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ORIGINAL ARTICLE

Laparoscopy-Assisted vs. Open Total Gastrectomy for Advanced Gastric Cancer: Long-Term Outcomes and Technical Aspects of a Case–Control Study

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Abstract
Background and Objectives An increasing number of studies comparing laparoscopy-assisted distal gastrectomy and conventional open distal gastrectomy have been reported; the technical feasibility and clinical efficacy have been confirmed. However, few data are available to compare laparoscopy-assisted total gastrectomy (LATG) and open techniques for the treatment of advanced gastric cancer (AGC). The aim of this study is to compare the oncologic efficacy and long-term outcomes of LATG vs. open total gastrectomy (OTG) for AGC and to provide our experiences regarding these surgical difficulties as well.
Methods Using data from a clinical database of all operations performed in our department by a special surgical team, we retrospectively analysed data from 117 cases of LATG and matched OTG performed between January 2004 and December 2010. This analysis was a case–control study in which patients in the two groups were matched according to tumour location, age, gender, BMI and TNM stage via a propensity score matching method. Patient clinical characteristics, lymph node retrieval, early postoperative complications, recurrence and long-term outcomes were compared.
Results The demographics, preoperative data and characteristics of the tumour were similar in both groups. No significant differences were found in the LATG group compared with the OTG group with regard to the number of retrieved lymph nodes or distance from the proximal margin. Operating time was longer in the LATG group than in the OTG group (292.8± 49.5 vs. 242.1±47.4, $p<0.05$). Significant differences were found between LATG and OTG with regard to blood loss, postoperative hospitalisation and times of analgesic injection. The early postoperative complication rates in the LATG group were significantly lower than in the OTG group (11.1 vs. 16.3 %, $p<0.05$). Operative mortality was zero in both groups. During a median follow-up of 61.2 (range, 6–84) months, the overall 5-year survival rates in the LATG group and OTG group were 49.3 and 46.5 %, respectively; there was no significant difference between the two groups ($p=0.756$).
Conclusion Our results suggest that LATG is technically feasible for advanced gastric cancer patients and can yield good short- and long-term oncologic outcomes as compared with conventional OTG.

Keywords Laparoscope · Total gastrectomy · Gastric cancer · Outcome

With recent advances in instrument design and surgical techniques, laparoscopy-assisted distal gastrectomy (LADG) has become an excellent surgical option for the treatment of gastric cancer.[1–4] However, laparoscopy-assisted total gastrectomy (LATG) is performed only at a limited number of hospitals; the most important reason for its low degree of popularity is that LATG is more technically difficult than LADG. In contrast to LADG, LATG requires paracardial lymph node dissection, vascular procedures along the greater curvature of the upper stomach, and vagotomy along the abdominal oesophagus; reconstruction is also more complicated in LATG than in LADG; a field of view is especially difficult to secure at the time of oesophagojejunostomy.[5] In

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recent years, there have been several reports on the safety and feasibility of LATG, and the short-term outcomes have also been evaluated. However, these studies mostly focused on early gastric cancer and presented with a small number, lacking large sample sizes and long-term follow-up results.[6–9] In China, gastric cancer is the most common neoplasm and the second most frequent cause of cancer-related death after lung cancer, predominantly with advanced gastric cancer in all hospitalised patients (accounting for more than 90 %). In the present study, we described our experience with LATG in the treatment of advanced gastric cancer (AGC) and evaluated the oncologic safety and long-term outcome of this approach through a case–control study.

Patient Sample and Data Collection

From January 2004 to December 2010, 241 patients with gastric cancer underwent laparoscopy-assisted total surgery, and 253 cases underwent open surgery, which was performed by an exclusive surgical team which consisted of five surgeons at our centre with permission from our institutional review board. Surgical procedure (LATG or open total gastrectomy, OTG) was chosen by the patients after obtaining informed consent following explanation of the advantages, disadvantages and any possible outcomes of LATG and OTG in detail. Inclusion criteria of the case–control study were the following: histologically confirmed adenocarcinoma of the stomach, performance status of ECOG 0–1, location of the tumour in the upper third of the stomach, no evidence of distant metastasis or invasion to adjacent organs, and depth of invasion confined to the muscle or serosal layer (T2 and T3); all underwent radical total gastrectomy. Exclusion criteria included an operation under emergency conditions such as bleeding or perforation, total gastrectomy for remnant gastric cancer or early gastric cancer, patients submitted to palliative gastrectomy, combined major organ resection (spleen or colon), preoperative chemotherapy or radiation therapy, and patients with nonepithelial tumours (i.e., GIST). Based on the exclusion and inclusion criteria, those meeting the requirements were left for the following propensity score matching. The propensity score for an individual was calculated given the covariates of tumour location, gender, BMI and TNM stage using a multivariable logistic regression model. Because we sought to evaluate the technical feasibility of laparoscopic total gastrectomy (LTG) according to the extent of lymph node dissection, lymph node dissection was not considered as a covariate in the propensity score derivation model. Using these propensity scores, we finally compared these 117 LTG patients with 117 matched OTG patients with respect to long-term surgical outcomes.

Surgical Technique

In the laparoscopic group, surgery was performed under general anaesthesia with the patient placed in the supine position and with legs separated.[10] Five surgical ports were inserted in the upper abdomen, as previously described.[11] The surgeon stood on the left side of the patient, and routine exploration of the abdominal cavity was performed.

Lymphadenectomy was performed according to the 14th edition of Japanese gastric cancer guidelines.[12] An identical operative strategy was performed that involves the following steps: first, the left greater omentum and lymph nodes along the left gastroepiploic vessels (no.4 sb) were dissected. In the second step, lymph nodes 4sa along the short gastric vessels were dissected. Third, the left-cardia nodes (no. 2) were dissected. Fourth, the infra-pyloric nodes (no. 6) and the nodes along the superior mesenteric vein (no. 14v) were dissected. Fifth, the stomach was turned towards the head to expose the gastropancreatic fold, the nodes along the left gastric artery (no. 7), the nodes around the celiac artery (no. 9), the nodes along the common hepatic artery (no. 8a) and the proximal splenic artery (no. 11p) were dissected in sequence. Sixth, the suprapyloric nodes (no. 5) and the nodes along the proper hepatic artery (no. 12a) were dissected. Seventh, the less omentum was dissected, and both vagus nerves were cut off; the right-cardia lymph nodes were dissected as well. The duodenum was transected 1–2 cm distally to the pylorus as the eighth step.

A longitudinal laparotomy was performed using a 4–6-cm skin incision below the xiphoid appendix, and the entire stomach was removed. The proximal margin was also sent for frozen pathology when necessary.

Alimentary tract reconstruction is technically difficult. At the outset of our study, the anastomosis was performed extracorporeally by means of Roux-en-Y oesophagojejunostomy under direct vision through the laparotomy incision, which is the same as in the open surgery group. Simply, the oesophagus was transected at the planned plane, and the purse-string suture was completed, followed by anvil placement. The Roux-en-Y limb was then brought up via the antecolic route to create an oesophagojejunostomy, the jejunal stump was closed with an endoscopic linear stapler and side-to-side jejunojejunostomy (Y-anastomosis), using an endoscopic linear stapler, was performed. The antecolic Roux-en-Y reconstruction was completed.

However, it may be difficult to perform the anastomosis through mini-laparotomy under direct vision when the patient is obese or if the planned transection line is at a high level. Less commonly, when the oesophagus is relatively narrow in diameter, the purse-string suture and placement of the anvil are very difficult.

Subsequently, we developed a modified method of laparoscopic side-to-side oesophagojejunal anastomosis, which

was described in detail in our previous study.[12] Briefly, after the stomach had been completely mobilised, the oesophagus was encircled with a string for retraction. The jejunum was brought up to the right side of the oesophagus. A small opening was made in the antimesenteric wall of the jejunum opposite the denuded site of the jejunum and on the right side of the oesophagus, respectively. A 60-mm endo-GIA (Covidien, Norwalk, CT, USA) was introduced, and the two limbs of the endolinear cutter (60-mm endo-GIA, Covidien) were inserted into the jejunum and the oesophagus through these openings. The two limbs were mated to fashion the side-to-side oesophagojejunal anastomosis. A small incision was made immediately above the umbilicus or in the middle part of the abdomen. This incision was also used for completion of the side-to-side jejunojejunal anastomosis and removal of the resected gastric specimen. However, this procedure is complicated, and a modified version was desired.

Recently, due to the technical difficulties of creating a purse-string suture and placement of the anvil, we developed a modified method, which does not require the employment of a purse-string clamp. This technique involves a continuous purse-string suture in the muscle layer of the oesophagus created through the laparoscopic use of a conventional needle, followed by dissection of the anterior oesophagus along the planned transection line with ultrasonically activated coagulation shears (SonoSurg, Olympus Inc, Japan). Then, the anvil of a circular stapler (CDH, 25 mm, Covidien) was inserted into the oesophageal stump, the purse-string line was tied off and the posterior wall of the oesophagus was dissected (Fig. 1). The completion of Roux-en-Y oesophagojejunostomy was performed as previously described.

Postoperative Chemotherapy

All the patients enrolled in our study underwent postoperative chemotherapy, the FOLFOX protocol comprised oxaliplatin (Hengrui Pharmaceutical Co., Ltd, Jiangsu, China) intravenously infused at 130 mg/m^2 on day 1, 5-FU (Roche Pharmaceutical Co., Ltd, Shanghai, China) given as a continuous intravenous infusion at 500 mg/m^2 from day 1 to 5 after oxaliplatin and CF (Mayne Pharma Pty., Ltd., Salisbury, Australia) infused at 200 mg/m^2 from day 1 to 5. The treatment course was repeated six times with a 21-day interval between each cycle.

Follow-up

The follow-up programme consisted of a physical examination, laboratory blood tests, endoscopy and ultrasonography or computed tomography. Recurrence was diagnosed based on clinical, radiologic or laparoscopic exploration or endoscopic signs of disease.

Statistical Analysis

All values are presented as means ± standard error. Statistical analyses were performed using the Mann–Whitney *U* test, the chi-square test or the independent-samples *t* test as appropriate.

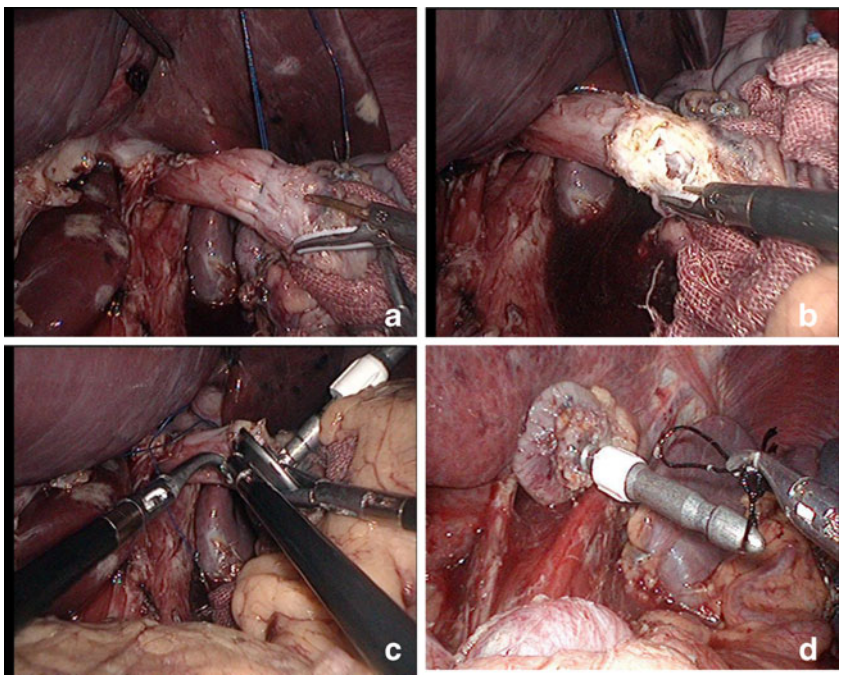

Fig. 1 Laparoscopic purse-string suture and placement of the anvil into the oesophagus. **a** Continuous purse-string suture in the serosal-muscle layer of the oesophagus. **b** Dissecting the intended transection line of the anterior oesophagus. **c** Placement of the anvil into the oesophagus. **d** Tying off the purse line, followed by dissection of the posterior wall of the oesophagus

The overall survival rate was assessed by Kaplan–Meier analysis and compared by the log-rank test. Significance was taken as $p<0.05$.

Results

Patient Characteristics

A total of 234 patients (117 matched pairs) were included in the study. As defined by the study design, patients in the laparoscopic and open groups were comparable in age, gender, TNM staging (based on the International Union Against Cancer (UICC) classification scheme) and tumour location (Table 1). Most tumours were located in the upper third of the stomach. Other characteristics, such as body mass index and TNM stage, were comparable (Table 1).

Clinicopathologic Outcomes

Tumours were staged according to the seventh edition of UICC TNM Classification of Malignant Tumours. Clinicopathologic variables are compared in Table 2. The median operating time was significantly longer in the LATG group as compared to the OTG group (292.8±49.5 vs. 242.1±47.4, $p=0.039$). Blood loss, incision length, times of analgesic injection, time to the first flatus and starting day of liquid diet were significantly less or shorter in the LATG group as compared to the OTG group. The proximal tumour clear margins in the LATG group were not significantly different from those in the OTG group (3.5±1.2 vs. 3.2±0.9; $p=0.517$). Furthermore, no difference in the number of harvested lymph nodes was observed between the LATG and OTG group (35.2±11.7 vs. 37.4±13.2; $p=0.132$) (Table 2). There was no significant difference between groups with regard to the reconstruction type ($p=0.183$). No serious intraoperative complication was encountered in our series. We recorded 13 recent postoperative complications in the LATG group, including four cases of duodenal stump leakage, one case of lymphatic fistula, one case of anastomotic leakage, one case of anastomotic bleeding, two cases of infection of incision, one case of lower extremity deep venous thrombosis and three cases of pulmonary infection. The overall complication rate was 11.1 %. All of these complications were cured or ameliorated after palliative medical treatment without reoperation. In contrast, 19 complications occurred in the open group, including four cases of duodenal stump leakage, one case of anastomotic leakage, seven cases of incision infection, one case of lower extremity deep venous thrombosis and six cases of pulmonary infection; the overall early complication rate was 16.3 %, which was significantly higher than that in the LATG group ($p<0.05$) (Table 2).

Table 1 Comparison of clinicopathologic characteristics between laparoscopy-assisted and open total gastrectomy groups

	LATG ($n=117$)	OTG ($n=117$)	p value
Clinical characteristics			
Age (years)	54.5±10.6	52.6±13.6	0.39
BMI (kg/m^2)	21.1±3.0	21.7±3.8	0.84
Male/female	82/35	80/37	0.45
Pathologic characteristics			
Tumour location			0.54
Upper third	64	65	
Middle third	23	21	
Middle and upper	30	31	
Depth of invasion			0.42
pT2	50	47	
pT3	67	70	
pN category			0.38
N0	29	26	
N1	42	47	
N2	46	44	
Stage distribution			0.62
Ib (T2N0M0)	6	4	
II (T2N1M0, T3N0M0)	40	38	
IIIa (T2N2M0, T3N1M0)	52	55	
IIIb (T3N2M0)	19	20	

Data are mean ± SD or number. Tumour staging was classified by UICC staging

BMI body mass index

Tumour Metastasis and Survival

Twenty-three patients in the LATG group died during the course of follow-up, including 15 cases of peritoneal metastasis, 4 cases of liver metastasis, 1 case of osseous metastasis and 3 cases of systemic metastasis. Twenty-six patients in the OTG group died during the course of follow-up, including 20 cases of peritoneal metastasis, 2 cases of liver metastasis and 4 cases of systemic metastasis. The major cause of death in both groups was peritoneal metastasis. The overall 5-year survival rates in the LATG group and OTG group were 49.3 and 46.5 %, respectively. There was no significant difference in the cumulative 5-year survival rates between the LATG and OTG groups ($\chi^2=0.097$, $p=0.756$) (Fig. 2). The overall 5-year survival rates for the T2 stage in the LATG and OTG groups were 72.7 and 65.5 %, respectively (no significant difference found between the groups in T2 stage, $\chi^2=0.277$, $p=0.598$). The overall 5-year survival rates for the T3 stage in the LATG and OTG groups were 37.6 and 36.0 %, respectively; there was no significant difference between the T3 stage patients in both groups ($\chi^2=0.063$, $p=0.802$).

Table 2 Comparison of cancer clearance, postoperative recovery and operative indices between laparoscopy-assisted and OTG

	LATG (117 cases)	OTG (117 cases)	*p* value
Operation time (min)	292.8±49.5	242.1±47.4	0.039
Intraoperative blood loss (ml)	196.9±88.4	358.2±158.7	0.024
Number of retrieved lymph nodes	35.2±11.7	37.4±13.2	0.132
Length from proximal margin (cm)	3.5±1.2	3.2±0.9	0.517
Incision length (cm)	5.2±0.9	22.5±2.2	0.000
Time to first flatus (days)	3.4±1.5	3.9±1.2	0.469
Starting day of liquid diet	4.5±1.1	5.3±2.1	0.002
Times of analgesic injection	1.4±0.1	3.9±1.4	0.035
Time to ground activities (days)	3.1±0.6	5.3±1.4	0.041
Postoperative hospital stay (days)	7.4±2.2	10.7±2.8	0.047
Reconstruction type			0.183
End-to-side oesophagojejunal anastomosis (Roux-en-Y)	98	101	
side-to-side oesophagojejunal anastomosis	19	16	
Early complications			0.045
Duodenal stump leakage	4	4	
Lymphatic fistula	1	0	
Anastomotic leakage	1	1	
Anastomosis bleeding	1		
Incision infection	2	7	
Lower extremity deep venous thrombosis	1	1	
Pulmonary infection	3	6	
Total	13 (11.1 %)	19 (16.3 %)	

Discussion

With recent advances in instruments and techniques, laparoscopy-assisted partial gastrectomy has been gradually increasing in popularity around the world,[13,14] whereas LATG has not yet met with widespread acceptance and remains limited to only a few centres. One of the biggest obstacles to popularisation may be the more difficult surgical procedure involved in the laparoscopic operation. Specifically, extended lymphadenectomy and reconstruction of the digestive tract are considered the two major technical problems for the treatment of advanced gastric cancer.[7]

In our series, lymphadenectomy was conducted according to the 14th edition of the Japanese Rules of Gastric Cancer Research. Accordingly, the patients enrolled in our study were mainly those with advanced gastric cancer, and D2 lymphadenectomy was generally requested. In a previous study, we presented our experiences with distal gastrectomy with extended lymphadenectomy.[10] Compared with distal gastrectomy, the resection of lymph nodes residing around perisplenic vessels and the splenic hilum is generally performed for total gastrectomy with gastric cancer located in the middle or upper portion of the stomach, which is more technically difficult. A few studies showed that pancreatectomy and splenectomy were adopted concurrently to enable thorough dissection of lymph nodes 10 and 11.[15] Uyama et al.[16] reported, for the first time, a successful laparoscopic approach that was applied to two patients with advanced upper gastric cancer, which

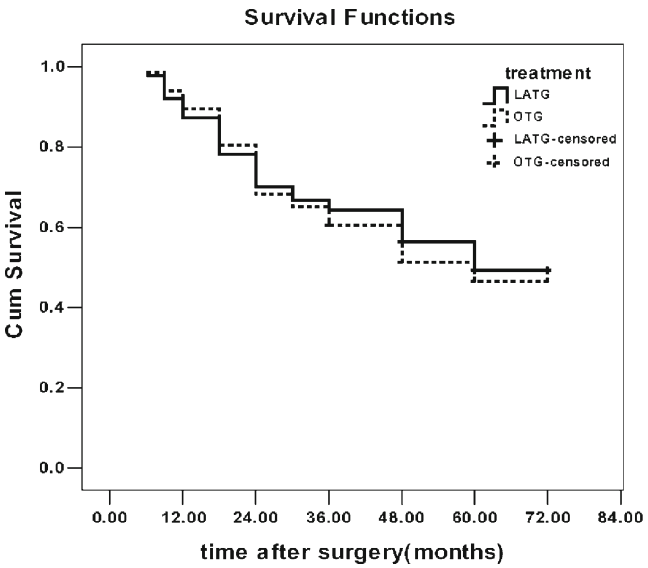

Fig. 2 Comparison of cumulative overall survival rate according to operation methods during a median follow-up of 61.2 (range, 6–84) months by log-rank test (p=0.756)

included a distal pancreaticosplenectomy for complete D2 lymph node dissection. As this surgical style was much more invasive, a higher occurrence of surgical morbidity was observed compared with pancreas- and spleen-preserving surgery.[9] Total gastrectomy combined with splenectomy and distal pancreatectomy was seldom performed. We summarised the indications as follows: (1) direct tumour invasion of the distal pancreas or spleen and (2) suspicious metastatic lymph nodes existing along the splenic artery or at the splenic hilum, with difficulty in completing the lymph node dissection alone. Based on these indications, careful patient selection is required when performing laparoscopic pancreaticosplenectomy with D2 lymph node dissection. In our series, laparoscopic pancreas- and spleen-preserving lymph node dissection was performed successfully in all cases.

The alimentary tract reconstruction in LATG is another recognised technical difficulty, as has been addressed in several reports.[17,18] Although significant efforts have been made to solve this problem in recent years, no ideal method has yet been identified. At the outset of our series, we performed end-to-side oesophagojejunal anastomosis with the circular stapler from the mini-laparotomy, which is the same as the conventional open surgical procedure. However, these procedures are hindered when patients are obese or barrel chested or if the intended oesophageal transection plane is higher than usual. Therefore, completion of the purse-string suture and placement of the anvil into the oesophagus through the mini-laparotomy is very difficult under direct vision. Such technically difficult procedures might lead to serious complications. To address the anastomosis, we have developed a modified laparoscopic side-to-side oesophagogastrostomy using a linear stapler, as reported in our previous study.[12]This procedure is feasible and safe, and it avoids the problems related to creation of a purse-string suture and placement of the anvil.[16] However, it is not as ideal as we expected and still seems complicated. Another prominent shortcoming of this procedure is that cancer clearance in the oesophageal stump cannot be determined until the anastomosis has been accomplished. Therefore, we continue to attempt to develop a more suitable method. Revolving around the technical difficulties related to the purse-string suture and anvil placement, we have developed a third method. Compared with previous approaches, this method shows several primary advantages. First, a continuous purse-string suture was created in the muscle layer of the oesophagus laparoscopically, which obviated the need for transection of the oesophagus for a full-thickness suture, which is easier to perform. The transection plane was at a higher level than was possible with previous methods. In addition, dissecting the planned transection line of the anterior oesophagus alone and containing the continuous posterior wall of the oesophagus when inserting the anvil from the anterior openings can maintain continuous downward traction; this avoids oesophagus stump retraction to the chest cavity. This method has been found to be very useful when performing the technically difficult insertion of the anvil and is now widely used in our centre. In fact, for the most difficult cases, laparoscopic alimentary tract reconstruction can be easier to perform than open surgery when using this approach.

Other obstacles to the popularisation of LATG include concerns regarding the adequacy of surgical resection and its feasibility. In our series, perioperative parameters reflecting the radical extent of the procedure, such as length from the proximal margin and the number of lymph nodes retrieved, did not differ significantly between the laparoscopic group and the open group. Furthermore, LATG has shown several advantages over conventional open surgery including less invasiveness, less pain and earlier recovery. No patients died during surgery in either group, and no serious complications occurred perioperatively. The complication rate was significantly lower in the LATG group as compared to the OTG group (11.2 vs. 16.7 %). Thus, our study demonstrated that LATG can achieve favourable short-term results and oncologic safety as compared with open surgery.

The majority of recent studies on laparoscopic surgery for gastric cancer have focused on early gastric cancer. Only a few studies have addressed the application of a laparoscopic procedure to patients with AGC and evaluated its safety with regard to clinicopathologic surgical outcomes and long-term follow-up results.[19,20] Moreover, most of these reports have mainly concerned cases with depth of invasion extending toT2 or lower. The number and proportion of T3 cases in these studies are very small. Though controversy still exists as to whether laparoscopic curative surgery for T3 AGC is effective, some scholars wonder if there could be an increased risk of peritoneal seeding when performing LATG for T3-type AGC due to CO_2 pneumoperitoneum pressure and factors related to surgery.[21] The results of the present case–control study showed that the overall 5-year survival rates of T3-stage AGC were not significantly different in the LATG group as compared to the OTG group (37.6 vs. 36.0 %), though the follow-up results showed that the major cause of death in the LATG group was postoperative peritoneal metastasis. The incidence was equivalent to that in the OTG group, which somewhat eliminates worries about promoting peritoneal metastasis during laparoscopic surgery. There are no large-sample studies on the long-term outcome of LATG in previous studies. Our study showed, for the first time, that there was no significant difference in 5-year overall survival between the LATG and OTG groups, suggesting that survival was not influenced by the surgical approach and confirming the feasibility and radicality of LATG for the treatment of AGC.

Conclusion

Our study indicated that LATG is a feasible and safe alternative to standard open gastric resection, with similar short- and long-term results that testify to the oncologic radicality of the procedure. These findings support the acceptance and application of LATG for AGC. Certainly, the results of this retrospective nonrandomised clinical analysis should be further confirmed by large-scale prospective randomised trials.

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