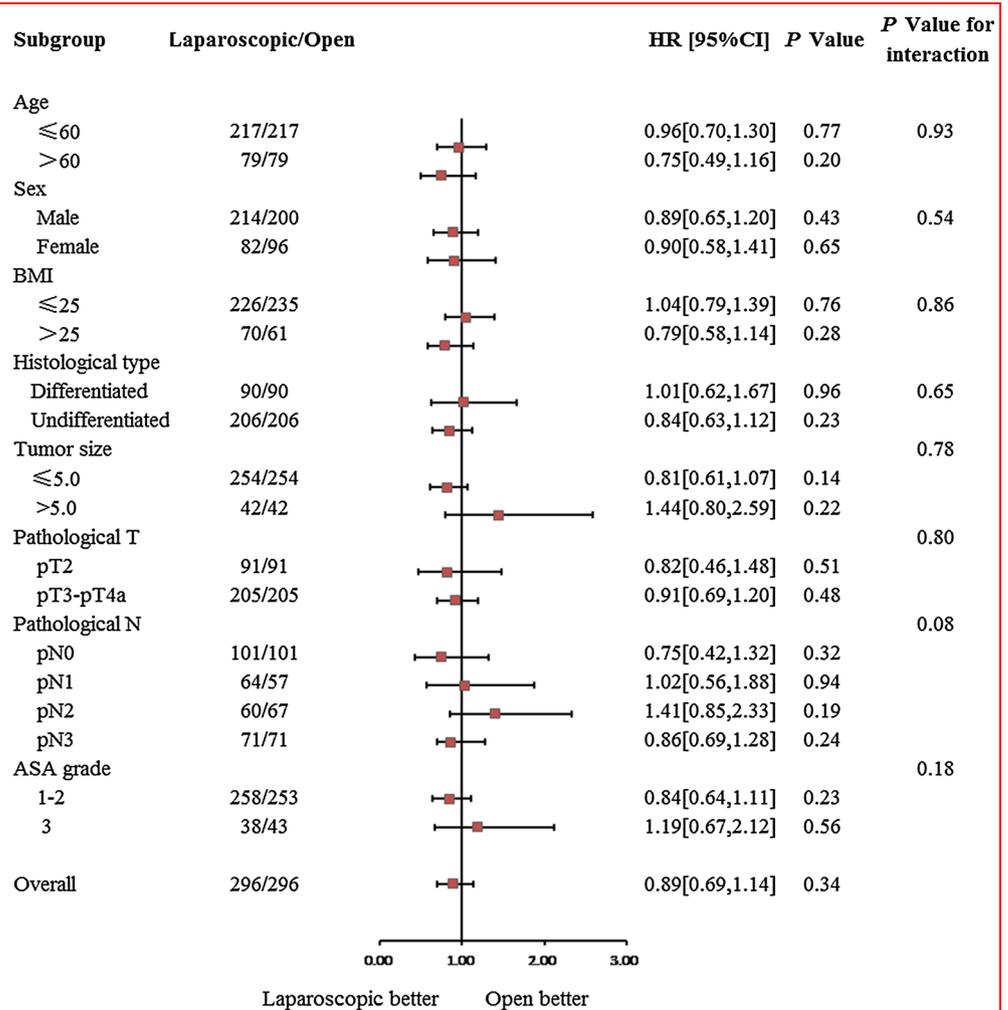
significant differences were found in major complications such as the anastomotic leakage, abdominal abscess, and pulmonary complications between the two groups.

Previous studies reported that postoperative complication was a predictor of adverse clinical outcome after radical resection of gastric cancer [22–25]. Except for old age, our result indicated that the combined with splenectomy was an independent risk factor of complications. Up to now, the role of splenectomy for gastric cancer still remains controversial. A prospective RCT demonstrated that prophylactic splenectomy should be avoided for patients with AGC not invading the greater curvature, which could therefore improve surgical safety without decreasing prognostic outcomes [26]. In recent years, some

studies reported that the laparoscopic spleen-preserving splenic hilar lymph node dissection (SHLND) is feasible by experienced surgeons in laparoscopic techniques for proximal gastric cancer [27, 28]. At present, the impact of SHLND for tumors invading the greater curvature of the upper stomach is still inconclusive. A recent retrospective study reported that prophylactic splenectomy for gastric cancer invading the greater curvature was associated with increased postoperative complications without clearly prognosis benefits [29]. RCTs with sufficient follow-up that comparing long-term oncological are necessary to verify the above conclusion.

Till now, published studies mainly focus on the application of LTG for EGC. In this study, all patients were at

**Fig. 5** Hazard ratios for overall survival in subgroups



pathologically proved advanced stages, indicating extended lymph node dissection was needed for these cases. The retrieval of at least 25 retrieved lymph nodes was recommended to improve long-term outcomes without compromising surgical safety for patients in AGC [30, 31]. The results of this study revealed that the average numbers of lymph nodes retrieved in LTG and OTG groups were 31.4 and 30.6, respectively, indicating that the LTG could obtain the result similar to those of OTG in terms of extent of lymphadenectomy. In addition, this result is also similar to those reported in high-volume centers [9, 15, 32]. In this study, patients who underwent LTG or OTG all performed R0 resection with negative resection margin. Previous studies also reported that the laparoscopic technique was able to obtain adequate proximal esophageal and distal duodenal margins [13, 15, 16, 33]. These results demonstrated that LTG could be safely performed in patients with AGC.

Regarding the long-term survival outcomes, Eom et al. [18] reported that the 5-year DFS in the LTG group was comparable to that in the OTG group with a median follow-up of 52.6 months (95% vs. 87.6%,  $P > 0.05$ ). Other retrospective studies also demonstrated that OS or DFS did not differ between LTG and OTG [34, 35]. Lee et al. [36] reported a similar result between the LTG and OTG groups in a case-matched study. However, patients in the above studies were in relatively early stages, which is therefore associated with excellent survival outcomes. For AGC, Bo et al. [15] reported that the 5-year OS was similar between LTG and OTG (49.3% in LTG group and 46.5% in OTG group). In the present study, cases in pathological stages II and III account for 84.1%. The results of this study revealed that the 5-year OS and DFS rates of LTG group were similar with those in the OTG group.

Several limitations of the present research should be acknowledged. First, this is a single-center retrospective study. Additionally, propensity score matching method

could not offset all biases. Third, some patients were not followed up to 5 years which may be associated with a higher survival rates. Therefore, large multicenter prospective RCTs should be conducted to confirm this rationale.

In conclusion, for patients with locally AGC, LTG provides surgical benefits and comparable survival outcomes when compared to OTG.

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#### Compliance with ethical standards

**Conflicts of interest** Drs. Zhengyan Li, Yezhou Liu, Bin Bai, Deliang Yu, Bo Lian, and Qingchuan Zhao have no conflicts of interest or financial ties to disclose.

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