Laparoscopic Sentinel Node Navigation Surgery for Stomach Preservation in Patients With Early Gastric Cancer: A Randomized Clinical Trial

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abstract

PURPOSE To compare postoperative complications, long-term survival, and quality of life (QOL) after laparoscopic sentinel node navigation surgery (LSNNS) and laparoscopic standard gastrectomy (LSG).

METHODS Five hundred eighty patients with preoperatively diagnosed stage IA gastric adenocarcinoma (≤3 cm) were assigned to undergo either LSG or LSNNS. Observers were not blinded to patient grouping. The primary outcome was 3-year disease-free survival (3y-DFS). Secondary outcomes included postoperative complications, QOL, 3-year disease-specific survival (3y-DSS), and 3-year overall survival (3y-OS).

RESULTS In total, 527 patients were included in the modified intention-to-treat analysis population for the primary outcome (LSG, 269; LSNNS, 258). Stomach-preserving surgery was performed in 210 patients (81%) in the LSNNS group. During the median follow-up duration, the 3y-DFS rates in the LSG and LSNNS groups were 95.5% and 91.8%, respectively (difference: 3.7%; 95% CI, –0.6 to 8.1). Three patients with recurrence and five with metachronous gastric cancer in the LSNNS group underwent standard surgery. Two patients with distant metastasis in both groups were treated with palliative chemotherapy. The 3y-DSS and 3y-OS rates in the LSG and LSNNS groups were 99.5% and 99.1% (P = .59) and 99.2% and 97.6% (P = .17), respectively. Postoperative complications occurred in 19.0% of the LSG group and 15.5% of the LSNNS group (P = .294). The LSNNS group showed better physical function (P = .015), less symptoms (P < .001), and improved nutrition than the LSG group.

CONCLUSION LSNNS did not show noninferiority to LSG for 3y-DFS, with a 5% margin. However, the 3y-DSS and 3y-OS were not different after rescue surgery in cases of recurrence/metachronous gastric cancer, and LSNNS had better long-term QOL and nutrition than LSG.

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INTRODUCTION

Gastric cancer is a common malignancy and a leading cause of cancer death globally.1 In areas where gastric cancer incidence is relatively high, the proportion of early gastric cancer (EGC) is increasing because of well-organized screening programs.2 Consequently, gastric cancer survival in these regions is the highest worldwide.3

Patients with EGC are generally treated with laparoscopic standard gastrectomy (LSG), consisting of gastrectomy with lymph node dissection (LND) and GI reconstruction.4,5 The survival rate in patients with EGC is >95%. However, quality of life (QOL) in these long-term survivors is impaired because of postgastrectomy symptoms.7

To reduce postgastrectomy symptoms, endoscopic resection (ER) is becoming popular in patients with minimal risk of lymph node metastasis (LNM).8 However, the indications for ER are limited. Laparoscopic sentinel node navigation surgery (LSNNS) has been suggested as an option that would allow for the omission of perigastric LND and the preservation of much of the stomach, after primary tumor resection, in cases in which sentinel node biopsy (SNB) shows negative results.9 Consequently, postgastrectomy symptoms can be prevented, and QOL can be improved in long-term survivors.10

However, two relatively large-scale multicenter studies and many single-center studies have reported contradictory results concerning the feasibility of SNB for EGC.11,12 The high false-negative rate reported by a Japanese study is an obstacle to the clinical adoption of SNB.12 However, another Japanese study reported a high rate of accuracy, which is promising.13 A phase II
study of LSNNS in South Korea also found this procedure to be feasible in patients with EGC. However, a randomized controlled trial is warranted.14

The SEntinel Node ORIented Tailored Approach (SENO-RITA) trial was a phase III, multicenter, randomized, controlled clinical trial conducted in South Korea to compare postoperative complications, long-term survival, and QOL after LSNNS and LSG.

METHODS

Study Design and Patients

This study was a prospective multicenter randomized controlled trial conducted at seven institutions in South Korea.15 Patients age between 20 and 80 years, with an Eastern Cooperative Oncology Group performance status score of 0 or 1, were eligible if they had histologically proven gastric adenocarcinoma, were preoperatively classified as stage IA by endoscopy and computed tomography, and/or endoscopic ultrasonography according to the American Joint Committee on Cancer (seventh edition) criteria, and were scheduled for curative laparoscopic surgery.16 Additional inclusion criteria were tumor size ≤ 3 cm and location > 2 cm from the cardia or pylorus, regardless of histologic type. Exclusion criteria were absolute indications for ER: tumor size > 2 cm, mucosal lesion, and differentiated histology.4 Patients with synchronous gastric cancer or malignancies in other organs, those who had undergone preoperative chemotherapy or radiotherapy, those who had undergone upper abdominal surgery (except laparoscopic cholecystectomy), those who were pregnant or had a history of mental illness, and those with other malignancies within 5 years were also excluded. This trial was approved by the Institutional Review Board of each institution and was conducted in accordance with the principles of the Declaration of Helsinki.17 Written informed consent was obtained from all patients before enrollment. An independent data monitoring committee reviewed the progress of the trial.

Random Assignment and Masking

Before surgery, the enrolled patients were randomly assigned to undergo LSG or LSNNS in a 1:1 ratio. The stratification factors were tumor depth (mucosa vs submucosa), tumor size (< 2 vs > 2 cm), and institution. The enrolled patients were registered at the Clinical Research Coordination Center within the National Cancer Center in South Korea through a web-based clinical trial management system18 (eVelos System; Velos, Fremont, CA). Random assignment was performed by Velos, and the assignments were communicated to the surgeons and patients. Surgeon blinding of random assignment did not occur because of the surgical nature of the trial, and the Institutional Review Boards did not recommend patient blinding because of patient rights.

Procedures

Surgery was performed within 6 weeks after random assignment. In the LSG group, several types of laparoscopic gastrectomies were performed with lymphadenectomy in accordance with the Korean guidelines.4 In the LSNNS group, stomach-preserving surgeries (intraoperative ER, endoscopic full-thickness resection, wedge resection, and

CONTEXT

Key Objective
Laparoscopic sentinel node navigation surgery (LSNNS) has been suggested to improve quality of life (QOL) by stomach preservation in long-term survivors from early gastric cancer. This study was performed to prove the noninferiority of LSNNS to laparoscopic standard gastrectomy (LSG) in terms of 3-year disease-free survival (3y-DFS) and to compare QOL in 580 patients. This study, to our knowledge, was the first prospective multicenter randomized controlled trial on this issue.

Knowledge Generated
The 3y-DFS in the LSG and LSNNS groups was 95.5% and 91.8%, respectively (difference: 3.7%; 95% CI, –0.6 to 8.1). The LSNNS group showed better physical function, less symptoms, and improved nutrition than the LSG group.

Relevance
LSNNS did not show noninferiority to LSG for 3y-DFS, with a 5% margin, although better long-term QOL and nutrition. Clinical application of LSNNS should be cautious considering the survival and QOL.
segmental resection) were performed in cases involving negative SNB results, as previously described with proposed indications. Dual indocyanine green (2 mL, 5 mg Diagnogreen; Daiichi-Sankyo, Tokyo, Japan) and Technetium-99m human serum albumin (2 mL, 0.1 mCi/mL) tracers were intraoperatively injected submucosally to detect sentinel nodes. SNB was performed by basin dissection instead of pick-up biopsy to minimize false-negatives. Sentinel basin was defined within 2 cm margin from detected hot or green nodes, not lymph node station. Standard surgery was performed in cases with positive SNB findings and negative SNB results if stomach-preserving surgery was technically difficult. Postoperative surveillance (endoscopy, computed tomography, tumor marker analysis, and basic laboratory tests) was performed every 6 months for 3 years and then annually for 2 years. Data from patients lost to follow-up and those who withdrew from the trial were censored at the last surveillance visit.

Pathologic staging was performed according to the American Joint Committee on Cancer/Union for International Cancer Control (seventh edition) criteria. Histologic evaluation was performed according to the WHO classification. The pathologic protocol for intraoperative and postoperative examination has been previously described. All harvested sentinel basin nodes (SBNs) from the LSNNS group were sectioned at 2-mm intervals parallel to the long axis and evaluated intraoperatively with hematoxylin and eosin staining. Any SBNs with tumor cells were classified as positive, regardless of the size of metastatic foci. Resected primary tumors were also evaluated for margin involvement using frozen sections. In cases of primary tumor margin involvement, further resection was performed until negative margins were achieved. Postoperatively, all SBNs were evaluated again using hematoxylin and eosin staining, and cytokeratin immunohistochemistry was conducted on additional sections from paraffin blocks. Primary tumor resection margins were also evaluated again with sections from paraffin blocks. Additional surgery was recommended after LSNNS in cases of postoperative findings with (1) cancer cells in SBNs in the form of macrometastases measuring > 2 mm, (2) tumor involvement of margin of resected specimen, and (3) pT2 or deeper lesions. In the LSG group, postoperative pathologic evaluation of harvested lymph nodes was performed using hematoxylin and eosin staining of a representative section taken along the long axis.

Outcomes
The primary outcome was the 3-year disease-free survival (3y-DFS) rate. DFS was defined as the time from surgery to gastric cancer recurrence, development of metachronous gastric cancer in the residual stomach, development of cancer in other organs, or death from any cause, after surgery. Secondary outcomes included the 3-year disease-specific survival (3y-DSS) and 3-year overall survival (3y-OS) rates. DSS was defined as the time from surgery to gastric cancer-related death, and OS was defined as the time from surgery to death from any cause. Other secondary outcomes were postoperative complications and QOL.

QOL and Nutritional Parameters
The QOL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC stomach module (STO22) at 3, 12, 24, and 36 months after surgery. Nutritional parameters of body mass index, hemoglobin, and total protein were also measured simultaneously.

Statistical Analyses
On the basis of an expected 3y-DFS rate of 97% in the LSG group, a noninferiority margin of 5%, a type I error of 5%, a power of 80%, an expected recruitment period of 4 years, and a follow-up surveillance period of 3 years from the enrollment of the last patient, 261 patients were needed in each group, with 24 target events. Assuming a 10% dropout rate, 290 patients were needed in each group (total, 580). One interim analysis was performed after 12 events (50%) had occurred. Using the O’Brien-Fleming alpha spending function, the two-sided nominal significance level for the interim analysis was 0.0054. Full analysis was performed mainly in the modified intention-to-treat population and, additionally, in the per-protocol population. Survival was evaluated using the Cox proportional hazards model and log-rank test. The Kaplan-Meier method was used for survival estimation. Statistical analyses were conducted using STATA software version 16.0 (STATA Corp, College Station, TX) and SAS software version 9.4 (SAS Institute Inc, Cary, NC). The linear mixed model was used to evaluate QOL.

RESULTS
Patients
A total of 580 patients were randomly assigned after screening from March 27, 2013, to December 28, 2016 (Fig 1). Of these, 527 were included in the modified intention-to-treat population (269, LSG group; 258, LSNNS group) after 53 patients were excluded. The most common reasons for exclusion were withdrawal from the trial (n = 26) and patient desire to switch to the nonassigned surgery (n = 13). Surgery was performed in 511 patients according to the protocol, and these patients made up the per-protocol population. Open surgery was performed instead of laparoscopic surgery in three patients in the LSG group. Standard surgery was performed in 13 patients in the LSNNS group because the intraoperative findings were inconsistent with the preoperative workup. The patient and tumor characteristics were comparable between the LSG and LSNNS groups (Table 1). Among the 245 patients in the LSNNS group, treated according to the protocol, stomach-preserving surgery (210 patients) and standard surgery were performed (35 patients). The median duration
of follow-up was 48.1 months (interquartile range, 41.5-58.7 months; maximum, 62.2 months).

### Primary Outcome

During the median follow-up of 48.1 months, the 3y-DFS rate was 95.5% in the LSG group and 91.8% in the LSNNS group (difference, 3.7%; 95% CI, –0.6 to 8.1; Fig 2). The disease events are listed in Table 2, and more detailed information regarding patients with recurrence is listed in Appendix Table A1 (online only), including precise pathologic information from the initial surgery.

Primary tumor site recurrence occurred in two patients in the LSNNS group after laparoscopic wedge resection, and both were treated with standard laparoscopic distal gastrectomy. Lymph node recurrence occurred in one patient after laparoscopic wedge resection with sentinel basin dissection (Appendix Fig A1, online only). Standard laparoscopic distal gastrectomy was performed in this patient, followed by adjuvant chemotherapy. Distant metastasis was detected and treated with palliative chemotherapy in two patients in each group.

Five patients in the LSNNS group developed metachronous gastric cancer in the residual stomach after laparoscopic wedge resection. Depending on the characteristics and location of metachronous cancer, ER or standard gastrectomy was performed.

Fourteen patients in the entire cohort developed malignancies in other organs. Four patients in the LSNNS group died: two from accidents, one from liver cirrhosis, and one from sepsis secondary to urinary tract infection. One patient in the LSG group died after laparoscopic distal gastrectomy from sepsis due to duodenal stump leakage.

### Secondary Outcomes

During the follow-up, the 3y-DSS rate was 99.5% (95% CI, 96.7 to 99.3) in the LSG group and 99.1% (95% CI, 96.4 to 99.8) in the LSNNS group ($P = .59$; Fig 3). One patient in...
| Variable                                      | Modified Intention-to-Treat Population | Per-Protocol Population |
|----------------------------------------------|---------------------------------------|-------------------------|
|                                              | LSG (n = 269)                         | LSNNS (n = 258)         |
|                                              | LSG (n = 266)                         | LSNNS (n = 245)         |
| Age, years, mean (range)                     | 56 (26-80)                           | 55 (26-80)              |
|                                              | 56 (26-80)                           | 55 (26-80)              |
| Male, No. (%)                                | 143 (53)                             | 153 (59)                |
|                                              | 140 (53)                             | 147 (60)                |
| BMI, kg/m², mean (range)                     | 24 (17-40)                           | 23 (14-35)              |
|                                              | 24 (17-40)                           | 23 (14-35)              |
| ECOG PS, No. (%)                             | 265 (99)                             | 253 (98.1)              |
|                                              | 265 (98.5)                           | 240 (98.1)              |
|                                              | 4 (2)                                | 5 (1.9)                 |
|                                              | 4 (1.5)                              | 5 (2.0)                 |
| Longitudinal tumor location, No. (%)         | 17 (6)                               | 14 (5.4)                |
|                                              | 17 (6.4)                             | 14 (5.7)                |
|                                              | Upper                                | 155 (58)                |
|                                              | Lower                                | 97 (36)                 |
|                                              | 96 (36.1)                            | 84 (34.3)               |
|                                              | Upper                                | 17 (6)                  |
|                                              | Middle                               | 157 (60.9)              |
|                                              | Lower                                | 87 (33.3)               |
|                                              | 98 (36.8)                            | 81 (33.1)               |
|                                              | Posterior                            | 40 (15)                 |
|                                              | 39 (14.7)                            | 44 (18.0)               |
| Preoperative histologic classification, No. (%) | 174 (65)                           | 149 (57.8)              |
|                                              | 172 (64.7)                           | 143 (58.4)              |
|                                              | Signet ring cell carcinoma           | 95 (35)                 |
|                                              | 94 (35.3)                            | 101 (41.2)              |
|                                              | Adenocarcinoma in situ               | 0 (0)                   |
|                                              | 0 (0.4)                              | 1 (0.4)                 |
|                                              | Clinical tumor size, cm, mean (range) | 2 (0-3)                |
|                                              | 1.7 (0-3.0)                          | 1.9 (0-3.0)             |
|                                              | 1.7 (0-3.0)                          | 1.7 (0-3.0)             |
|                                              | Clinical tumor depth, No. (%)         | 179 (67)                |
|                                              | 171 (66.3)                           | 177 (66.5)              |
|                                              | 164 (66.9)                           | 81 (33.1)               |
|                                              | Submucosa                            | 90 (34)                 |
|                                              | 87 (33.7)                            | 89 (33.5)               |
| Type of operation, No. (%)                   | Lapa distal gastrectomy              | 217 (81)                |
|                                              | 40 (15.5)                            | 217 (81.6)              |
|                                              | 28 (11.4)                            |                           |
|                                              | Lapa total gastrectomy               | 10 (4)                  |
|                                              | 4 (1.6)                              | 10 (3.8)                |
|                                              | 3 (1.2)                              |                           |
|                                              | Lapa pylorus-preserving gastrectomy  | 28 (10)                 |
|                                              | 3 (1.2)                              | 28 (10.5)               |
|                                              | 3 (1.2)                              |                           |
|                                              | Lapa proximal gastrectomy            | 8 (3)                   |
|                                              | 0 (0)                                | 8 (3)                   |
|                                              | 0 (0)                                |                           |
|                                              | Open distal gastrectomy              | 4 (2)                   |
|                                              | 1 (0)                                | 1 (0)                   |
|                                              | 1 (0)                                |                           |
|                                              | Open total gastrectomy               | 2 (1)                   |
|                                              | 0 (0)                                | 2 (1)                   |
|                                              | 0 (0)                                |                           |
|                                              | Lapa wedge resection without EFTR    | 0 (0)                   |
|                                              | 179 (69)                             | 0 (0)                   |
|                                              | 179 (73)                             |                           |
|                                              | Lapa wedge resection with EFTR       | 0 (0)                   |
|                                              | 11 (4)                               | 0 (0)                   |
|                                              | 11 (5)                               |                           |
|                                              | Lapa segmental resection             | 0 (0)                   |
|                                              | 18 (7)                               | 0 (0)                   |
|                                              | 18 (7)                               |                           |
|                                              | Endoscopic submucosal dissection      | 0 (0)                   |
|                                              | 2 (1)                                | 0 (0)                   |
|                                              | 2 (1)                                |                           |
| Pathologic tumor stage, No. (%)              | pT1a                                  | 161 (60)                |
|                                              | 154 (60)                             | 158 (60)                |
|                                              | 147 (60)                             |                           |
|                                              | pT1b                                  | 84 (31)                 |
|                                              | 88 (34)                              | 84 (32)                 |
|                                              | 84 (34)                              |                           |
|                                              | pT2                                   | 16 (6)                  |
|                                              | 9 (4)                                | 16 (6)                  |
|                                              | 9 (4)                                |                           |
|                                              | pT3                                   | 6 (2)                   |
|                                              | 7 (3)                                | 6 (2)                   |
|                                              | 5 (2)                                |                           |
|                                              | pT4a                                  | 1 (0)                   |
|                                              | 0 (0)                                | 1 (1)                   |
|                                              | 0 (0)                                |                           |
|                                              | Pathologic tumor size, cm, mean (range) | 2 (0-14)               |
|                                              | 2 (0-8)                              | 2 (0-9)                 |
|                                              | 2 (0-8)                              |                           |

(continued on following page)
the LSNNS group with lymph node recurrence ultimately developed liver metastasis and died, even after curative laparoscopic distal gastrectomy and chemotherapy. One patient in the LSNNS group with para-aortic LNM after curative laparoscopic gastrectomy (positive SNB findings) also died after palliative chemotherapy. There were no other disease-specific deaths in the LSNNS group after rescue surgery for recurrence or metachronous gastric cancer. One postoperative death in the LSG group, due to sepsis, was recorded as a disease-specific death.

The 3y-OS rate was 99.2% (95% CI, 96.6 to 99.8) in the LSG group and 97.6% (95% CI, 94.6 to 98.9) in the LSNNS group (P = .17; Fig 4). One patient in the LSG group developed metachronous lymphoma after gastric cancer surgery and died after being treated with chemotherapy. Four patients in the LSNNS group died.

### TABLE 1. Patient and Tumor Characteristics and Postoperative Results (continued)

| Variable | Modified Intention-to-Treat Population | Per-Protocol Population |
|----------|----------------------------------------|-------------------------|
|          | LSG (n = 269) | LSNNS (n = 258) | LSG (n = 266) | LSNNS (n = 245) |
| Pathologic nodal stage, No. (%) | | | | |
| pN0 | 244 (91) | 225 (87) | 241 (91) | 215 (88) |
| pN1 (1-2 nodes) | 15 (6) | 24 (9) | 15 (6) | 23 (9) |
| pN2 (3-6 nodes) | 7 (3) | 6 (2) | 7 (3) | 4 (2) |
| pN3a (7-15 nodes) | 2 (1) | 3 (1) | 2 (1) | 3 (1) |
| Pathologic tumor stage, No. (%) | | | | |
| IA | 226 (84) | 217 (84) | 223 (84) | 208 (85) |
| IB | 28 (10) | 24 (9) | 28 (11) | 23 (9) |
| IIA | 9 (3) | 10 (4) | 9 (3) | 8 (3) |
| IIB | 2 (1) | 5 (2) | 2 (1) | 5 (2) |
| IIIA | 1 (0) | 1 (0) | 1 (0) | 0 (0) |
| IIIB | 2 (1) | 1 (0) | 2 (1) | 1 (0) |

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; EFTR, endoscopic full-thickness resection; Lapa, laparoscopic; LSG, laparoscopic standard gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery.

*Tumor location was classified according to the Japanese classification of gastric carcinoma.

*Tumor histologic classification was performed according to the WHO criteria.
TABLE 2. Three-Year Disease-Free Survival Events

| Event                          | LSG (n = 11) | LSNNS (n = 20) |
|-------------------------------|-------------|---------------|
| Primary tumor recurrence      | 0           | 2 (LW → LDG)  |
| Lymph node recurrence         | 0           | 1 (LW → LDG and adjuvant chemotherapy) |
| Distant metastasis            |             |               |
| LDG → palliative chemotherapy | 2           | 1             |
| LW → palliative chemotherapy  | 0           | 1             |
| Metachronous gastric cancer   |             |               |
| LW → ESD                      | 0           | 1             |
| LW → LDG                      | 0           | 2             |
| LW → LTG                      | 0           | 2             |
| Cancers in other organs       |             |               |
| Lung                          | 3           | 2             |
| Colon                         | 1           | 1             |
| Prostate                      | 1           | 1             |
| Thyroid                       | 1           | 1             |
| Breast                        | 0           | 1             |
| Gallbladder                   | 1           | 0             |
| Lymphoma                      | 1           | 0             |
| Other deaths                  |             |               |
| Postoperative mortality (LDG) | 1           | 0             |
| Accidents                     | 0           | 2             |
| Sepsis (UTI)                  | 0           | 1             |
| Liver cirrhosis               | 0           | 1             |

NOTE. Data are No. of patients.

Abbreviations: ESD, endoscopic submucosal dissection; LDG, laparoscopic distal gastrectomy; LSG, laparoscopic standard gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery; LTG, laparoscopic total gastrectomy; LW, laparoscopic wedge resection; UTI, urinary tract infection.

Postoperative complications occurred in 51 patients in the LSG group (19.0%) and 40 (15.5%) in the LSNNS group (P = .294). Complication with a Clavien-Dindo grade of III or higher occurred in 16 (5.9%) and 13 (5.0%) patients in the LSG and LSNNS groups, respectively (P = .547).

The LSNNS group had a better functional score than the LSG group in scales of EORTC-C30 (P = .015; Appendix Figs A2 and A3, online only). Regarding the EORTC QLQ-ST022, pain, eating restriction, anxiety, and taste were better in the LSNNS group than in the LSG group (P = .024, <.001, <.009, and <.010, respectively; Appendix Fig A4, online only). The summary score of EORTC QLQ-ST022 was also better in the LSNNS group (P <.001; Appendix Fig A5, online only). Body mass index, hemoglobin, and total protein were significantly higher in the LSNNS group (P <.001, P <.001, P <.001, respectively).

DISCUSSION

In this prospective multicenter trial, LSNNS did not show noninferiority to LSG for 3y-DFS with a 5% margin. However, after rescue surgery for recurrence or metachronous gastric cancer in the LSNNS group, 3y-DSS and 3y-OS were not different in both groups. Conditions requiring rescue surgery are not life-threatening and can be resolved in most cases after stomach-preserving LSNNS.

The results of previous studies on the feasibility and safety of stomach-preserving LSNNS in patients with EGC are controversial. Numerous small single-center trials found a wide range of SNB false-negative rates and produced inconsistent results.11,22,23 Two relatively large multicenter trials from Japan also reported contradictory results.12,13 In their multicenter feasibility study, Miyashiro et al14 reported a high false-negative rate of 46%, mainly because of problems with intraoperative histologic examination, which is an obstacle for the clinical adoption of LSNNS. In another multicenter feasibility study, Kitagawa et al15 reported a low false-negative rate of 7%, which is encouraging. Analysis of the four false-negative cases in their study showed that most cases involved tumors that had invaded the muscle layer and were > 4 cm in diameter. They also found that the missed metastatic lymph nodes were located at the same sentinel basin and, therefore, recommended sentinel basin dissection to reduce the SNB false-negative rate. In this study, one patient had lymph node recurrence after sentinel basin dissection, resulting in a false-negative rate of 3.2%. This patient was treated using rescue surgery and adjuvant chemotherapy. However, the patient developed distant metastasis and ultimately died.

There are doubts about the curative ability of primary tumor resection by ER, wedge resection, and segmental resection compared with that of standard gastrectomy. Park et al14 investigated 100 patients who underwent LSNNS in the phase II study and reported a 3-year relapse-free survival rate of 96.0%. In that study, there were three cases of intragastric recurrence; one patient refused rescue surgery, developed distant metastasis, and died of liver metastasis.

Another important issue is the development of metachronous gastric cancer in the residual stomach after stomach-preserving surgery. In some patients in the previous study, metachronous gastric cancer developed during the follow-up period after ER when the whole stomach was preserved; its incidence is non-negligible, and close monitoring and additional treatment are required.24 Several factors, such as Helicobacter pylori infection, have been reported to be related to the development of metachronous gastric cancer after ER, and it has been hypothesized that these factors also exist after stomach-preserving LSNNS.25

In this study, the conversion rate to gastrectomy after stomach-preserving LSNNS was 9% (19/210). The reasons for gastrectomy were risk of advanced disease, according to the protocol, in 10 patients; stenosis in two patients; recurrence in three patients; and metachronous gastric cancer in four patients.5,26 Considering that the gastrectomy...
conversion rate is 12%-28% after ER, LSNNS may be another acceptable option for stomach preservation.27,28

The postoperative complications showed similar results between the LSNNS and LSG groups.26 Although the reduced range of LND and gastric resection of LSNNS, thorough surgical techniques and learning curves are required as the LSG.

Several function-preserving surgeries have undergone trials. However, their ability to improve QOL remains controversial.29 Therefore, the main objective of stomach-preserving LSNNS is the improvement in QOL after gastrectomy in patients with EGC. The QOL of the LSNNS group showed better physical function and many postoperative symptoms. Not only QOL but also nutritional parameters were also improved after LSNNS than LSG as expected.

Widespread adoption of a new procedure, such as LSNNS, is another issue in real-world clinical practice. There is a learning curve for new procedures, and quality assurance is necessary for safety.30,31 Before our multicenter phase III trial, all investigating institutions participated in a quality control study to overcome the learning curve and standardize the procedure. This process is necessary and facilitates the general adoption of this new procedure by surgeons.

This study has several limitations. First, the eligibility criteria of this trial included the expanded indications for ER, which were previously defined.4,5 Therefore, more patients with
EGC, who meet the expanded indications for ER, should have been included in this study. Second, patients in whom LSNNS is indicated are mainly concentrated in areas with a high prevalence of EGC. Therefore, the practice of LSNNS may be limited geographically. Third, full analysis was performed mainly in the modified intention-to-treat population instead of intention-to-treat because most of the excluded patients did not receive the surgery.

In conclusion, LSNNS did not show noninferiority to LSG for 3y-DFS, with a 5% margin. However, after rescue surgery for recurrence or metachronous gastric cancer in the LSNNS group, 3y-DSS and 3y-OS were not different between the two groups. In addition, LSNNS had better long-term QOL and nutrition than LSG. The intense and sophisticated follow-up is mandatory to adopt LSNNS.

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Primary tumor, 2.1-cm sized poorly differentiated pT1b
Sentinel basin nodes at station 4d
Recurred lymph nodes at station 6, 7, 11p
1 year later after laparoscopic sentinel node navigation surgery

**FIG A1.** Details of a case with lymph node recurrence after laparoscopic sentinel node navigation surgery. A schematic of laparoscopic sentinel node navigation surgery in a case with lymph node recurrence. The primary tumor was located at the proximal antrum, greater curvature, and anterior wall side and was 2.1 cm in size, poorly differentiated, and pT1b. The sentinel basin was detected at lymph node station 4d, and there were three negative SBNs. Laparoscopic wedge resection was performed. Lymph node recurrence around the left gastric artery was suspected on follow-up computed tomography 1 year after surgery. Curative laparoscopic distal gastrectomy revealed metastatic lymph nodes at lymph node stations 6 (2/2), 7 (1/2), and 11p (1/3). Consecutive adjuvant chemotherapy was also administered. Multiple distant metastases developed 1.5 years after laparoscopic distal gastrectomy. The patient died 3 years after initial laparoscopic sentinel node navigation surgery, although palliative chemotherapy was administered.
FIG A2. Results of EORTC QLQ-C30 (function scale): (A) global health, (b) physical function, (C) role function, (D) emotional function, (E) cognitive function, and (F) social function. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LSG, laparoscopic standard gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery.
FIG A3. Results of EORTC QLQ-C30 (symptom scale): (A) fatigue, (B) nausea/vomiting, (C) pain, (D) dyspnea, (E) insomnia, (F) appetite loss, (G) constipation (H) diarrhea, (I) financial difficulties, and (J) total score of EORTC C30. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LSG, laparoscopic standard gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery.
**FIG A4.** Results of EORTC QLQ-STO22: (A) dysphagia, (B) pain, (C) reflux, (D) eating restriction, (E) anxiety, (F) dry mouth, (G) taste, (H) body image, (I) hair loss, and (J) total Score of EORTC STO22. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LSG, laparoscopic standard gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery; STO22, EORTC stomach module.

**FIG A5.** Summary score of EORTC (A) QLQ-C30 and (B) STO22. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LSG, laparoscopic standard gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery; STO22, EORTC stomach module.
| Recurrence Site                  | Group       | Initial Operation | Postoperative Pathology                                                                 | Interval | Treatment for Recurrence               | Survival Status |
|---------------------------------|-------------|-------------------|-----------------------------------------------------------------------------------------|----------|----------------------------------------|----------------|
| Primary tumor                   | LSNNS       | LW                | Adenocarcinoma, tubular, poorly differentiated 3.6 × 2.5 cm Muscularis mucosa Margin 0.8, 1.0, 2.4, 0.6 cm Sentinel nodes 0/5 pT1aN0 | 6 months | LDG                                    | Survived       |
| Primary tumor                   | LSNNS       | LW                | Signet ring cell carcinoma 2.7 × 2.4 cm Submucosa 1 (0.07 cm) Margin 0.6, 0.4, 0.6, 0.5 cm Sentinel nodes 0/23 pT1bN0 | 3 years  | LDG                                    | Survived       |
| Lymph node                      | LSNNS       | LW                | Signet ring cell carcinoma 2.1 × 1.9 cm Submucosa 3 (0.14 cm) Margin 0.9, 1.0, 1.2, 1.0 cm Sentinel nodes 0/3 pT1bN0 | 1 year   | LDG and adjuvant chemotherapy          | Cancer mortality |
| Distant (peritoneal)            | LSG         | LDG               | Signet ring cell carcinoma 2.5 × 2.0 cm Submucosa 2 (0.67 cm) Margin 6.0, 9.0 cm Lymph nodes 4/58 pT1bN2 | 7 months | Palliative chemotherapy                | Survived       |
| Distant (peritoneal)            | LSG         | LDG and adjuvant chemotherapy | Signet ring cell carcinoma 6.5 × 5.0 cm Subserosa Margin 4.5, 4.7 cm Lymph nodes 11/23 pT3N3a | 3 years  | Palliative chemotherapy                | Survived       |
| Distant (para-aortic)           | LSNNS       | LDG (metastatic sentinel node) and adjuvant chemotherapy | Adenocarcinoma, tubular, poorly differentiated 2.2 × 2.0 Subserosa Margin 7.5, 9.5 cm Lymph nodes 1/26 pT3N1 | 9 months | Palliative chemotherapy                | Cancer mortality |
| Distant (para-aortic)           | LSNNS       | LW                | Adenocarcinoma, tubular, moderately differentiated 1.6 × 1.3 Submucosa 2 (0.07 cm) Margin 0.9, 0.8, 0.4, 1.2 cm Sentinel nodes 0/2 (ITC+) pT1bN0 | 2 years  | Palliative chemotherapy                | Survived       |
| Metachronous                    | LSNNS       | LW                | Signet ring cell carcinoma 2.2 × 2.0 cm Muscularis mucosa Margin 0.4, 1.6, 1.0, 1.4 cm Sentinel nodes 0/2 pT1aN0 | 1 year   | ESD                                    | Survived       |
| Metachronous                    | LSNNS       | LW                | Signet ring cell carcinoma 2.2 × 1.5 cm Lamina propria Margin 2.5, 0.6, 0.6, 0.8 cm Sentinel nodes 0/13 pT1aN0 | 2.5 years | LDG                                    | Survived       |
| Metachronous                    | LSNNS       | LW                | Signet ring cell carcinoma 3.4 × 2.2 cm Muscularis mucosa Margin 0.3, 0.1, 0.4, 0.5 cm Sentinel nodes 0/2 pT1aN0 | 3 years  | LDG                                    | Survived       |

(continued on following page)
| Recurrence Site | Group     | Initial Operation | Postoperative Pathology                                                                 | Interval | Treatment for Recurrence | Survival Status |
|-----------------|-----------|-------------------|----------------------------------------------------------------------------------------|----------|--------------------------|-----------------|
| Metachronous    | LSNNS     | LW                | Adenocarcinoma, tubular poorly differentiated 1.3 × 1.2 cm Submucosa 3 (0.3 cm) Margin 1.1, 4.5, 1.0, 2.3 cm Sentinel nodes 0/14 pT1bN0 | 6 months | LTG                      | Survived        |
| Metachronous    | LSNNS     | LW                | Adenocarcinoma, tubular poorly differentiated 3.0 × 2.4 cm Submucosa 2 (0.15 cm) Margin 0.4, 0.6, 0.2, 0.1 cm Sentinel nodes 0/17 pT1bN0 | 3 years  | LTG                      | Survived        |

Abbreviations: ESD, endoscopic submucosal dissection; ITC, isolated tumor cell; LDG, laparoscopic distal gastrectomy; LSG, laparoscopic standard gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery; LTG, laparoscopic total gastrectomy; LW, laparoscopic wedge resection.