J Gastric Cancer. 2019 Jun;19(2):157-164
https://doi.org/10.5230/jgc.2019.19.e12
pISSN 2093-582X·eISSN 2093-5641

jgc Journal of Gastric Cancer

Original Article

Prospective Multicenter Feasibility Study of Laparoscopic Sentinel Basin Dissection after Endoscopic Submucosal Dissection for Early Gastric Cancer: SENORITA 2 Trial Protocol

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Received: Oct 20, 2018
Revised: Jan 9, 2019
Accepted: Mar 4, 2019

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ABSTRACT

Purpose: Although standard radical gastrectomy is recommended after noncurative resection of endoscopic submucosal dissection (ESD) for early gastric cancer in most cases, residual tumor and lymph node metastasis have not been identified after surgery. The aim of this study is to evaluate the feasibility of sentinel node navigation surgery after noncurative ESD.
Materials and Methods: This trial is an investigator-initiated, multicenter prospective phase II trial. Patients who underwent ESD for clinical stage T1N0M0 gastric cancer with noncurative resections were eligible. Qualified investigators who completed the prior phase III trial (SENORITA 1) are exclusively allowed to participate. In this study, 2 detection methods will be used: 1) intraoperative endoscopic submucosal injection of dual tracer, including radioisotope and indocyanine green (ICG) with sentinel basins detected using gamma-probe; 2) endoscopic injection of ICG, with sentinel basins detected using a fluorescence imaging system. Standard laparoscopic gastrectomy with lymphadenectomy will be performed. Sample size is calculated based on the inferior confidence interval of the detection rate of 95%, and the calculated accrual is 237 patients. The primary endpoint is detection rate, and the secondary endpoints are sensitivity and postoperative complications.
Conclusions: This study is expected to clarify the feasibility of laparoscopic sentinel basin dissection after noncurative ESD. If the feasibility is demonstrated, a multicenter phase III trial will be initiated to compare laparoscopic sentinel node navigation surgery versus laparoscopic standard gastrectomy in early gastric cancer after endoscopic resection.

Trial Registration: ClinicalTrials.gov Identifier: NCT03123042

Keywords: Gastric cancer; Sentinel lymph node; Endoscopic submucosal dissection

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Funding
This research was supported by the National Cancer Center, Republic of Korea (Grant 1710160-2).

Author Contributions
Conceptualization: E.B.W., R.K.W.; Funding acquisition: E.B.W., R.K.W.; Investigation: E.B.W., Y.H.M., M.J.S., C.I., P.J.H., J.M.R., H.H., K.Y.W., P.Y.K., R.K.W.; Methodology: E.B.W., N.B.H., R.K.W.; Writing - original draft: E.B.W.; Writing - review & editing: Y.H.M., M.J.S., C.I., P.J.H., J.M.R., H.H., K.Y.W., P.Y.K., N.B.H., R.K.W.

Conflict of Interest
The authors declare that they have no competing interests. The funder has had no role in any of the following: the design of the study, data collection, analysis, and interpretation, and was not involved in preparing the manuscript.

INTRODUCTION

To date, a number of feasibility studies for sentinel node mapping in gastric cancer have been conducted and have produced favorable results in terms of detection rate, accuracy, and sensitivity. A recent meta-analysis concluded that sentinel lymph node mapping in gastric cancer is technically feasible with acceptable sensitivity. A Japanese multicenter phase II clinical trial also came to a similar conclusion with a false-negative rate of 7% [1,2].

To confirm the oncological safety of sentinel basin dissection for patients with gastric cancer, the Sentinel Node Oriented Tailored Approach (SENORITA) 1 trial, which is a multicenter randomized controlled phase III trial with a noninferiority design, is being performed in Korea [3]. In this study, the enrolled patients are randomized to either laparoscopic stomach-preserving surgery with sentinel basin dissection or standard gastrectomy, and 3-year disease-free survival will be evaluated as the primary endpoint. The enrollment was completed in March 2017, and now regular follow-up data is being collected.

In Korea, the proportion of early gastric cancer is gradually increasing with the expansion of a national cancer screening program [4]. Frequency of endoscopic submucosal dissection (ESD) has also been increasing, and the indications for ESD have been expanding. When ESD is considered as noncurative at the pathological evaluation, additional surgery is recommended because of the possibility of lymph node metastasis [5,6]. However, in recent studies, only 5%–10% of patients were revealed to have lymph node metastasis after the additional gastrectomy, and approximately 90% patients had neither residual tumor nor lymph node metastasis [7-10]. If the absence of lymph node metastasis is identified using sentinel node mapping, unnecessary gastrectomy could be avoided.

In this study, we aim to evaluate the feasibility of laparoscopic sentinel basin dissection in patients who underwent noncurative ESD for early gastric cancer.

MATERIALS AND METHODS

Sites and registration

The SENORITA 2 trial is an investigator-initiated, prospective multicenter phase II feasibility study (**Fig. 1**). This study involves 7 hospitals (National Cancer Center, Dongnam Institute of Radiological and Medical Science, Soonchunhyang University Bucheon Hospital, Gyeongsang National University Hospital, Chonnam National University Hwasun Hospital, Ajou University Hospital, and Samsung Medical Center), and all investigators participated in the prior multicenter randomized phase III clinical trial (SENORITA 1 trial, NCT01804998).

The Institutional Review Board (IRB) of the National Cancer Center, Korea has approved this study (IRB No. NCC2017-0059). This study has also been approved by the local ethical committee of each participating institute (Dongnam Institute of Radiological and Medical Science [D-1705-004-001], Soonchunhyang University Bucheon Hospital [SCHBC-2017-09-012-001], Gyeongsang National University Hospital [GNUH 2017-04-006], Chonnam National University Hwasun Hospital [CNUHH-2017-094], Ajou University Hospital [AJIRB-MED-THE-17-144], and Samsung Medical Center [SMC-2017-05-003-002]). Written informed consent will be obtained from each patient before enrollment. This

https://doi.org/10.5230/jgc.2019.19.e12

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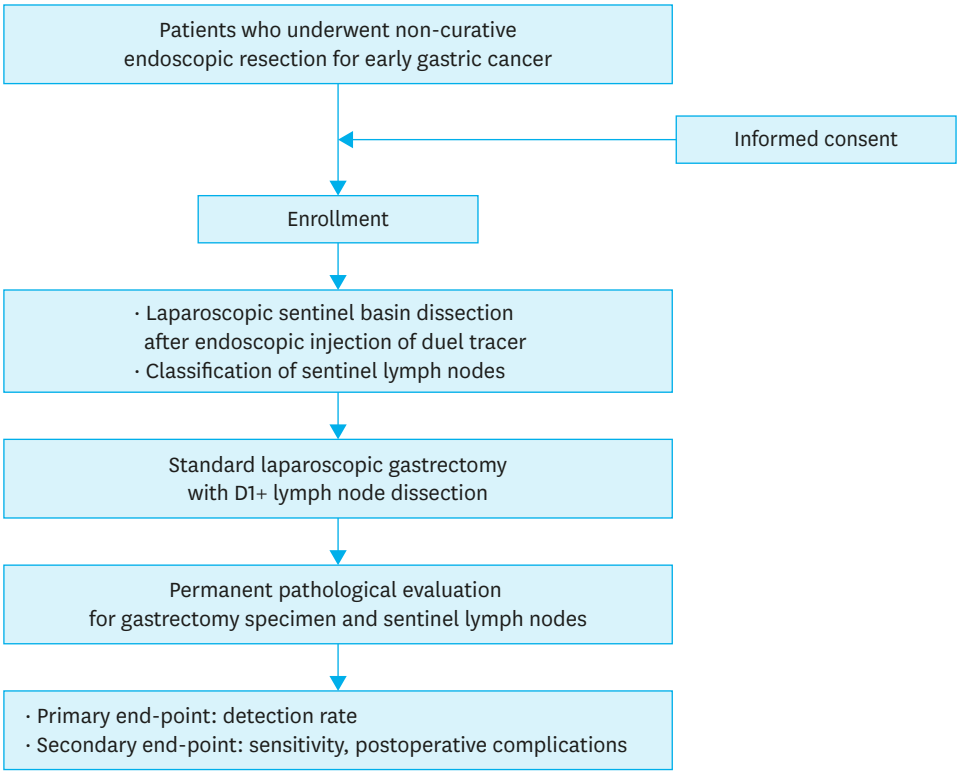

Fig. 1. Study scheme of the SENORITA 2 trial.
SENORITA = Sentinel Node Oriented Tailored Approach.

trial was registered at the National Institutes of Health (NIH) ClinicalTrial.gov database (NCT03123042) on April 10, 2017.

Trial status

The first participant in this trial was enrolled on April 5, 2017, and this trial is ongoing and actively recruiting. The total of enrollment period is presumed to be 3 years, and the date of anticipated completion is January 28, 2020.

Study population and eligibility criteria

The patient inclusion and exclusion criteria are as follows:

1. Inclusion criteria
   1) Patient has undergone ESD for early gastric cancer, and the tumor was determined to be within the scope of the expanded criteria for ESD. The expanded criteria for endoscopic resection are as follows.
      - Criterion I: intramucosal tumor without ulcerative findings and of differentiated type with size >2 cm
      - Criterion II: intramucosal tumor with ulcerative findings and of differentiated type with size ≤3 cm
      - Criterion III: intramucosal tumor without ulcerative findings and of undifferentiated type with size <2 cm
      - Criterion IV: submucosal invasion <500 μm and of differentiated type with size ≤3 cm
   2) Eastern Cooperative Oncology Group (ECOG) performance scale 0 or 1
   3) No age limitation if the patient is available for gastrectomy

https://doi.org/10.5230/jgc.2019.19.e12

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2. Exclusion criteria
   1) Patient is inoperative due to severe cardiovascular or pulmonary disease
   2) Patient has had previous gastric surgery
   3) Patient has undergone previous upper abdomen surgery, except cholecystectomy, or radiation therapy on the upper abdomen
   4) Patient has hypersensitivity to any medicine
   5) Patient is pregnant

Intervention

After induction of anesthesia, 5 trocars are placed in the abdomen including the umbilicus. Partial omentectomy and opening and dissection of the lesser sac are performed to examine stained lymph nodes around the stomach. The proximal jejunum is clamped using a laparoscopic bowel grasper to prevent passage of gas into the small bowel during intraoperative endoscopy.

Detection of sentinel basin

In this study, 2 detection methods will be available. One is to use a dual tracer including a radioisotope and indocyanine green (ICG), and the other is ICG fluorescence imaging. In the former method, a 4-mL volume of the dual tracer, which is a mixture of ICG (Diagnogreen®, Daiichi Sankyo Co., Ltd., Tokyo, Japan; 2 mL, 5 mg/mL) and radiolabeled phytate (^{99m}Tc-phytate; 2 mL, 0.1 mCi/mL), is injected into the submucosal layer in 4 quadrants of the ESD scar (1 mL for each quadrant) via intraoperative gastroscopy (**Fig. 2**). Fifteen minutes after the tracer injection, the sentinel basins containing sentinel nodes are identified based on green color staining or radioactivity of laparoscopic gamma probe (green or hot, respectively) (**Fig. 3A**) [11]. In the latter method, a 2-mL volume of ICG (5 mg/mL) is injected (0.5 mL for each quadrant), and the sentinel basins are identified using an infrared camera system (NOVADAQ, Stryker, Kalamazoo, MI, USA). ICG-stained lymph nodes exhibiting green/blue/bright fluorescence are considered the sentinel nodes (**Fig. 3B-D**). Laparoscopic basin dissection is carefully performed, and then the harvested sentinel basins are dissected to isolate lymph nodes at the back table. All the isolated lymph nodes from the sentinel basins, defined as sentinel basin nodes (SBNs), will be classified into 4 groups: hot nodes (HN: radioactive nodes), green nodes (GN: stained nodes), both hot and green nodes (HGN), and basin nodes (BN: nodes within the sentinel basins but neither hot nor green).

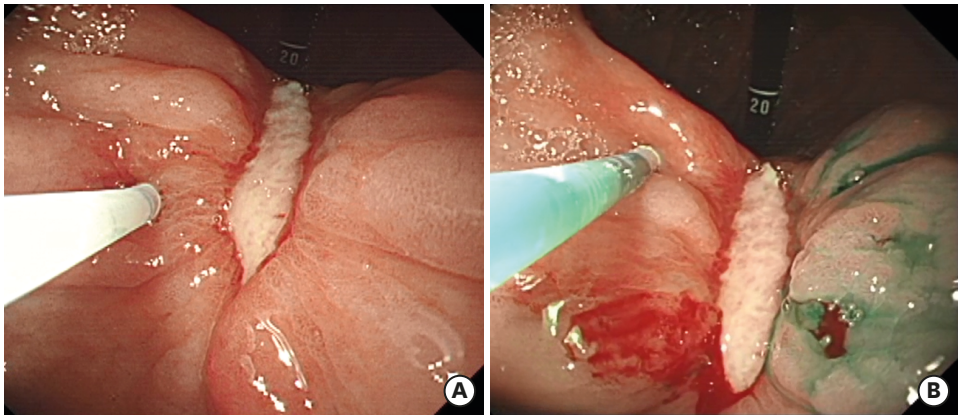

Fig. 2. First endoscopic injection of dual tracer around the ESD ulcer scar (A). Final endoscopic injection around the ESD ulcer scar. Elevated mucosa around the ESD scar by tracer injection is observed (B).
ESD = endoscopic submucosal dissection.

https://doi.org/10.5230/jgc.2019.19.e12

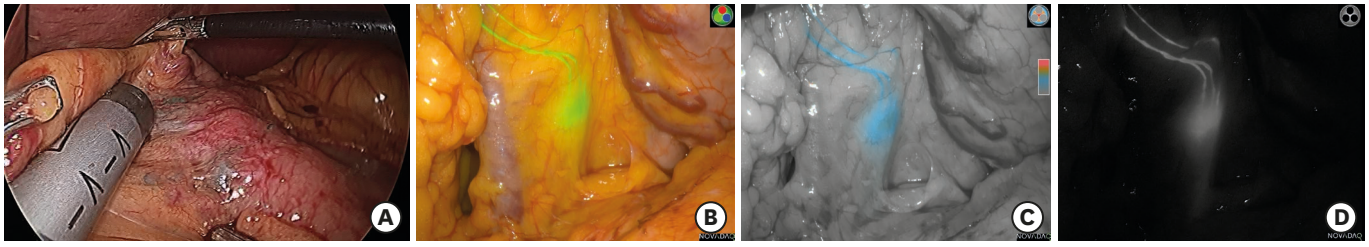

Fig. 3. Intraoperative identification of sentinel basins. Green-stained basin after injection of dual tracer (A) and indocyanine green fluorescence imaging (B-D). Lymphatic vessels draining the tumor and sentinel node are visualized by green (B), blue (C), and bright fluorescence (D).

The dissected nodes will be labeled with the respective lymph node station numbers and sent to the pathologist for definitive histological evaluation.

Conventional gastrectomy

After sentinel basin dissection, all patients will undergo standard laparoscopic gastrectomy, which includes laparoscopic distal gastrectomy, laparoscopic total gastrectomy, laparoscopic proximal gastrectomy, and laparoscopic pylorus-preserving gastrectomy, with D1+ lymphadenectomy [5].

Pathological evaluation for sentinel lymph nodes

The retrieved sentinel lymph nodes will be examined by hematoxylin and eosin (H&E) staining, and 1 representative section of the paraffin-embedded SBN will be evaluated.

Outcome measurement

The primary endpoint of this trial is the detection rate of the sentinel lymph node. The detection rate is defined as the proportion of patients having lymph nodes in the sentinel basin among all enrolled patients. The secondary endpoints are sensitivity and postoperative complications within 30 days after surgery. Sensitivity is defined as the proportion of patients whose metastatic lymph nodes are located in the sentinel basin among all patients who had metastatic lymph nodes. Postoperative complications are classified by the Clavien-Dindo severity classification [12].

Data management and safety assessment

All patient data collected during this trial will be managed using an electronic case report form (eCRF) in a web-based central platform (Velos eResearch System, Velos, Inc., Fremont, CA, USA) at the Clinical Research Coordination Center within the National Cancer Center, Korea. The management team will review the eCRFs, and queries will be sent out to each participating institute regularly. Data monitoring will also be conducted by way of site visits. The data will be managed and analyzed according to the study protocol.

When serious adverse events occur during sentinel basin evaluation, it will be documented in the medical records as well as in the eCRF and reported to the IRB by the responsible investigator in accordance with the local regulations. A serious adverse event is defined as a complication grade III or above based on the Clavien-Dindo classification system [12].

Statistical analysis

Sample size calculation

The required sample size was calculated based on a hypothesis that the detection rate of sentinel lymph nodes after ESD is similar to the detection rate of sentinel lymph nodes for primary gastric cancer without previous ESD. Recent meta-analyses revealed a 94%–98%

https://doi.org/10.5230/jgc.2019.19.e12

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sentinel lymph node detection rate in a pooled analysis [1,13]. Therefore, we assumed a 95% detection rate and 3% lower confidence limit with 0.05 type I error and 80% statistical power. As a result, we calculated that a sample size of 237 is required.

Analysis variables

The detection rate, the primary endpoint of this trial, will be calculated as the number of cases having lymph nodes in the sentinel basin, divided by the total number of enrolled patients. Whether the detection rate of sentinel lymph node exceeds 92%, which is 3% of the lower confidence limit, will be evaluated.

Sensitivity, the secondary endpoint, will be calculated as the number of cases whose metastatic lymph nodes are located in the sentinel basin, divided by the number of patients who had metastatic lymph nodes. Postoperative complications will be determined by the proportion of patients with complications among all enrolled patients and further categorized into each grade according to the Clavien-Dindo classification system for evaluation.

Continuous variables are shown as the means±standard deviations or medians with interquartile ranges, and categorical variables are presented as proportions. Differences will be tested using the Student's t-test or the Wilcoxon rank-sum test for continuous variables, and the χ^2 test or Fisher's exact test will be used for categorical variables.

Data analyses will be conducted using SAS version 0 (SAS Institute Inc., Cary, NC, USA). P-values less than 0.05 will be considered to be statistically significant.

DISCUSSION

For the clinical application of sentinel basin mapping, an intact lymphatic channel is a prerequisite. Injected tracer can run through the intact lymphatic channel and reach the metastatic lymph node. If some lymphatic channels are damaged and cut off, the tracer will follow an alternative path and can arrive at a nonmetastatic lymph node. During ESD, all soft tissues including lymphatic channels around tumors are dissected, and the remnant tissue is transformed by the inflammatory reaction and wound healing process. These changes can make the lymphatic network more complex and likely to affect lymphatic flow. Therefore, many investigators doubt that the concept of sentinel node mapping is applicable to patients who have undergone noncurative endoscopic resection.

Nevertheless, some investigators have performed sentinel basin mapping in patients who underwent noncurative ESD and have shown favorable results [14,15]. In 2 previous studies, both the detection rate and sensitivity were 100% (detection rate, 16/16 and 40/40; sensitivity, 2/2 and 1/1), and there were no false-negatives. These findings suggest that gross lymphatic channels flowing toward metastatic nodes may be preserved in patients after endoscopic resection and indicate feasibility of sentinel node navigation surgery for such a patient. However, the 2 studies had small sample sizes with insufficient statistical power. The present study (SENORITA 2 trial), a multicenter prospective clinical trial, could confirm the feasibility of sentinel basin mapping in such patients.

Dual tracer, which is a combination of radioisotope and dyes, has been recommended to decrease the false-negative rate in sentinel node navigation surgery [1,16]. In the SENORITA 1

https://doi.org/10.5230/jgc.2019.19.e12

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trial, we used ^{99m}Tc-human serum albumin and ICG as the dual tracer. However, ^{99m}Tc-human serum albumin is no longer available in Korea and has been replaced with ^{99m}Tc-phytate in the SENORITA 2 trial. Therefore, we will evaluate whether ^{99m}Tc-phytate works well and results in similar sentinel basin detection rates compared with the SENORITA 1 trial, using several patients as preliminary cases.

One limitation of this study is that the primary endpoint is not sensitivity but detection rate. Sensitivity (or false negative rate) is the most important index to evaluate the feasibility of sentinel basin dissection. The crucial point is how many patients who had metastatic lymph nodes would be missed by sentinel evaluation. However, too large a sample size is needed to get sensitivity with sufficient statistical power because the incidence of patients having metastatic lymph node is less than 10% after noncurative endoscopic resection. Therefore, considering practical availability, investigators decided the detection rate as the primary endpoint for this trial.

In conclusion, the proposed SENORITA 2 trial represents a multicenter prospective feasibility study to elucidate the feasibility of laparoscopic sentinel basin mapping in patients who underwent noncurative endoscopic resection. We believe that this trial will significantly contribute to the extension of sentinel navigation surgery and function-preserving surgery. Finally, unnecessary additional gastrectomy could be reduced after noncurative ESD and improve patients' quality of life.

ACKNOWLEDGMENTS

We would like to acknowledge all endoscopists and pathologists from all of the participating institutions for their contribution in this ongoing clinical trial.

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