

Review Article



Recent Advances in Sentinel Node Navigation Surgery for Early Gastric Cancer

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Conflicts of Interest

No potential conflict of interest relevant to this
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ABSTRACT

Maintaining the postoperative quality of life (QOL) while ensuring curability without overtreatment is important in the treatment of early gastric cancer. Postoperative QOL is anticipated to be maintained through minimally invasive function-preserving gastrectomy in early gastric cancer. The concept of the sentinel lymph node (SN) basin is essential to maintain the curability of early gastric cancer using minimally invasive function-preserving gastrectomy. However, additional resection after surgery is difficult to perform in gastric cancer. Thus, the SN basin theory is important. Recently, a multicenter randomized phase III trial in South Korea (SENIORITA trial) proved that laparoscopic sentinel node navigation surgery (LSNNS) for stomach preservation results in better postoperative QOL compared with standard gastrectomy in patients with early gastric cancer. LSNNS contributes to patients' QOL based on the concept that curability is not impaired. A multicenter nonrandomized phase III trial is ongoing in Japan, and oncologic safety is expected to be demonstrated. LSNNS has been established as a treatment option for selected patients with early gastric cancer, and its application will become widespread in the future.

Keywords: Sentinel lymph node; Minimally invasive surgery; Gastric cancer

INTRODUCTION

Gastric cancer is the fifth most common malignancy and the main cause of cancer-related mortality worldwide owing to its high malignant potential and poor prognosis. It is widely prevalent in Eastern Asian countries, including Japan, South Korea, and China [1]. According to the Japanese gastric cancer treatment guidelines, the standard treatment for advanced gastric cancer is gastrectomy with D2 lymphadenectomy [2]. However, advancements in perioperative chemotherapy have improved long-term outcomes for advanced gastric cancer [3]. The quality of life (QOL) of patients may be compromised in the pursuit of curability in advanced gastric cancer treatment. Although the rate of lymph node (LN) metastasis in early gastric cancer is low, the decreased QOL of patients after standard gastrectomy needs to be addressed.

Sentinel lymph node (SN) biopsy was initially applied in melanoma and extended to solid tumors such as breast cancers to predict LN metastasis from the primary tumor [4,5]. Later

it was also used in gastric cancer as intraoperative SN biopsy reduces unnecessary radical lymphadenectomy and improves patient QOL. To date, several studies have been conducted to prove the feasibility of the SN concept in gastric cancer [6,7]; however, with controversial applications. Recently, the results of a phase III trial (SENORITA trial) investigating the non-inferiority of laparoscopic sentinel node navigation surgery (LSNNS) compared with laparoscopic standard gastrectomy (LSG) were reported [8]; thus, becoming the basis for future treatment strategies. Here we have reviewed the recent updates from the phase III trial and discussed the current issues of sentinel node navigation surgery (SNNS) in early gastric cancer.

CONCEPT OF SENTINEL NODE AND BASIN THEORY

The SN is considered the first LN to receive lymphatic drainage from the primary tumor and metastasis from the primary lesion [9,10]. If this theory is correct, all regional LNs can be predicted to be negative for metastasis when the SN is pathologically negative for cancer. Radical LN dissection can be omitted more than necessary by performing intraoperative SN mapping and biopsy based on the SN concept [11].

In 1992, SN navigation surgery using patent blue as a tracer was first applied to patients with melanoma [10]. Unnecessary radical lymphadenectomy can be omitted in the case of negative SN metastasis by performing minimally invasive surgery based on the SN concept, thus preventing various postoperative complications [11]. The SN concept has since been extended to patients with breast cancer and other solid tumors [12,13]. Several studies investigating the SN concept for early gastric cancer showed acceptable SN detection rate and accuracy in predicting LN metastasis status [7,9]. A large meta-analysis of 38 studies including 2,128 patients with early-stage gastric cancer showed an SN detection rate and LN status diagnostic accuracy of 94% and 92%, respectively [14].

SN mapping was initiated in Japan in the 1990s to accurately diagnose whether a patient had LN metastasis during surgery and to develop an individualized surgical treatment for early gastric cancer [15-18]. A dual-tracer method combining a radioisotope and blue dye was proposed to evaluate SN distribution [19]. Lymphatic drainage pathways are highly diverse in gastric cancer compared with malignant melanoma and breast cancer [20]. Lee et al. found skip metastases in 462 patients with pT1 or T2 gastric cancer, indicating that drainage LNs are difficult to predict based on the primary tumor location [21]. The results demonstrate the importance of preoperative or intraoperative detection and assessment of drainage LNs. Kinami et al. [22] defined five independent lymphatic basins per feeding artery surrounding the stomach to classify lymphatic pathways. Then, the efficacy of SN biopsy was investigated on a lymphatic basin. Thus, even though LN metastasis was detected in non-SN, LN metastasis can be eradicated in SN biopsy as long as non-SN with metastasis is included in the same lymphatic basin as SN [20]. Therefore, the SN basin theory has rescued false-negative cases. The SN basin theory also has the advantage of covering uncertainties in intraoperative pathological diagnosis. Basin resection may also remove cancer cells in primary lymphatic vessels that connect the primary tumor and the SN. Additional resection after surgery is relatively easy to perform in breast cancer and melanoma which are located on the body surface; however, difficult to perform in gastric cancer, which is located in the abdominal cavity. Thus, the SN basin theory is important.

Table 1. Prospective multicenter trials on sentinel node navigation surgery for gastric cancer

Author (yr)	No. of cases (total)	cT factor	Tracers	SN detection rate (%)	Assessment of the SN concept (%)		
					Sensitivity	False-negative rate	Accuracy rate
Kitagawa et al. (2013) [19]	397	cT1-T2	Dual (radioisotope using tin colloid and dye)	97.5 (387/397)	93 (53/57)	7 (4/57)	99.0 (383/387)
Miyashiro et al. (2014) [28]	440	cT1	Dye	97.7 (304/311)	86 (24/28)	14 (4/28)	98.7 (300/304)
Lee et al. (2015) [25]	108	cT1-T2	Dual (radioisotope using human serum albumin and dye)	92.6 (100/108)	100 (10/10)	0 (0/10)	100 (100/100)

SN = sentinel node.

In the 2000s, the Japanese Society of SNNS conducted a prospective multicenter trial to demonstrate the feasibility of SN mapping and biopsy in early gastric cancer (**Table 1**) [19]. In this study, SN mapping was performed by using a dual-tracer technique for 397 patients with previously untreated cT1 or cT2 gastric cancer with a primary lesion <4 cm in tumor diameter. The study resulted in an SN detection rate of 97.5% and nodal metastatic status diagnostic accuracy of 99.0%. False-negative SN biopsy was observed in four (7.0%) out of 57 patients. Among them, three patients had primary tumors with pT2 or >4 cm in size. The results of this study established the SN basin concept and cT1N0M0 with primary lesion <4 cm in tumor diameter without indication for endoscopic submucosal dissection (ESD) became the current indication for SN in Japan.

After reviewing 385 patients diagnosed with cT1N0 or cT2N0 gastric cancer, Niihara et al. confirmed that the SN concept was secured in cT1 with a tumor diameter of 4 cm or lesser [23]. In another study, Shimada et al. [24] reported that the common hepatic artery LN had lymphatic flow from the right and left gastric artery basins or right gastroepiploic artery basin. Therefore, the location of the SN basin is difficult to predict based on the preoperative tumor location.

The SN basin area is slightly different between Japan and South Korea. In Japan, gastric lymphatic basins are classified into five directions along the main gastric feeding arteries as follows: left gastric artery (LN station 1, 3a, and 7); right gastric artery (LN station 3b, 5, and 8a); left gastroepiploic artery (LN station 4sa and 4sb); right gastroepiploic artery (LN station 4d and 6); and posterior gastric artery (LN station 11) [22]. In contrast, gastric lymphatic basins are classified into 10 nodal stations in South Korea as follows: (LN station 1, 3, 4sa or 4sb, 4d, 5, 6, 7, 8a, 9, and 11) [25].

SN MAPPING DURING SNNS

A Japan Clinical Oncology Group study (JCOG0302) used a single-tracer method with indocyanine green (ICG) in a clinical trial (**Table 1**). The results showed a high false-negative rate of 46.4%. The high false-negative rate was attributed to the single-tracer method, which had a low SN detection rate, and direct subserosal injection of ICG, which could not be injected accurately into the primary tumor. However, the false-negative rate decreased to 14% when additional sections were used for pathological assessments. This decrease was probably owing to the heterogeneous distribution of metastatic foci in LNs [26,27]. Several studies concluded that intraoperative histological examination using only one plane is an inappropriate method for the clinical application of SN biopsy and that underestimation of the learning curve of only five patients may negatively affect the high false-negative rate [28,29].

The endoscopic dual-tracer method combining a radioisotope and blue dye was developed for detecting SN with high sensitivity during surgery in Japan (**Table 1**) [30,31]. On the day

before surgery, a solution of technetium-99 m tin colloid is injected using an endoscopic puncture needle into the four quadrants of the submucosa surrounding the primary cancer lesion. The tracer injected from the mucosal side is considered more accurate than that from the submucosal side. Among various commonly available radiotracers such as tin, phytic acid, and sulfur nanocolloids, tin colloids have been preferentially used owing to their large particle size and low false-negative rate [17,32]. Additionally, this trial recommended 30 cases for a reasonable learning curve.

In South Korea, human serum albumin has been used as radiotracers (**Table 1**) [25]. ICG and isosulfan blue are currently used as blue dyes [20]. Previous studies demonstrated that a combination of radioisotopes and dyes can increase the rate of SN identification and accuracy of SN biopsies [30,33]. Therefore, dual-tracer methods using radiocolloids and visible dyes have become the mainstay for SN detection.

An image-guided mapping procedure using ICG was introduced to overcome the limitations of conventional mapping procedures [29]. Initially, Nimura et al. [34] reported that infrared ray electronic endoscopy using ICG injection was an efficient procedure and showed acceptable results with a sensitivity of 100% for SN detection. Moreover, a prospective multicenter study conducted by Takahashi et al. [35] demonstrated the feasibility and high accuracy of infrared ICG imaging for SN detection.

ICG fluorescence imaging has emerged as a novel technique for the detection of SNs since the late 2000s [36]. It allows easy visualization of SNs and has shown promising results in a previous study [37]. Tajima et al. [38] performed SN mapping using ICG fluorescence imaging by utilizing an infrared camera system with specific light sources and detectors. The results demonstrated the feasibility and high sensitivity of ICG fluorescence imaging for intraoperative SN mapping in gastric cancer. At present, the feasibility and safety of ICG fluorescence imaging for SN detection have been reported by many studies [35,39-42]. Based on these promising results, ICG fluorescence imaging is expected to be widely applied in gastric cancer and other solid tumors and to replace radioisotope-based SN mapping methods [29].

Recently, ICG can be observed intraoperatively through robot-assisted surgery using the Da Vinci Robotic Xi™ Systems (Intuitive Surgical Inc., Sunnyvale, CA, USA) [43]. Given that ICG fluorescence imaging is expensive and the preoperative application only needs little organizational effort without requiring further equipment (FireFly™ camera Intuitive Surgical Inc.), the application of robot-assisted surgery has spread in gastric cancer surgery [44,45]. Thus, robot-assisted surgery will become the mainstay of SNNS for early gastric cancer in the future.

INTRAOPERATIVE PATHOLOGICAL DIAGNOSIS IN SNNS

The establishment of rapid and accurate intraoperative pathology is essential for determining SN metastasis [29]. Many studies have evaluated frozen sections of dissected SNs using hematoxylin and eosin (HE) staining. However, the sensitivity of HE-stained frozen sections is approximately 85% under optimal conditions, and 15%–20% of metastases may be missed during surgery [46]. A multicenter prospective study (JCOG0302) was also discontinued owing to high false-negative rates, which were attributed to the

unreliability of intraoperative single-plane frozen sectioning [47]. Therefore, efforts have been made to identify more reliable methods and increase the sensitivity of intraoperative pathology [29]. Alternative methods for intraoperative diagnosis have been reported, including immunohistochemical analysis, reverse transcription-polymerase chain reaction, and one-step nucleic acid amplification [48-50]. These methods target specific markers unique to gastric cancer, including cytokeratin (CK) 19, CK20, and carcinoembryonic antigen. These methods have improved the sensitivity of intraoperative pathology [51-54]. However, the drawbacks of molecular detection that can lead to false positives should be comprehended; for example, tumor cell heterogeneity can lead to the loss of typical markers targeted in the assay [20].

SN MAPPING AFTER ENDOSCOPIC RESECTION (ER)

Recently, the indications for ESD for early gastric cancer have expanded, and the number of cases undergoing ESD is increasing [2]. Along with this trend, the number of cases undergoing noncurative resection with ESD is increasing. Gastric cancer treatment guidelines recommend standard gastrectomy in noncurative cases [2]. In a previous study, patients who underwent additional surgery after noncurative ER had no LN metastasis; therefore, additional surgery with standard lymphadenectomy may be considered an overtreatment [55]. Hence, SN biopsy after noncurative ER might be a novel treatment option that can avoid standard surgery if there is no SN involvement [29].

Whether SN mapping is as feasible after endoscopic mucosal resection and ESD as before ER is ambiguous. These procedures may alter gastric lymph flow [56]. Several studies have evaluated the role of SN mapping after noncurative ESD, and the results showed a high detection rate and no false-negative nodules. These studies concluded that ER does not significantly affect the SN and that SN biopsy can be performed after noncurative ER [26,57]. Nohara et al. [58] investigated the lymph flow distribution before and after ESD in a porcine model. The results showed that the flow distribution remained unchanged in 83% of all lesions and that the lymphatic flow did not change in most parts of the stomach after ESD. Mayanagi et al. [57] conducted a retrospective data analysis and reported that ER did not significantly affect the SN basin. Arigami et al. [49] in a retrospective analysis from a single institution found that the SNs of patients who had previously undergone noncurative ER included metastatic LNs. The Japanese Society of SNNS conducted a retrospective multicenter study to validate the accuracy of the SN concept after ER. Individual data of 132 patients who underwent SN mapping after ER were collected from eight institutions. The SN basin distribution was compared between patients with gastric cancer who underwent ER (n=132) and those who did not (n=275). SNs were not identified in two patients who underwent single-tracer SN biopsies, with an SN detection rate of 98.5%. Among nine cases (6.8%) with LN metastasis, eight had metastatic LN within the SN, and one had non-SN metastasis within the SN basin. The diagnostic sensitivity of SN biopsy did not show a significant difference between the two groups (88.9% and 95.7% in the post-ER and non-ER groups; $P=0.490$). The diagnostic accuracy of LN metastasis on SN biopsy was 99.2% and 99.6% in the post-ER and non-ER groups ($P=0.539$), respectively. These findings revealed the feasibility of the SN concept in patients with gastric cancer who underwent prior ER [20,26,59]. In South Korea, the SENORITA2 trial (a prospective multicenter feasibility study) is ongoing and expected to clarify the feasibility of SNNS after noncurative ESD [60].

SURGICAL PROCEDURE COMBINING LOCAL RESECTION AND SN BIOPSIES

Various local resection patterns can be conceived under the condition that local resection of gastric cancer can be safely performed by SN biopsy. Aoyama et al. found that 53% of study participants were considered eligible for local resection based on SN distribution, especially if tumors were present in the upper third of the stomach [61].

Endoscopic cooperative full-thickness gastrectomy has been gradually attempted with the development of ER techniques and instruments [62]. Hiki et al. [62] introduced laparoscopic endoscopic cooperative surgery (LECS) for treating gastric subepithelial tumors. In this procedure, the precise location of the tumor and the appropriate line of resection can be obtained using intraluminal endoscopy [63]. However, LECS is limited by the risk of peritoneal contamination and cancer cell dissemination due to iatrogenic gastric perforation and gastric leakage.

Thus, Goto et al. [64] developed nonexposed endoscopic wall-inversion surgery (NEWS) to prevent these problems. In NEWS, circumferential seromuscular incisions are performed after marking the primary lesion. Thereafter, a continuous seromuscular suture is performed, and the lesion is inverted toward the inside of the stomach. Finally, a circumferential mucosal incision is performed similar to the ESD technique, and the lesion is transorally retrieved. Several studies used a combined approach with SN biopsy for gastric cancer [65,66]. NEWS is expected to be a promising minimally invasive procedure to achieve full-thickness resection without transluminal access [67].

Recently, Kim et al. [66] developed a non-exposure simple suturing endoscopic full-thickness resection (NESS-EFTR). In this procedure, an endoscopic circumferential mucosal incision is placed after mucosal marking. Next, serosal marking is performed along the mucosal incision line, and laparoscopic seromuscular suturing is performed using barbed suture threads without seromuscular dissection. Endoscopic suturing of the resected margins is performed with endo-loops and clips after EFTR with an inverted lesion. This technique simplifies laparoscopic surgery compared with NEWS. The SENORITA3 trial reported acceptable results of NESS-EFTR combined with SN basin dissection in 20 patients with early gastric cancer [67]. However, NESS-EFTR requires an experienced endoscopist, and collaboration with the surgeon is critical for a successful procedure. Therefore, further large prospective clinical trials are needed to demonstrate the efficacy of NESS-EFTR [29].

ONCOLOGICAL SAFETY OF SNNS AND QOL AFTER LAPAROSCOPIC SNNS FOR STOMACH PRESERVATION

A multicenter nonrandomized phase III trial is now ongoing in Japan (**Table 2**) [68]. Based on a previous multicenter study [19], the major inclusion criterion is previously untreated gastric cancer in patients diagnosed as T1N0 with a single lesion (≤ 40 mm). The primary endpoint is 5-year relapse-free survival. Dual tracers are used to identify SNs, which are then subjected to immediate intraoperative pathological assessment. Minimized gastrectomy with SN basin dissection is performed for patients with negative SN metastasis. A total of 225 patients will be accrued from 13 hospitals from the Japanese Society of SNNS, which are experienced in SN mapping. The secondary endpoint is postoperative QOL. This trial will verify the superiority of minimally invasive function-preserving gastrectomy with SN biopsy for early gastric cancer.

Table 2. Multicenter phase III trials investigating the safety and efficacy of SNNS

Country (yr)	Randomization	Inclusion criteria	No. of cases (total)	Primary outcome	Long-term outcomes	QOL
Japan (ongoing) [68]	Nonrandomized SNNS* vs. standard gastrectomy with D2 LN dissection	cT1NOMO ≤4 cm in tumor size	225	Five-year RFS Ongoing	Ongoing	Ongoing
South Korea (2022) [8]	Randomized SNNS* vs standard gastrectomy with D2 LN dissection	cT1NOMO ≤3 cm in tumor size	580	Three-year DFS Not met	Equivalent	SNNS > standard gastrectomy

SNNS = sentinel node navigation surgery; QOL = quality of life; LN = lymph node; RFS = relapse-free survival; DFS = disease-free survival; SNB = sentinel node biopsy. *SNNS: stomach-preserving surgery is performed in cases with negative SNB results, and standard surgery is performed in cases with positive and negative SNB results if stomach-preserving surgery is technically difficult.

Recently, a multicenter randomized phase III trial began in China (ClinicalTrials.gov, NCT05160753). This trial was designed to elucidate the oncologic safety of laparoscopic gastric preservation surgery compared to standard laparoscopic gastrectomy. The oncologic safety of laparoscopic gastric preservation surgery with anterior basal dissection compared to standard laparoscopic gastrectomy. The estimated enrollment was 580 patients with estimated study completion by December 2024. The primary end-point is 3-year disease-free survival (DFS) with a non-inferiority design, and results are awaited.

In South Korea, the SENORITA trial was conducted to investigate the efficacy of SN navigation surgery for gastric cancer [69]. The major inclusion criterion was cT1NOMO gastric adenocarcinoma, with a diameter of 3 cm or less. This inclusion criterion was also based on a multicenter study in Japan [19]. In total, 290 patients per group were randomized to either LSNNs or LSG. The primary endpoint was 3-year DFS. Overall, 269 and 258 patients underwent LSNNs and LSG, respectively, and SN basin was detected in 97% of patients in the LSNNs group. In terms of LSG details, laparoscopic distal gastrectomy, pylorus-preserving gastrectomy, total gastrectomy, and proximal gastrectomy accounted for 81%, 10%, 4%, and 3%, respectively. In terms of LSNNs details, wedge resection, segment resection, and endoscopic procedure accounted for 73%, 7%, and 1%, respectively. Postoperative complications occurred in 51 (19%) and 40 (16%) patients in the LSG and LSNNs groups, respectively (P=0.294). Complications with a Clavien–Dindo grade of III or higher occurred in 16 (6%) and 13 (5%) patients in the LSG and LSNNs groups, respectively (P=0.647). LSNNs for early gastric cancer showed a comparable rate and severity of complications to LSG with LN dissection [70].

The SENORITA trial conducted primary survival analysis and reported the postoperative QOL. The results showed that the 3-year DFS was 95.5% in the LSG group and 91.8% in the LSNNs group (difference, 3.7%; 95% confidence interval, -0.6 to 8.1), and LSNNs was superior to LSG in terms of 3-year DFS as the primary endpoint (Table 2).⁸ Three-year DFS events occurred in 11 and 20 cases in the LSG and LSNNs groups, respectively. In the LSNNs group, two cases had primary tumor recurrence, one case had LN recurrence, and five cases had metachronous gastric cancer. These eight cases underwent rescue surgery including ESD. Given that gastrectomy rescued the metachronous gastric cancer in the remnant stomach, the 3-year disease-specific survival (DSS) was 99.5% in the LSG group and 99.1% in the LSNNs group. Moreover, the 3-year overall survival (OS) was 99.5% in the LSG group and 97.6% in the LSNNs group. This finding implies that LSNNs could be an alternative to LSG. We should pay attention to metachronous gastric cancer and intragastric recurrence and the importance of rescue surgery for recurrence.

Regarding the QOL investigation in the SENORITA trial, the LSNNS group showed better physical function ($P=0.015$), fewer symptoms ($P<0.001$), and improved nutrition than that in the LSG group [8]. This trial proved for the first time the superiority of LSNNS, which might be a promising alternative to LSG in selected patients with early gastric cancer. Postoperative stenosis was observed in 2.3% of patients in the LSNNS group, and the rate was lower compared with that in other groups [71]. The reason for the low rate of stenosis in the SENORITA trial may be the small area of the SN basin. The results of the phase III trials from Japan and China are awaited; moreover, future investigation of the SN basin area is also necessary to maintain postoperative QOL after function-preserving gastrectomy.

CONCLUSION

Several decades have passed since the concept of the SN basin was applied to early gastric cancer. However, its oncological safety and superiority remain controversial. Although the SENORITA trial could not demonstrate the noninferiority of LSNNS in terms of 3-year DFS, the DSS and OS were comparable with appropriate treatment for recurrence [8]. The SENORITA trial proved for the first time the superiority of LSNNS regarding postoperative QOL. Although the radicality of SNNS must be thoroughly verified, LSNNS is expected to become one of the promising treatment options for early gastric cancer in the future. Moreover, if there is no SN metastasis, resection of the SN basin without gastrectomy is expected to become the treatment option for noncurative cases after ESD.

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