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Comparison of robotic- and laparoscopic-assisted gastrectomy in advanced gastric cancer: updated short- and long-term results

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Abstract

Background Emerging evidence has demonstrated that either laparoscopic-assisted gastrectomy (LAG) or robotic-assisted gastrectomy (RAG) could be adopted as standard treatment for early gastric cancer. However, the long-term survival and recurrence rate after LAG or RAG for locally advanced gastric cancer (AGC) has seldom been reported.

Methods We retrospectively analyzed the data from 339 patients who underwent LAG and 163 patients who underwent RAG from a prospectively established database in the Chinese People's Liberation Army General Hospital. We compared the short- and long-term oncological outcomes of the RAG group versus the LAG group in the entire cohort, and in a propensity score-matched cohort.

Results Before propensity score matching (PSM), the two groups revealed comparable 3-year overall survival rates (OS, RAG vs. LAG: 76.1 vs. 81.7%, $p=0.118$), and recurrence-free survival rates (RFS, RAG vs. LAG: 73.0 vs. 67.6%, $p=0.297$). Similar results were obtained in the propensity score-matched cohort; the respective overall survival rates in the propensity score-matched RAG and LAG groups were 76.1 and 79.8% ($p=0.552$), and the respective RFS rates were 73.0 and 68.7% ($p=0.386$). After PSM, RAG was still associated with a significantly longer mean operating time (249.46 ± 63.26 vs. 232.17 ± 65.39 min, $p=0.008$) and higher total costs (133.38 ± 41.62 vs. 95.34 ± 29.39 10^3 RMB, $p<0.001$) than LAG; the two groups did not significantly differ in other surgical and oncological characteristics.

Conclusion Although there were some differences in the outcomes of RAG versus LAG in AGC patients, both RAG and LAG were similar in short-term recovery and long-term oncological outcomes.

Keywords Gastric cancer · Robotic-assisted gastrectomy · Laparoscopic-assisted gastrectomy · Clinical outcomes

Gastric cancer (GC) remains the fourth most common and the second leading cause of cancer-related death worldwide [1]. Minimal invasive surgery (MIS) including laparoscopic- and robotic-assisted surgery has offered new alternative surgical approaches and became more acceptable in the treatment of gastric cancer. Emerging evidence has showed that laparoscopic-assisted gastrectomy (LAG) has similar oncological outcomes as conventional open surgery and could be considered as a standard procedure in treating early gastric cancer (EGC) [2, 3]. And also a limited lymph node dissection can guarantee curability due to the little possibility of lymph node metastasis in early cancer [4]. In East Asia, especially in China, advanced gastric cancer (AGC) patients account for a large proportion of the total GC patients. Based on the experience of EGC, more and more experienced surgeons have applied these techniques in locally AGC.

Another emerging MIS procedure, robotic-assisted gastrectomy (RAG) has been increasingly performed and several clinical studies including our previous report have

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revealed its same safety and efficacy as LAG in treating gastric cancer [5, 6]. Theoretically, the Da Vinci system enjoyed several technologic advantages such as more freedom of movement and filtration of thrill and might reduce blood loss and hospital stay with comparable oncologic pathologic outcomes [5]. Robotic surgery seems more acceptable for surgeons to perform than laparoscopic surgery due to the shorter the learning curve of it [7, 8].

Studies have revealed the short-term results of LAG and RAG in AGC, yet the long-term outcomes lacking [9, 10]. But with the favorable initial experiences, some experts recommended laparoscopic surgery as a standard procedure in part of the AGC patients (cTNM I–IIIA) performed in high-volume medical centers in China [11] while there was no global consensus on the application of RAG and LAG in AGC. Therefore, we aimed to assess the short- and long-term safety and efficacy of RAG and LAG in AGC patients.

Materials and methods

Patients

We retrospectively analyzed data from a prospective database built and updated by the Department of General Surgery, Chinese People's Liberation Army General Hospital, Beijing, China. A total of 811 patients who underwent RAG or LAG in the period from January 2011 to December 2014 were assessed for potential enrollment in the present study (Fig. 1). All patients underwent a MIS procedure by surgeons who had each performed over 30 MIS surgeries [12]. Before evaluation, all patients provided written informed consent, including consent to the extra costs of robotic surgery. Three hundred and nine of these 811 patients were excluded from the present study due to the presence of early stage GC ($n = 147$), hybrid surgery ($n = 54$), palliative surgery ($n = 31$), and pathological conditions other than gastric adenocarcinoma ($n = 77$). Hence, a final total of 339 patients who underwent LAG and 163 patients who underwent RAG were included. The present study was approved by the institutional review board of the Chinese People's Liberation Army General Hospital (S2013-116-01).

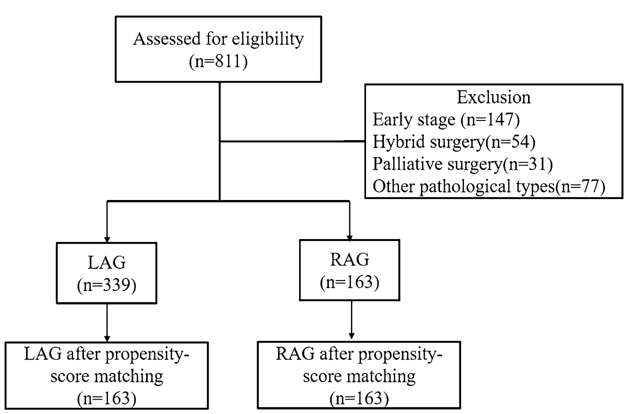

Fig. 1 Patient enrollment flowchart

Surgery and other treatments

All the enrolled patients had undergone curative gastrectomy with lymphadenectomy. The extent of resection (total or distal subtotal gastrectomy) was decided according to the tumor location. The extent of lymph node dissection, D1 or D2, was performed according to the Japanese gastric cancer treatment guidelines. The Da Vinci Surgical System Si (Intuitive Surgical Inc. Sunnyvale, CA) was used for all of the robotic gastrectomy. The detail procedures performed for robotic and laparoscopic gastrectomy have been described as before [5, 13]. Adjuvant chemotherapy with 5-fluorouracil (5-FU)-based regimens (e.g., XELOX or SOX regimens) was recommended to each patient.

Propensity score matching (PSM) analysis

We used PSM to overcome possible patient selection bias due to the retrospective study design. Potential variables associated with the selection of patient treatment, including age, sex, body mass index, tumor location, depth of invasion (T stage), and lymph node metastasis (N stage) were compared at baseline. Variables with intergroup differences of $p < 0.05$ were included in the PSM analysis. A 1:1 matching ratio was set using the nearest-neighbor matching method, with no replacement performed. This procedure was conducted using R statistical software, version 3.4.2.

Follow-up

A prospectively set follow-up protocol was used for all patients. Physical examination and laboratory testing, including assessment of tumor markers, were performed every 3 months for the first year postoperatively and then every 6 months thereafter. Imaging examinations including abdominal B-type ultrasonography and abdominopelvic computed tomography were performed every 6 months in the first year postoperatively, and at then least once in the subsequent 4 years. Endoscopy was scheduled once a year. All patients were followed-up either by clinic visitations or telephone until death or until December 31, 2017.

Statistical analysis

SPSS version 21.0 (Chicago, IL, USA) was used for statistical analyses. Continuous variables for the two groups were checked for normality of distribution by the one-sample

Kolmogorov–Smirnov test, and then compared using the Student's t test or the Mann–Whitney U test. Pearson's χ^2 test was used for categorical variables.

The Kaplan–Meier method was used to calculate the overall and recurrence-free survival (RFS) rates, and the differences between the survival curves were assessed using the log-rank test.

Results

Patients baseline characteristics

The patient characteristics of the entire cohort and the PSM groups are shown in Table 1. The RAG group comprised more male patients than the LAG group (74.2 vs. 59.3%, $p = 0.001$). In addition, tumors in the RAG group were more advanced regarding depth of tumor invasion, nodal involvement, and pathological stage compared with those in the LAG group ($p = 0.001$). Patient age, body mass index, and comorbidities were comparable in the two groups. The proportion of chemotherapy administration was also similar between groups (Table 1, $p = 0.658$). Therefore, PSM performed in a 1:1 ratio matched by sex, tumor size, and TNM stage resulted in the inclusion of 163 patients in both the LAG and RAG groups.

Operative factors

The intraoperative characteristics are shown in Table 2. The mean operation time was significantly longer in the RAG group compared with the LAG group

Table 1 Baseline and clinicopathological characteristics of LAG and RAG group in the entire cohort and after PSM

Variables	Entire cohort			After PSM		
	LAG (n = 339)	RAG (n = 163)	p	LAG (n = 163)	RAG (n = 163)	p
Sex			**0.001**			0.700
Male	201	121		125	121	
Female	138	42		38	42	
Age (years)	59.36 ± 11.08	60.27 ± 10.50	0.190	59.88 ± 11.72	60.27 ± 10.50	0.376
BMI (kg/m^2)	23.44 ± 3.47	23.77 ± 3.11	0.151	23.25 ± 3.26	23.77 ± 3.11	0.071
Tumor size (mm)	28.36 ± 11.4	31.8 ± 13.6	**0.001**	30.1 ± 13.7	31.8 ± 13.6	0.131
Tumor location			0.171			0.736
Upper third	65	31		28	31	
Middle third	96	59		55	59	
Lower third	178	73		80	73	
pTNM stage[a]			**0.001**			0.491
IIa	102	22		32	22	
IIb	67	35		31	35	
IIIa	94	46		43	46	
IIIb	70	59		54	59	
IIIc	6	1		3	1	
Comorbidity			0.535			0.791
Diabetes	26	15		24	15	
Hypertension	52	34		51	34	
Pulmonary disease	19	6		12	6	
Cardiac diseases	25	13		14	13	
Hepatic diseases	20	7		15	7	
Chemotherapy			0.658			0.930
Adjuvant	193	85		91	85	
Neoadjuvant	42	21		19	21	
Perioperative	57	28		26	28	
None or unknown	47	29		27	29	

BMI body mass index, *LAG* laparoscopic-assisted gastrectomy, *RAG* robotic-assisted gastrectomy, *PSM* propensity score matching

p value shown in bold is statistically significant ($p < 0.05$)

[a]AJCC/UICC 7th edition

Table 2 Operative characteristics and postoperative parameters of LAG and RAG group in the entire cohort and after PSM

Variables	Entire cohort			After PSM		
	LAG ($n = 339$)	RAG ($n = 163$)	*p*	LAG ($n = 163$)	RAG ($n = 163$)	*p*
Resection extent			0.314			0.511
Proximal	81	38		31	38	
Distal	157	63		72	63	
Total	111	62		60	62	
R0 resection	337	163	0.821[c]	163	163	–
OT (min)	229.05 ± 63.07	249.40 ± 63.23	**< 0.001**	232.17 ± 65.39	249.46 ± 63.26	**0.008**
EBL (ml)	111.25 ± 75.62	101.47 ± 121.84	0.136	109.48 ± 69.12	101.47 ± 121.84	0.233
LN dissection extent			0.920			0.729
D1+	119	56		60	56	
D2	220	107		103	107	
LN retrieval	25.28 ± 9.89	30.55 ± 10.13	**< 0.001**	29.34 ± 9.76	30.55 ± 10.13	0.137
Conversion surgery	3	2	0.662	1	2	0.250
Liquid diet (POD)	3.42 ± 1.22	3.26 ± 0.96	0.071	3.30 ± 1.19	3.26 ± 0.96	0.370
Flatus (POD)	2.99 ± 1.60	2.82 ± 1.48	0.127	2.89 ± 1.60	2.82 ± 1.48	0.320
Hospital stay (POD)	7.44 ± 5.09	7.09 ± 4.30	0.225	7.55 ± 4.79	7.09 ± 4.30	0.181
Postop morbidity (Clavien Dindo)			0.335			0.559
I	12	10		8	10	
II	26	9		13	9	
III	6	3		2	3	
IV	2	0		1	0	
V	0	0		0	0	
Postop mortality	0	0	–	0	0	–
Total cost (1000 RMB)	91.02 ± 27.65	133.38 ± 41.62	**< 0.001**	95.34 ± 29.39	133.38 ± 41.62	**< 0.001**

Values shown in bold are statistically significant ($p < 0.05$)

OT operation time, *EBL* estimated blood loss, *LN* lymph nodes, *POD* postoperative day, *c* continuity correction

(249.46 ± 63.26 vs. 232.17 ± 65.39 min, $p = 0.008$). There was no significant difference between the two groups in intraoperative estimated blood loss in both the entire cohort and the PSM groups. Although the analysis of the entire cohort indicated that the RAG group had significantly more lymph nodes removed than the LAG group (RAG vs. LAG: 30.55 ± 10.13 vs. 25.28 ± 9.89, $p < 0.001$), this phenomenon was not observed after PSM (RAG vs. LAG, 30.55 ± 10.13 vs. 29.34 ± 9.76, $p = 0.137$).

We experienced three conversions (0.88%) to open surgery in the laparoscopic surgery group due to uncontrollable intraabdominal bleeding during surgery, serosal involvement identified at the beginning of the surgery, severe abdominal adhesion, whereas two robotic procedures (1.22%) were converted to open surgery due to intraabdominal bleeding (RAG vs. LAG, $p = 0.718$). Furthermore, only two patients in the LAG group had positive margins and the R0 resection rate was comparable between these two groups ($p = 0.821$).

Short-term outcomes

The postoperative recovery characteristics in the RAG and LAG groups are shown Table 2. There was no significant difference between the two groups regarding time to first flatus and time to first liquid diet either in the entire cohort or the PSM groups. Although the RAG group tended to have a slightly shorter postoperative hospital stay than the LAG group, this difference was not significant (entire cohort: $p = 0.225$; after PSM: $p = 0.181$). The incidence and extent of postoperative complications did not significantly differ between the two groups (entire cohort: $p = 0.335$; after PSM: $p = 0.559$). There was no postoperative mortality in either group. The total cost was significantly higher in the RAG group than the LAG group (entire cohort, 133.38 ± 41.62 vs. 91.02 ± 27.65 10^3 RMB, $p < 0.001$; After PSM, 133.38 ± 41.62 vs. 95.34 ± 29.39 10^3 RMB, $p < 0.001$).

Long-term outcomes

The median follow-up period for patients that survived until the cutoff date was 50.5 months (range 36–72 months). The 3-year overall survival rate did not significantly differ between the two groups in either the entire cohort (Fig. 2, RAG vs. LAG: 76.1 vs. 81.7%, $p=0.118$) or after PSM (RAG vs. LAG: 76.1 vs. 79.8%, $p=0.552$). Similar results were observed regarding 3-year RFS either in the entire cohort (Fig. 3, RAG vs. LAG: 73.0 vs. 67.6%, $p=0.297$) or after PSM (RAG vs. LAG: 73.0 vs. 68.7%, $p=0.386$).

Discussion

Robotic-assisted surgery is rapidly replacing conventional open or laparoscopic surgery in complex and difficult procedures, such as prostate or cardiac surgery [14, 15]; however, its application in gastrectomy, especially in AGC, is still under investigation, and the results remain controversial [16]. We performed a retrospective study with PSM to evaluate RAG versus LAG, and found that RAG was as feasible and oncologically safe as LAG, but was associated with a longer operation time and higher cost.

While the long-term outcomes of large-scale randomized controlled trials comparing LAG with open gastrectomy have not yet been published [17, 18], the application of LAG has been well accepted in clinical practice, especially in treating early GC [19]. Moreover, investigational studies evaluating patients with AGC have proven the feasibility and safety of both LAG and RAG [10, 20]. However, clinically significant benefits of robotic approaches over laparoscopic approaches in gastrectomy have not been sufficiently proven. Lymph node retrieval could ensure the oncological safety in GC treatment [21, 22]; however, although our study showed that RAG retrieved more lymph nodes than LAG in the entire cohort analysis, this difference was not significant after

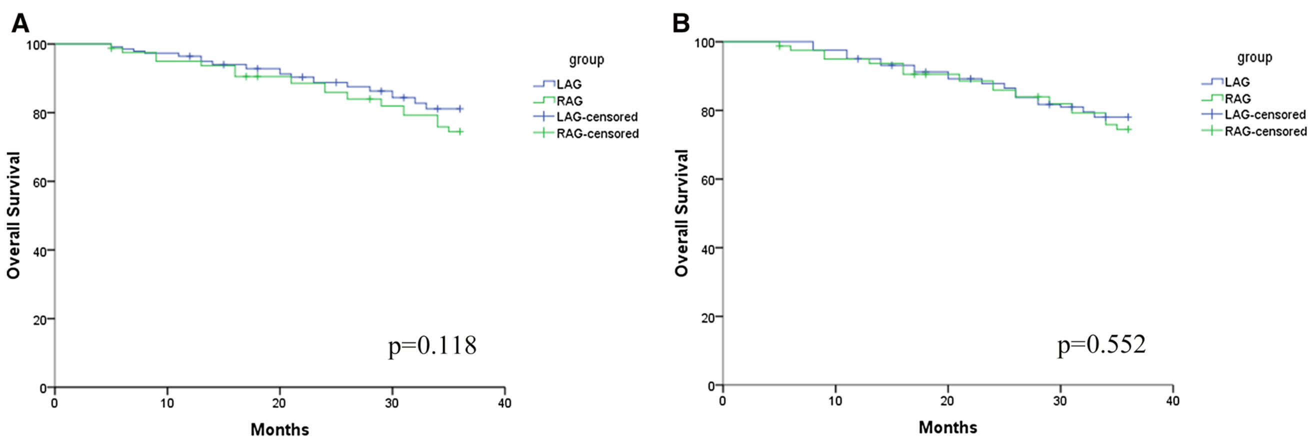

Fig. 2 Kaplan–Meier estimates of overall survival in the entire cohort (**A**) and the propensity score matched cohort (**B**)

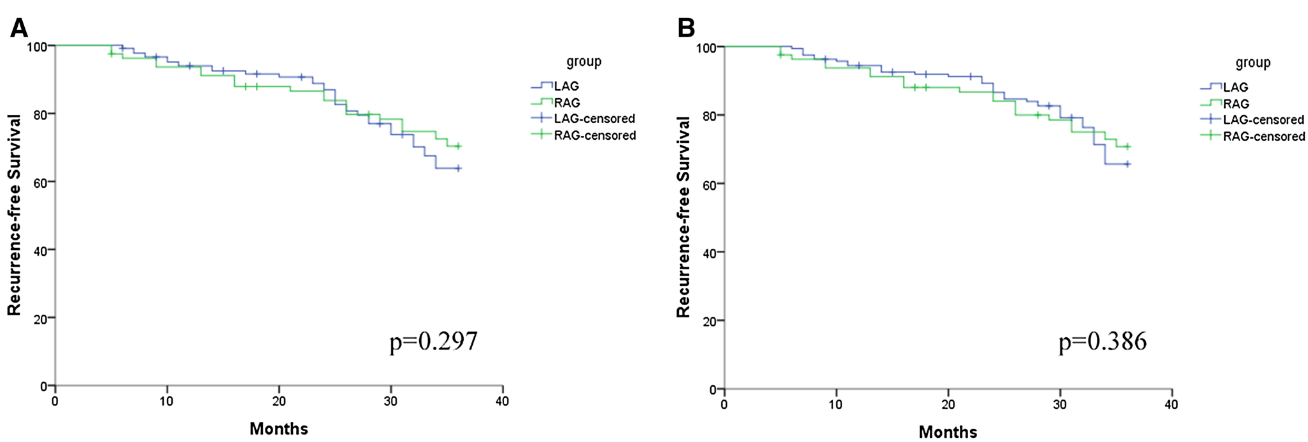

Fig. 3 Kaplan–Meier estimates of RFS in the entire cohort (**A**) and the propensity score matched cohort (**B**)

PSM. Comparable long-term outcomes of these two MIS approaches are expected, as the same surgical extent is performed with a similar operative environment and perioperative treatment regimen. The only differences between RAG and LAG are the surgical instruments and imaging systems, which might enable surgeons to more easily learn the RAG procedure than the LAG procedure [23].

To minimize the learning curve effect of MIS approaches, all cases in the present study underwent surgery performed by experienced surgeons who had performed at least 30 procedures using each approach [12]. In our study, we did not recommend a particular MIS procedure, but let the patients choose for themselves between RAG and LAG. It seems that RAG was chosen more often than LAG by males and by those with more advanced disease. Therefore, the additional installation and docking time might not be the only reason for the longer operation time in the RAG group compared with the LAG group; the RAG group might also have required more complex procedures and dissection operations in patients of more advanced stage.

While it has been hypothesized that a robotic approach for more AGC would be superior to a laparoscopic approach due to more precise dissection and less complications [24], our study failed to confirm this. In our institution, optimal perioperative surgical procedures (such as the enhanced recovery after surgery protocol) have already been applied in laparoscopic surgery, leaving little room for improvement via robotic surgery [25]. Theoretically, RAG has advantages over LAG of dexterity and accuracy because of a tremor filter, three-dimensional imaging, and an internal EndoWrist with seven degrees of freedom. The benefits of a robotic approach might be more evident in complex patients, such as those with a high body mass index, and those undergoing distal subtotal gastrectomy with D2 lymphadenectomy, particularly in terms of blood loss and consistent quality of lymphadenectomy [4]; more studies focused on this issue are required to confirm this.

Several limitations of our study should be addressed. First, even with the performance of PSM to reduce the selection bias, the retrospective nature of our study still limited the evidence level of our conclusions. Second, the median follow-up time was still not long enough to draw a full conclusion. Third, although most patients underwent 5-fluorouracil- or platinum-based adjuvant chemotherapy and the rate of chemotherapy administration was similar between two groups, the differences in chemotherapy regimens and courses might also affect the individual survival time.

In conclusion, our study showed that although there were some differences in the outcome of RAG versus LAG, RAG is a feasible and safe alternative procedure for AGC when performed by experienced surgeons. More multicenter, prospective, clinical trials with longer follow-up periods are still warranted to verify our findings.

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Compliance with ethical standards

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