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Original Article

Long-term Survival Outcomes of Laparoscopic Gastrectomy for Advanced Gastric Cancer: Five-year Results of a Phase II Prospective Clinical Trial

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ABSTRACT

Purpose: Despite an increased acceptance of laparoscopic gastrectomy (LG) in early gastric cancer (EGC), there is insufficient evidence for its oncological safety in advanced gastric cancer (AGC). This is a prospective phase II clinical trial to evaluate the feasibility of LG with D2 lymph node dissection (LND) in AGC.
Materials and Methods: The primary endpoint was set as 3-year disease-free survival (DFS). The eligibility criteria were as follows: 20-80 years of age, cT2N0-cT4aN3, American Society of Anesthesiologists score of 3 or less, and no other malignancy. Patients were enrolled in this single-arm study between November 2008 and May 2012. Exclusion criteria included cT4b or M1, or having final pathologic results as EGC. All patients underwent D2 lymphadenectomy. Three-year DFS rates were estimated by the Kaplan-Meier method.
Results: A total of 157 patients were enrolled. The overall local complication rate was 10.2%. Conversion to open surgery occurred in 11 patients (7.0%). The mean follow-up period was 55.0±20.4 months (1–81 months). The cumulative 3-year DFS rates were 76.3% for all stages, and 100%, 89.3%, 100%, 88.0%, 71.4%, and 35.3% for stage IB, IIA, IIB, IIIA, IIIB, and IIIC, respectively. Recurrence was observed in 37 patients (23.6%), including hematogenous (n=6), peritoneal (n=13), locoregional (n=1), distant node (n=8), and mixed recurrence (n=9).
Conclusions: In addition to being technically feasible for treatment of AGC in terms of morbidity, LG with D2 LND for locally advanced gastric cancer showed acceptable 3-year DFS outcomes.

Trial Registration: ClinicalTrials.gov Identifier: NCT01441336

Keywords: Surgery; Treatment

INTRODUCTION

Laparoscopic gastrectomy (LG) for early gastric cancer (EGC) has gained wide acceptance due to benefits such as shorter hospital stays, less postoperative pain, and faster mobilization [1]. Since laparoscopic distal gastrectomy (DG) was first introduced in 1994 [2], gastric surgeons have been gaining experience and improving surgical skill. In addition, cutting-edge

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

innovations in minimally-invasive surgical devices have attributed to the growing feasibility of applying laparoscopic surgery to more complex and difficult procedures. Hence, many surgeons are able to achieve the same benefits as LG would have had for EGC by extending their field of laparoscopy to treat resectable advanced gastric cancer (AGC).

However, the use of LG in the treatment of AGC remains controversial due to the technical difficulties associated with complete D2 lymphadenectomy and lack of evidence for oncological long-term safety. Some concerns lie in the danger of handling large tumors with long, thin laparoscopic instruments, in addition to the possible crushing effect of laparoscopic devices on tumors or metastatic lymph nodes (LN) [3]. Some retrospective studies that report the safety and feasibility of LG in AGC with satisfactory oncological outcomes [4-6] exist, but the number of these studies and sample sizes are still inadequate to provide sufficient evidence for its use. Additionally, most of the studies included clinically diagnosed EGC patients and were often limited to cancer in the lower thirds of the stomach with limited reports on the feasibility of laparoscopic total gastrectomy (TG) for AGC.

This study was designed to examine the long-term feasibility and safety of LG in AGC in the context of a phase II prospective study. Short-term outcomes of this study have been previously reported [7] and the final results of the study are reported in this article.

METHODS

Patients and study design

The study was planned as a prospective, single-arm, clinical phase II study, and patients were enrolled from November 2008 to June 2012. Inclusion criteria for the patients were as follows: 1) a histologically confirmed adenocarcinoma of the stomach, 2) clinical staging of cT2-4aN0-3M0 according to the American Joint Committee on Cancer (AJCC)/Union Internationale Contre le Cancer 7th edition, 3) age of 20 to 80 years, 4) an American Society of Anesthesiologists score of 3 or less, and 5) no other malignancy. Exclusion criteria were as follows: 1) adjacent organ invasion or peritoneal seeding, and 2) postoperative diagnosis of EGC. The primary endpoint was 3-year disease-free survival (DFS). Secondary endpoints were morbidity and mortality, along with 3, 5, and 7-year overall survival (OS). The reference date for survival is the last follow-up period (November 2017). All participants were well oriented by the investigators and a formal written consent form was received. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Research Board Committee of the institution (B-0604/032-018). It was registered under the code NCT01441336 in ClinicalTrials.gov.

Surgical techniques

All surgeries were performed in a single center by a single surgeon. DG was indicated for a tumor in the lower third of the stomach and TG was performed for tumors in or above the middle third of the stomach. LG was performed with six trocars, a 10 mm flexible scope (Olympus Medical, Tokyo, Japan), and an ultrasonic energy device (Harmonic scalpel; Ethicon Endo-Surgery, Cincinnati, OH, USA). D2 lymph node dissection was performed in all patients and total omentectomy was performed when serosal invasion was suspected. After DG, Billroth I (BI), Billroth II (BII), or uncut Roux-en Y (UCRY) was performed for reconstruction. Uncut Roux-en Y reconstruction was preferred in patients under 70 with low-stage disease and longer life expectancy to reduce bile reflux and heighten patient quality

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of life. After TG, end-to-side esophagojejunostomy was performed intracorporeally using a purse-string laparoscopic instrument (Lap-Jack; Eterne, Seongnam, Korea) [8]. Splenectomy was performed when number 10 lymph node metastasis was suspected or when a tumor of the upper third invaded the serosa.

Postoperative care and adjuvant chemotherapy

Follow up was scheduled at 3-month intervals for the first 2 years, then 6-month intervals for 3 years, and then annually until the patient's death. Patients underwent physical examination, laboratory blood tests, abdominal ultrasonography, and computed tomography every 6 months; annual endoscopy was performed for follow-up surveillance. Recurrence was diagnosed through endoscopy and computed tomography imaging with clinical correlations. Recurrence was then classified into five groups for pattern analysis: 1) locoregional for recurrence in the anastomosis, gastric bed, adjacent organs, and regional lymph nodes, 2) hematogenous for recurrence in the liver, lung, bone, brain, or other distant organs, 3) peritoneal for peritoneal seeding or a Krukenburg's tumor, 4) distant lymph nodes, and 5) mixed for patients experiencing more than one category of recurrence at the time it was discovered. Indications for adjuvant chemotherapy were in concordance with the Japanese gastric cancer treatment guidelines [1]. The chemotherapy regimen was based on the ACTS-GC [9] trial and the CLASSIC trial [10], composed of either S-1 or capecitabine and oxaliplatin.

Statistical analysis and sample size calculation

Sample size calculation was based the results of a multicenter study on AGC with oral adjuvant chemotherapy [9]. The expected 3-year recurrence-free survival rate was 70%, and with 80% power, threshold of 60% at a 5% significance level, and a 10% dropout rate, the calculated sample size was 157 [7]. Descriptive data were presented as mean±standard deviation or median (range). The Kaplan-Meier method was used to analyze the survival data. Significance was defined as a P-value of <0.05. All statistical analyses were performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 204 patients were assessed. Among them, 16 patients were excluded due to adjacent organ invasion or peritoneal seeding diagnosed via laparoscopic examination. After LG, 31 patients were diagnosed with EGC and were also excluded from the study. A resultant total of 157 patients were enrolled (**Fig. 1**).

Patient demographics and operative outcome are illustrated in **Table 1**. Men composed 105 of the enrolled patients with a mean age of 60.89±12.39 years and mean body mass index of 23.72±2.83 kg/m^2. DG was performed on 115 patients and TG was performed on the remaining 42 patients. The average number of resected LNs was 57.39±19.54. Seven patients had microscopic cancer cells in the margin of the specimen, consistent with an R1 resection; all other patients received an R0 resection. Among TG patients, combined splenectomy was performed in 23 total. All patients with TNM stage II or greater (137 patients, 87.1%) received adjuvant chemotherapy. The median follow-up period was 55.0±20.4 months (range 1–81 months), and there were no drop-outs during the follow-up period.

Eleven patients had open conversion during the laparoscopic surgery due to uncontrolled bleeding or vessel injury, severe adhesions from a previous surgery, arrhythmia caused by

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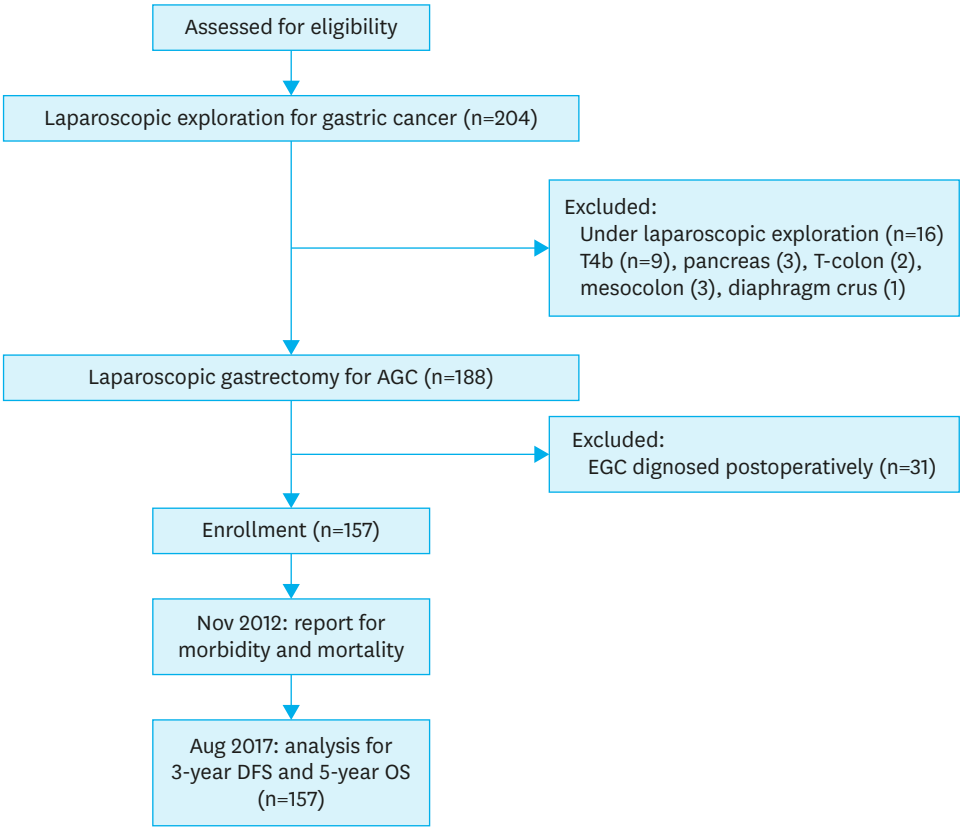

Fig. 1. CONSORT diagram.
AGC = advanced gastric cancer; EGC = early gastric cancer; DFS = disease-free survival; OS = overall survival.

pneumoperitoneum, and severe obesity. The systemic early-complication rate was 25.5% (27.8% for DG, 19.0% for TG) and the local early-complication rate was 10.2% (7.8% for DG, 16.7% for TG). One early mortality occurred due to aggravation of a patient's pulmonary and cardiac disease. Morbidity and mortality results of this study are further characterized in a previous study [7].

The 3-year DFS was 76.3%, and differences in 3-year DFS according to the AJCC stage are depicted in **Fig. 2A**. Mortality was not included in the calculation of DFS. The 3-year DFS of the DG and TG groups was 78.9% and 69.0%, respectively. There was no significant difference between the 2 DFS rates (**Fig. 2A**). The 5-year OS was 72.6% (**Fig. 2B**).

A total of 37 recurrences were observed during the follow-up period and recurrence patterns are summarized in **Fig. 3**. Peritoneal recurrence was observed in 13 patients, hematogenous recurrence in 6 patients, distant lymph node recurrence in 8 patients, locoregional recurrence in 1 patient, and mixed recurrence in 9 patients.

DISCUSSION

In addition to our previous study demonstrating acceptable short-term morbidity associated with LG for AGC, the survival data of this study suggest that LG for AGC is acceptable in terms of long-term oncological safety.

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Table 1. Patient characteristics and operative outcome

Characteristics	Total (n=157)	LDG (n=115)	LTG (n=42)
Age, Mean±SD (yr)	60.9±12.4	61.6±11.7	59.4±13.8
Sex, M:F	105:52	76:39	29:13
Body mass index, mean±SD (kg/m^2)	23.7±2.8	23.8±2.6	23.6±3.5
ASA score			
1	75 (47.7%)	50 (43.5%)	25 (59.5%)
2	72 (45.9%)	59 (51.3%)	13 (31.0%)
3	10 (6.4%)	6 (5.2%)	4 (9.5%)
Type of reconstruction			
Billroth I	35 (22.3%)	35 (30.4%)	0 (0.0%)
Billroth II with Braun anastomosis	8 (5.1%)	8 (6.9%)	0 (0.0%)
Roux-en Y (including uncut Roux-en Y)	114 (72.6%)	72 (62.6%)	42 (100.0%)
Combined splenectomy			
No	134 (85.4%)	115 (100.0%)	19 (45.2%)
Yes	23 (14.6%)	0 (0.0%)	23 (54.8%)
Combined other operation			
No	147 (93.6%)	112 (97.4%)	35 (83.3%)
Yes	10 (6.4%)	3 (2.6%)	7 (16.7%)
Omentectomy			
Total	39 (24.8%)	22 (19.1%)	17 (40.5%)
Partial	118 (75.2%)	93 (80.9%)	25 (59.5%)
Radicality			
R0	150 (95.5%)	112 (97.4%)	38 (90.5%)
R1	7 (4.5%)	3 (2.6%)	4 (9.5%)
pStage			
IB	25 (15.9%)	23 (20.0%)	2 (4.8%)
IIA	28 (17.8%)	21 (18.3%)	7 (16.7%)
IIB	17 (10.8%)	16 (13.9%)	1 (2.4%)
IIIA	25 (15.9%)	16 (13.9%)	9 (21.4%)
IIIB	28 (17.8%)	19 (16.5%)	9 (21.4%)
IIIC	34 (21.8%)	20 (17.4%)	14 (33.3%)
Retrieved number of LNs	57.4±19.5	55.1±19.2	63.8±19.4
Proximal margin	4.7±2.6	5.2±2.6	3.3±2.0
Distal margin	8.3±4.5	7.0±3.6	11.8±4.9

LDG = laparoscopic distal gastrectomy; LTG = laparoscopic total gastrectomy; SD, standard deviation; ASA = American society of anesthesiologists; LN = lymph node.

Although final outcomes of randomized phase III studies such as the KLASS01 trial and the JCOG0912 trial have yet to be reported, LG has currently gained wide acceptance in EGC with accumulating evidence of safety and feasibility [1,11]. Its application for AGC is still controversial, especially due to concern regarding D2 lymphadenectomy; few incidences have been reported in the literature. A phase II randomized trial of 180 patients showed that there was no difference in 6-month surgical outcome between open DG and laparoscopy-assisted DG with D2 lymphadenectomy for AGC [12]. Despite these reports, evidence of long-term oncologic safety is lacking. There was no difference in the incidence of recurrence or survival in the open versus laparoscopic randomized trial by Huscher et al. [13]; however, the sample size was limited to 59. In a meta-analysis published in 2016 by Quan et al. [14], the only prospective study included had a median follow-up time of 22.1 months [15]. The median follow-up time of this study was 55 months and the 3-year disease free survival data were higher than the expected 70%.

This study also collected the 5-year OS as a secondary endpoint, making it more feasible to compare the results of this study directly to reported outcomes of OS from other studies [11,16-19]. The results obtained in this study are better than previously reported OS with LG for AGC [16]. This may be attributed to the fact that all operations were performed by a

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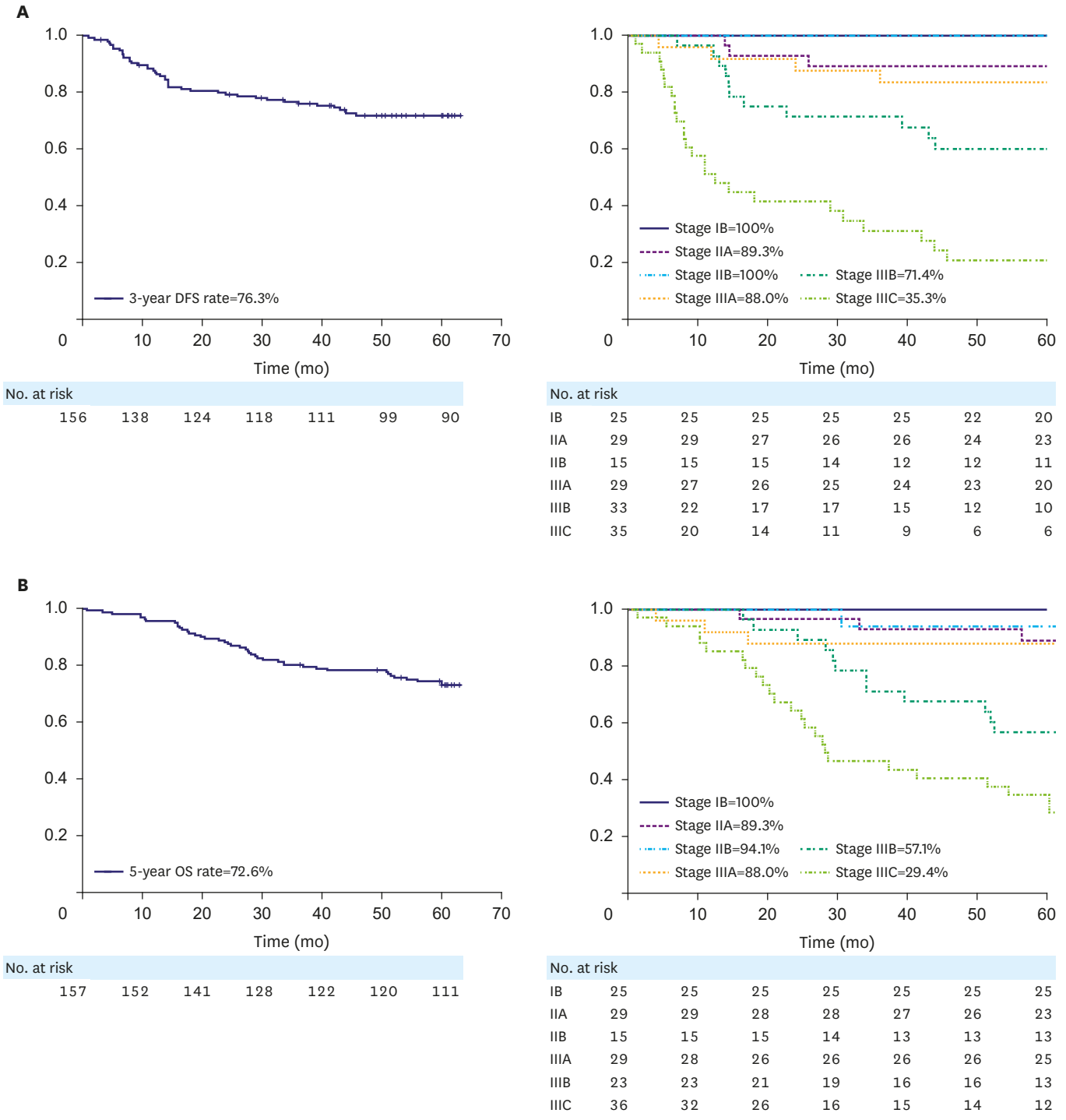

Fig. 2. Long-term outcomes of laparoscopic gastrectomy for advanced gastric cancer. (A) The total 3-year disease free survival (left) and individual survival curves grouped by TNM stage (right). (B) The total 5-year overall survival (left) and individual survival curves grouped by TNM stage (right).

single skilled surgeon who averages 350 cases of LG per year and has been doing so for the past 10 years. The availability of a well-trained scopist who specializes in LG and a well-organized team may also have contributed to the results. A recent survival study of AGC after gastrectomy and adjuvant S-1 chemotherapy in Japan showed the 5-year OS for pathological stages IIA, IIB, IIIA, IIIB, and IIIC to be 96.0%, 85.5%, 81.8%, 72.0%, and 51.1%, respectively

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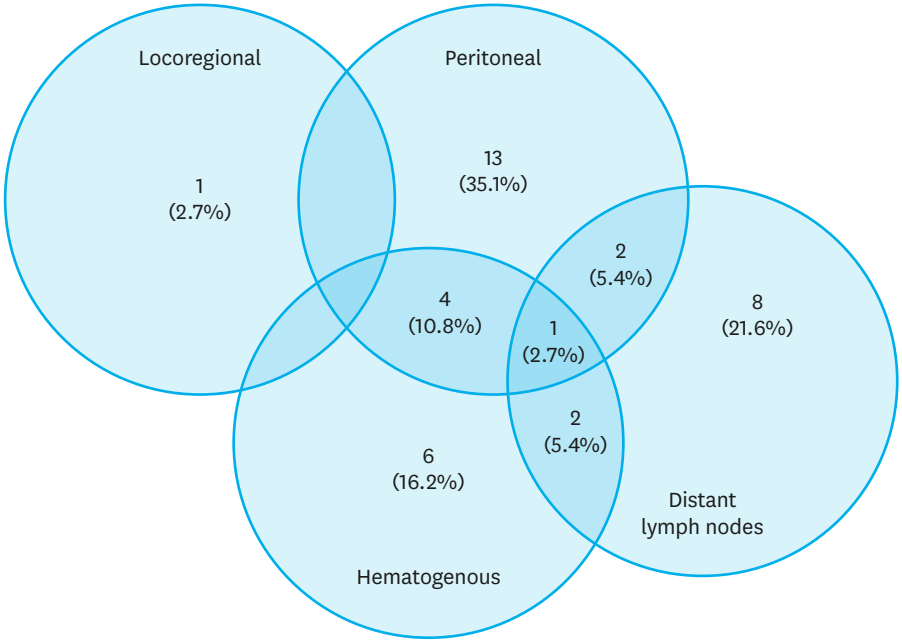

Fig. 3. Venn diagram of recurrence pattern.

[20]. It is difficult to compare this data directly since both are single-center studies, however, there are some discrepancies in stage IIIB and IIIC that could be further investigated in future randomized controlled trials.

Although this was not designed as a comparative study, the data hint that the use of LG for AGC as compared to open gastrectomy is not an inferior method. Despite initial preconceptions regarding laparoscopy as the more difficult approach to perform lymphadenectomy, laparoscopic views may enhance the likelihood of achieving fine lymph node dissection with the help of magnified imaging. The angulation of the flexible scope can provide a brighter, magnified view of lymph nodes, such as those in the ventral side of the pancreas, which may go unnoticed in open gastrectomy relying on the naked eye. In addition, better surgical instruments, such as energy devices and staplers, are being used more frequently in the era of laparoscopic surgery as compared to the open surgeries of the past. Recognizing concerns regarding the use of laparoscopic instruments in bulky tumors [3], the data show that handling of advanced stage cancers can be safely performed with an appropriate experience level.

Analysis of recurrence patterns showed a higher rate of peritoneal recurrence, followed by hematogenous recurrence, with only one patient experiencing locoregional recurrence. A multicenter retrospective study of 1,417 patients after LG reported a recurrence pattern of 34% hematogenous, 22% peritoneal, 20% locoregional, and 4% distant LN metastasis [21]. However, their data involved mostly earlier stage cancers, and the node metastasis of their patients was not as aggressive as that of clinically diagnosed AGC patients, making it difficult to compare its results directly with this study. Another study by Yoo et al. [22] analyzed 2,328 patients diagnosed with curative gastric cancer and found peritoneal recurrence to be most common, followed by hematogenous recurrence, similar to the recurrence pattern in this study. Though not directly stated in the aforementioned study, the enrollment period of 1987 to 1995 suggests that most, if not all, of the surgeries were accomplished using an

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open surgical method. The study detailed in this article is the only study that analyzes the recurrence pattern of purely AGC patients undergoing LG.

Furthermore, this is the only reported prospective study that considers long-term survival benefits with a patient group of AGC only. By only including clinically diagnosed AGC patients, the TNM stages of the cohort are evenly distributed, unlike previous studies of LG in AGC that focused mainly on earlier stages of disease. The application of laparoscopic TG for AGC is uncommon in literature and this study reports the survival outcomes of a cohort of 42 people. However, it is recognized that its widespread application may be hindered by the fact that this was performed by a single surgeon in a single center. For instance, survival for stage IIB (100.0%) was higher than that for stage IIA (89.3%), and the survival for stage IIIA (88.0%) seems unnaturally high. It is because this study is a single center cohort study, and may not represent the whole patient population. As a prospective study, the data are well controlled and there was no selection bias. However, it is not a randomized controlled study, so it can only provide limited evidence when compared to open gastrectomy. At the point of study development there was no well-designed format to back evidence for the application of laparoscopy in both AGC and EGC patients. The outcomes of KLASS02, a phase III multi-center randomized control trial comparing open and laparoscopic DG in AGC are yet to be published, and the results of this study will be able to provide more definitive clinical evidence for the application of LG for AGC [23].

In conclusion, survival outcomes of LG in AGC are comparable to previously reported data on open gastrectomy and the recurrence pattern is also similar to reports of previous studies. LG for AGC is feasible in terms of long-term oncological outcomes, and with this study as a stepping stone, results of well-designed randomized controlled trials are necessary to provide better evidence for its safety.

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