Review Article

Recent updates and current issues of sentinel node navigation surgery for early gastric cancer

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Abstract

With the increase in the incidence of early gastric cancer (EGC), several endoscopic and laparoscopic approaches, such as endoscopic submucosal dissection and function-preserving gastrectomy, have been accepted as standard treatments. Sentinel node navigation surgery (SNNS) is an ideal surgical option for preservation of most parts of the stomach and consequent maintenance of normal gastric function to improve quality of life in patients with EGC. Although many previous studies and clinical trials have demonstrated the safety and feasibility of the sentinel node concept in gastric cancer, the clinical application of SNNS is debatable. Several issues regarding technical standardization and oncological safety need to be resolved. Recently several studies to resolve these problems are being actively performed, and SNNS might be an important surgical option in the treatment of gastric cancer in the future.

Keywords: Sentinel node navigation surgery; function-preserving surgery; early gastric cancer; SENORITA

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Introduction

Gastric cancer is the fifth most common malignancy and the main cause of cancer-related mortality worldwide. It is widely prevalent in Eastern Asian countries, including South Korea, Japan, and China (1). The incidence of early gastric cancer (EGC) is gradually increasing with the development of cancer screening programs, and the 5-year survival rate in patients with EGC is 90% after standard surgery (2,3). Although lymph node metastasis is the most important prognostic factor of gastric cancer, the incidence of lymph node metastasis in EGC is relatively low. However, occasionally, standard gastrectomy with lymphadenectomy is performed in patients with EGC to treat possible lymph node metastasis (4,5). Since these standard surgeries are associated with significant postoperative complications and poor long-term quality of life (QOL) in EGC patients, several surgical modifications of lymphadenectomy and gastric resection have been suggested according to the status of the disease (4,5).

As there is a practical need to improve the QOL in these long-term survivors of EGC, many efforts have been made to reduce gastric resection and lymph node dissection for function-preserving surgery (FPS) to improve short-term surgical outcomes and long-term QOL. Laparoscopic proximal gastrectomy or pylorus-preserving gastrectomy is the representative FPSs; they have been increasingly performed in East Asia for the treatment of EGC. FPS has become an alternative treatment option to standard surgery for EGC (4). FPS is expected to improve postoperative patient QOL by reducing the extent of resection and preserving the physiologic function of the stomach. Several studies have reported the functional benefits and oncological safety of FPS (6,7). However, there are limitations due to several problems such as delayed gastric emptying, gastroesophageal reflux, and technical difficulty (8).

The sentinel node (SN) biopsy, which is used to predict lymph node metastasis from the primary tumor, was initially applied in melanoma and extended to solid tumors such as breast cancer (9,10). As the application of intraoperative SN biopsy allows the reduction of unnecessary radical lymphadenectomy and improves patient QOL, it is also used in gastric cancer. Several studies have been conducted to prove the feasibility of SN concept in gastric cancer (11,12). The results of these studies have suggested the possible clinical application of SN navigation surgery (SNNS); however, its application is controversial. The SN concept in EGC is expected to overcome the problems of FPS and improve patient QOL by reducing the extent of lymphadenectomy.

However, there are some controversial issues that need to be resolved before clinical application of SNNS in EGC is approved. These issues include standardization of technical problems and oncological safety (13). Here, we have reviewed the recent updates and discussed current issues of SNNS in EGC.

SN mapping during SNNS

The tracers for SN mapping should be effectively accumulated within the lymphatic plexus and easily detected during operation, and they should also meet some requirements such as non-toxicity, ease of availability, and cost-effectiveness. However, it is difficult to find substances that meet all these requirements, and it is unclear which tracer is appropriate for use in SN mapping in gastric cancer (14).

In the Japan Clinical Oncology Group trial (JCOG 0302), a single tracer method using indocyanine green (ICG) was used. Their results showed a high false-negative rate of 46.4%, and the trial concluded that intraoperative histological examination using only one plane is not an appropriate method for clinical application of SN biopsy (15). In contrast, in a multicenter trial conducted by Kitagawa *et al*. (16), a dual tracer mapping method using technetium-99m tin colloid and isosulfan blue was used; the authors confirmed the effectiveness of the endoscopic dual tracer method with a false-negative rate of 7%. The combination of radioactive isotopes and dye agents has been proven to increase the rate of SN identification and the accuracy of SN biopsy in previous studies (17,18). Therefore, the dual tracer method using both radioactive colloids and visible dye has become the mainstay for SN detection.

To overcome the limitations of conventional mapping procedures, image-guided mapping procedures using ICG have been introduced. Initially, Nimura *et al*. reported that SN detection using infrared ray electronic endoscopy with ICG injection is an efficient procedure and showed acceptable results with a sensitivity of 100% for SN detection (19). A prospective multicenter trial conducted by Takahashi *et al*. also demonstrated the feasibility and high accuracy of infrared ICG imaging for SN detection (20).

Recently, detection of SNs using ICG fluorescence imaging has been newly developed as a novel technique (21). This method can easily visualize SNs, and several studies have shown promising outcomes (22). Initially, in the study conducted by Tajima *et al*. (23), SN mapping using ICG fluorescence imaging was performed using an infrared camera system with a specific light source and detector. The results showed the feasibility and high sensitivity of ICG fluorescence imaging for intraoperative SN mapping in gastric cancer. To date, many studies have reported the feasibility and safety of ICG fluorescence imaging for SN detection (*Table 1*, *Figure 1*) (20,24-27). Based on these promising results, ICG fluorescence imaging is expected to be applied widely and replace the SN mapping method using radioisotopes not only in gastric cancer but also in other solid tumors.

SN mapping after endoscopic resection

Standard surgery is recommended for patients with EGC who have undergone non-curative endoscopic resection because of the potential for lymph node metastasis (4). However, the role of additional surgery is unclear (4,28). In a previous study, patients who underwent additional surgery after non-curative endoscopic resection had no lymph node metastasis; therefore, additional surgery with standard lymphadenectomy may be considered an overtreatment (29). Therefore, SN biopsy after non-curative endoscopic resection might be a novel option that can avoid standard surgery if there is no SN involvement.

It is unclear whether SN mapping is feasible after endoscopic mucosal resection and endoscopic submucosal dissection (ESD) because these procedures may alter the lymphatic flow of the stomach (30). Several studies have evaluated the role of SN mapping after non-curative ESD, and their results showed a high detection rate and no false-negative nodes. These studies concluded that SN was not significantly affected by endoscopic resection and that SN biopsy can be performed after non-curative endoscopic resection (31,32). Recently, Nohara *et al*. (33) evaluated

Table 1 Studies reported feasibility and safety of ICG fluorescence imaging for SN detection

Study	Year	Patients (N)	Fluorescence imaging system	Detection rate [% (n/N)]	False-negative rate [% (n/N)]
Nimura *et al*. (19)	2004	84	IREE (Olympus optical, Japan)	99 (83/84)	0 (0/11)
Tajima *et al*. (24)	2010	77	PDE-2 (Hamamatsu Photonics, Japan)	94.8 (73/77)	23.5 (4/17)
Yano *et al*. (25)	2012	130	IREE (Olympus optical, Japan)	100 (130/130)	0 (0/47)
Tummers *et al*. (26)	2016	26	Mini-FLARE NIR (Curadel, USA)	95 (21/22)	25 (2/8)
Kinami *et al*. (27)	2016	72	PDE/PDE neo (Hamamatsu Photonics, Japan)	100 (72/72)	9 (1/11)
Takahashi *et al*. (20)	2017	47	IRLS (Olympus Optical, Japan)	100 (44/44)	0 (0/7)

ICG, indocyanine green; SN, sentinel node; IREE, infrared ray electronic endoscopy; NIR, near-infrared; IRLS, infrared ray laparoscopic system.

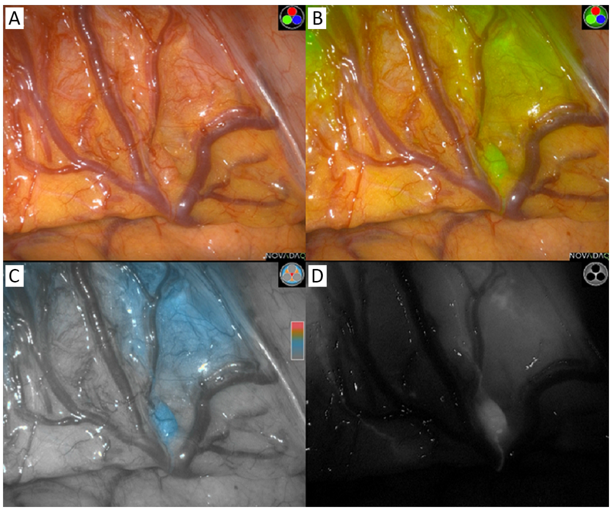

Figure 1 Intraoperative fluorescence imaging during sentinel node navigation surgery. For fluorescence imaging, Pinpoint™ system (NOVADAQ, Canada) was used. After injection of ICG, sentinel node and lymphatic flow are clearly visualized in three modes of Pinpoint™ system compared with routine image with naked eyes. (A) HD white light image after injection of ICG; (B) Pinpoint fluorescence mode; (C) Color segmented fluorescence mode; (D) Spy fluorescence mode. ICG, indocyanine green.

changes in gastric lymphatic flow before and after ESD in an *in vivo* survival model. They confirmed that the SN basins are not significantly influenced by ESD in most cases. These results provide evidence that SNNS can be sufficiently applicable even after endoscopic resection and that a combination of SN concept with endoscopic resection is expected to play a more important role in EGC treatment in the future. Therefore, further prospective studies and clinical trials are necessary to confirm this hypothesis. In South Korea, a prospective multicenter feasibility study, the SENORITA2 trial, is ongoing. This trial is expected to clarify the feasibility of SNNS after non-curative ESD (34).

Skip metastasis in gastric cancer

Intraoperative detection of SNs in gastric cancer is considered a difficult process for surgeons because of the complex lymphatic drainage of the stomach. It is considerably important for surgeons performing SNNS to understand these drainage patterns (14). Because of these complex lymphatic drainage patterns, there are chances of atypical and skip metastasis. This is an important issue in the wide-spread application of SNNS (35,36).

The pick-up method for SN biopsy is well known in the melanoma and breast cancer fields. However, lymphatic drainage of the stomach is very complex, and hence, there is a considerable risk of atypical or skip metastasis, resulting in a high false-negative rate. In 2003, Miwa *et al*. proposed the concept of sentinel basin dissection (SBD) according to the direction of lymphatic drainage along the main gastric arteries (12). The gastric lymphatic compartments (basins) are largely divided into five compartments based on their location along the major gastric arteries: left gastric artery, right gastric artery, right gastroepiploic artery, left gastroepiploic artery, and posterior gastric artery. Previous studies have reported the feasibility of SBD and markedly improved sensitivity of SBD compared to pick-up biopsy. The results of these studies revealed that SBD can improve the sensitivity from 50%−54.8% to 92.3%−96% (37). However, there were some practical challenges when performing SBD. First, a considerable number of patients had two or three sentinel basins. The complete SBD in these patients approximated D1 dissection, and minimal gastric resection was not possible due to reduced bloody supply. Second, intraoperative pathological determination of metastasis was required for many SB nodes, and depending on the pathological examination method used, this process can take considerable time. Third, the practical difficulty of laparoscopic SBD concerned intraoperative bleeding events, especially along the lesser curvature. A previous study has suggested that modified SBD around the SNs can be used instead of classic lymphatic compartment dissection (38).

Several factors such as tumor size, location, and differentiation are associated with an increased risk of atypical and skip metastasis. Generally, tumors located at the lower part and/or lessor curvature side of the stomach have a high risk of atypical metastasis, and poorly differentiated tumors increase the risk of skip metastasis (39,40). In a retrospective study (35), tumor size was an additional risk factor for skip metastasis and the rate of skip metastasis was 6.6% of patients with EGC.

Lee *et al*. (36) reported that although the rate of skip metastasis in gastric cancer has been reported to be up to 11% in patients with lymph node metastasis, 2.8% of the included patients with EGC showed skip metastasis. No. 7, 8, and 9 stations were the most common site of skip metastasis, and they recommended further exploration of those stations in case of negative SNs at the peri-gastric lymph nodes to reduce the false-negative rate of SN mapping.

Primary tumor control during SNNS

During SNNS, it is important to establish the most appropriate method for controlling primary tumors. The primary tumor control method has been suggested depending on the depth, size, histology, and location of the primary tumor (41). Since there are some problems of margin involvement by tumor and local recurrence after limited resection of the primary tumor, the primary tumor control method for EGC should be performed cautiously with adequate margins.

With the development of techniques and instruments for endoscopic resection, endoscopic cooperative full-thickness gastric resection has been gradually attempted (8). Unlike subepithelial tumors (SETs), EGC is usually not visible on the serosal side; hence, simple laparoscopic wedge resection has the potential for incomplete resection. Hiki *et al*. introduced laparoscopy endoscopy cooperative surgery (LECS) for the treatment of gastric SETs. In this procedure, the precise location of the tumor and appropriate resection line could be achieved using intraluminal endoscopy (42). However, LECS is associated with the risk of intra-abdominal contamination and dissemination of cancer cells due to iatrogenic gastric perforation and gastric fluid leakage.

To prevent these problems, non-exposed endoscopic wall-inversion surgery (NEWS) has been developed (43). In NEWS, after markings are made on both the mucosal and serosal sides, laparoscopic circumferential seromuscular dissection and suturing are performed, and the lesion is inverted to the intraluminal side. Finally, the lesion is resected endoscopically (44). A recent study of 42 patients who underwent NEWS for gastric SETs reported safe long-term outcomes and acceptable results in terms of operation time and perioperative complications (45). In addition, a case report also has reported the safety and feasibility of NEWS with SBD in EGC (46).

Recently, Kim *et al*. introduced non-exposure simple suturing endoscopic full-thickness resection (NESS-EFTR) (47). In this procedure, endoscopic circumferential mucosal incision is performed after mucosal marking. Serosal marking is performed along the line of mucosal incision and then laparoscopic seromuscular suturing with barbed suture thread is performed without seromuscular dissection. After EFTR of the inverted lesion, endoscopic suturing of the resected edge is performed with an endoloop and clips. This technique has the advantage of simplifying the laparoscopic procedure compared to NEWS. In a recent prospective SENORITA3 pilot study that evaluated the feasibility of NESS-EFTR with SBD in 20 patients with EGC, acceptable results were reported (48). However, the overall procedures in NESS-EFTR require considerable experience of endoscopists, and collaboration with a surgeon is important for a successful procedure. Therefore, further large-scale, prospective clinical trials are necessary to demonstrate the efficacy of NESS-EFTR.

Intraoperative pathological diagnosis in SNNS

Inaccurate intraoperative pathological diagnosis is another obstacle to SNNS. The establishment of rapid and accurate intraoperative pathology is important for determining metastasis in SNs. Many previous studies have evaluated the frozen sections of dissected SNs using hematoxylin and eosin (HE) staining. However, previous studies have reported that the sensitivity of HE frozen section is approximately 85% even under optimal conditions and that up to 15%−20% of metastases may be missed during operation (49). A multicenter prospective study (JCOG0302) was also discontinued due to a high false-negative rate, and the unreliability of intraoperative single-plane frozen section was one of the main reasons for this result (37). Therefore, efforts have been made to identify more reliable methods and increase the sensitivity of intraoperative pathology. Previous studies have reported alternative methods for intraoperative diagnosis, such as immunohistochemical analysis, reverse transcription polymerase chain reaction (RT-PCR), and one-step nucleic acid amplification (OSNA); these methods improved the sensitivity of intraoperative pathology (50-52). These additional pathological tools are expected to improve the conventional diagnostic method. However, these enhanced examinations can detect a very small lesion or even an isolated tumor cell (ITC) as SN positive. It is unclear whether additional lymph node dissection and gastrectomy are necessary in this situation. The examination level may vary depending on the method of SN biopsy. When SN biopsy is performed using the pick-up method, metastatic lesions may remain in the surrounding lymph nodes, making enhanced examination probably necessary. In contrast, when using the SBD method, the surrounding lymph nodes are removed together; hence, conventional examination may be sufficient (49). Therefore, further studies are required to establish the most accurate and optimal intraoperative diagnostic method for SNNS.

Learning curve for SN biopsy in gastric cancer

During SN biopsy in gastric cancer, there are some practical difficulties due to complex vascular and lymphatic anatomy of the stomach, which may affect the results of the procedure. The JCOG0302 trial reported that underestimation of the learning curve of just five patients may have a negative effect on the high false-negative rate (53). Lee *et al*. (54) conducted a cumulative sum analysis to assess the learning curves for SN identification. This study suggested 26 cases to achieve a 95% success rate. In addition, the multicenter trial conducted by Kitagawa *et al.* recommended 30 cases for a reasonable learning curve and reported acceptable results, with a false-negative rate of 7% (16). Therefore, consideration of the appropriate learning curve might be essential to obtain accurate and effective SN biopsy in gastric cancer.

Oncological safety of SNNS

To date, numerous studies have been conducted to prove the safety and feasibility of SN concepts in the field of gastric cancer, and several long-term outcomes have been reported. If the oncological safety of SN concepts in gastric cancer could be confirmed, SNNS will be a novel, individualized treatment option for EGC and would allow the development of minimally invasive and function-preserving gastric surgery. However, the oncological safety of SNNS is controversial. Hence, SNNS is not widely used in the treatment of EGC.

A previous multicenter trial conducted in Japan confirmed the safety and effectiveness of SN biopsy in EGC with a low false-negative rate of 7% (16). In contrast, the JCOG0302 trial revealed unacceptable results, with a high false-negative rate of 46.4%, and there were several limitations in using a single tracer and pathological examination using only one plane (53).

In South Korea, the long-term outcomes of SNNS in a phase II trial confirmed the safety and feasibility of laparoscopic SNNS and reported 3-year relapse-free and overall survival rates of 96% and 98%, respectively (55). To provide further evidence, the SENORITA group has conducted a prospective multicenter phase III trial to confirm the oncological safety of laparoscopic SBD with stomach-preserving surgery compared to conventional laparoscopic gastrectomy in stage IA gastric cancer (56). In addition, the SENORITA group has previously reported the interim results for 3-year disease-free survival (DFS) of 421 patients. In this analysis, the 3-year DFS rate after stomach-preserving surgery was not significantly different from that after conventional surgery (93% *vs*. 96%). However, follow-up was not sufficient to evaluate non-inferiority, and further follow-up was required (57). The full 3-year follow-up for enrolled patients is currently completed, and long-term results of this trial are expected to clarify issues about the oncological safety of SNNS.

Conclusions

Over the decades, the concept of SNs has been applied in the field of gastric cancer. SNNS is an ideal surgical approach to preserve gastric function and improve patient QOL by reducing the extent of resection of the stomach and regional lymph nodes in patients with EGC. Moreover, a combination of SN biopsy with endoscopic resection of EGC is expected to be a promising treatment option for EGC. Although many previous studies and clinical trials have demonstrated the safety and feasibility of SNNS, its clinical application is debatable. Many issues regarding the establishment of standard procedures for mapping and detection, skip metastasis, and oncological safety need to be resolved. However, further studies to resolve these problems are actively underway, and SNNS is expected to play an important role in the treatment of gastric cancer.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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