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

Sung Gon Kim, Bang Wool Eom, Hong Man Yoon, Chan Gyoo Kim, Myeong-Cherl Kook, Young-Woo Kim, Keun Won Ryu

Center for Gastric Cancer, Research Institute & Hospital, National Cancer Center, Goyang-si 410-769, Republic of Korea

Correspondence to: Keun Won Ryu, MD, PhD. Center for Gastric Cancer, Research Institute & Hospital, National Cancer Center, 323 Ilsan-ro Ilsandong-gu, Goyang-si 410-769, Republic of Korea. Email: docryu@ncc.re.kr.

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

Submitted Feb 19, 2021. Accepted for publication Mar 17, 2021.
doi: 10.21147/j.issn.1000-9604.2021.02.02
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2021.02.02

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...
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).

### Table 1

| 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.

### 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.

Acknowledgements

This work was supported by a grant (No. NCC 2010150-2) from the National Cancer Center, Republic of Korea.

Footnote

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

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Eom BW, Jung KW, Won YJ, et al. Trends in gastric cancer incidence according to the clinicopathological characteristics in Korea, 1999-2014. Cancer Res Treat 2018;50:1343-50.
3. Necula L, Matei L, Dragu D, et al. Recent advances in gastric cancer early diagnosis. World J Gastroenterol 2019;25:2029-44.
4. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean practice guideline for gastric cancer 2018: an evidence-based, multi-disciplinary approach. J Gastric Cancer 2019;19:1-48.
5. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21.
6. Tsujiura M, Hiki N, Ohashi M, et al. Excellent long-term prognosis and favorable postoperative nutritional status after laparoscopic pylorus-preserving gastrectomy. Ann Surg Oncol 2017;24:2233-40.
7. Takiguchi N, Takahashi M, Ikeda M, et al. Long-term quality-of-life comparison of total gastrectomy and proximal gastrectomy by postgastrectomy syndrome assessment scale (PGSAS-45): a nationwide multi-institutional study. Gastric Cancer 2015;18:407-16.
8. Hiki N, Nunobe S, Kubota T, et al. Function-preserving gastrectomy for early gastric cancer. Ann Surg Oncol 2013;20:2683-92.
9. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006;355:1307-17.
10. Kelley MC, Hansen N, McMasters KM. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Am J Surg 2004;188:49-61.
11. Ryu KW, Eom BW, Nam BH, et al. Is the sentinel node biopsy clinically applicable for limited lymphadenectomy and modified gastric resection in gastric cancer? A meta-analysis of feasibility studies. J Surg Oncol 2011;104:578-84.
12. Miwa K, Kinami S, Taniguchi K, et al. Mapping sentinel nodes in patients with early-stage gastric carcinoma. Br J Surg 2003;90:178-82.
13. Ryu KW. The future of sentinel node oriented tailored approach in patients with early gastric cancer. J Gastric Cancer 2012;12:1-2.
14. Symeonidis D, Tepetes K. Techniques and current role of sentinel lymph node (SLN) concept in gastric cancer surgery. Front Surg 2018;5:77.
15. Miyashiro I, Hiratsuka M, Sasako M, et al. High false-negative proportion of intraoperative histological examination as a serious problem for clinical application of sentinel node biopsy for early gastric cancer: final results of the Japan Clinical Oncology Group multicenter trial JCOG0302. Gastric Cancer 2014;17:316-23.
16. Kitagawa Y, Takeuchi H, Takagi Y, et al. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. J Clin Oncol 2013;31:3704-10.
17. Lee JH, Ryu KW, Kim CG, et al. Sentinel node biopsy using dye and isotope double tracers in early gastric cancer. Ann Surg Oncol 2006;13:1168-74.
18. Park DJ, Kim HH, Park YS, et al. Simultaneous indocyanine green and (99m)Tc-antimony sulfur colloid-guided laparoscopic sentinel basin dissection for gastric cancer. Ann Surg Oncol 2011;18:160-5.
19. Nimura H, Narimiya N, Mitsumori N, et al. Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer. Br J Surg 2004;91:575-9.
20. Takahashi N, Nimura H, Fujita T, et al. Laparoscopic
sentinel node navigation surgery for early gastric cancer: a prospective multicenter trial. Langenbecks Arch Surg 2017;402:27-32.

21. Miyashiro I, Miyoshi N, Hiratsuka M, et al. Detection of sentinel node in gastric cancer surgery by indocyanine green fluorescence imaging: comparison with infrared imaging. Ann Surg Oncol 2008;15:1640-3.

22. Xiong L, Gazyakan E, Yang W, et al. Indocyanine green fluorescence-guided sentinel node biopsy: a meta-analysis on detection rate and diagnostic performance. Eur J Surg Oncol 2014;40:843-9.

23. Tajima Y, Yamazaki K, Masuda Y, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer. Ann Surg 2009;249:58-62.

24. Tajima Y, Murakami M, Yamazaki K, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging during laparoscopic surgery in gastric cancer. Ann Surg Oncol 2010;17:1787-93.

25. Yano K, Nimura H, Mitsumori N, et al. The efficiency of micrometastasis by sentinel node navigation surgery using indocyanine green and infrared ray laparoscopy system for gastric cancer. Gastric Cancer 2012;15:287-91.

26. Tummers QR, Boogerd LS, de Steur WO, et al. Near-infrared fluorescence sentinel lymph node detection in gastric cancer: A pilot study. World J Gastroenterol 2016;22:3644-51.

27. Kinami S, Oonishi T, Fujita J, et al. Optimal settings and accuracy of indocyanine green fluorescence imaging for sentinel node biopsy in early gastric cancer. Oncol Lett 2016;11:4055-62.

28. Nie RC, Yuan SQ, Li YF, et al. Additional gastrectomy in early-stage gastric cancer after non-curative endoscopic resection: a meta-analysis. Gastroenterol Rep (Oxf) 2019;7:91-7.

29. Eom BW, Kim YI, Yoon HM, et al. Current status and challenges in sentinel node navigation surgery for early gastric cancer. Chin J Cancer Res 2017;29:93-9.

30. Arroyo-Martinez Q, Han WH, Eom BW, et al. The distribution pattern of metastatic lymph nodes after non-curative endoscopic resection in early gastric cancer. J Surg Oncol 2018;118:1257-63.

31. Arigami T, Uenosono Y, Yanagita S, et al. Feasibility of sentinel node navigation surgery after noncurative endoscopic resection for early gastric cancer. J Gastroenterol Hepatol 2013;28:1343-7.

32. Mayanagi S, Takeuchi H, Kamiya S, et al. Suitability of sentinel node mapping as an index of metastasis in early gastric cancer following endoscopic resection. Ann Surg Oncol 2014;21:2987-93.

33. Nohara K, Goto O, Takeuchi H, et al. Gastric lymphatic flows may change before and after endoscopic submucosal dissection: in vivo porcine survival models. Gastric Cancer 2019;22:723-30.

34. Eom BW, Yoon HM, Min JS, et al. Prospective multicenter feasibility study of laparoscopic sentinel basin dissection after endoscopic submucosal dissection for early gastric cancer: SENORITA 2 trial protocol. J Gastric Cancer 2019;19:157-64.

35. Kim DH, Choi MG, Noh JH, et al. Clinical significance of skip lymph node metastasis in gastric cancer patients. Eur J Surg Oncol 2015;41:339-45.

36. Lee SE, Lee JH, Ryu KW, et al. Sentinel node mapping and skip metastases in patients with early gastric cancer. Ann Surg Oncol 2009;16:603-8.

37. Wei J, Bu Z. Sentinel lymph node detection for gastric cancer: Promise or pitfall? Surg Oncol 2020;33:1-6.

38. Lee JH, Ryu KW, Kook MC, et al. Feasibility of laparoscopic sentinel basin dissection for limited resection in early gastric cancer. J Surg Oncol 2008;98:331-5.

39. Lee JH, Lee HJ, Kong SH, et al. Analysis of the lymphatic stream to predict sentinel nodes in gastric cancer patients. Ann Surg Oncol 2014;21:1090-8.

40. Su Z, Shu K, Zheng M, et al. Sentinel lymph node and skip metastases in gastric cancer: a prospective study. Hepatogastroenterology 2013;60:1513-8.

41. Park JY, Ryu KW, Eom BW, et al. Proposal of the surgical options for primary tumor control during sentinel node navigation surgery based on the discrepancy between preoperative and postoperative early gastric cancer diagnoses. Ann Surg Oncol 2014;21:1123-9.

42. Nunobe S, Hiki N, Gotoda T, et al. Successful application of laparoscopic and endoscopic cooperative surgery (LECS) for a lateral-spreading mucosal gastric cancer. Gastric Cancer 2012;15:338-42.

43. Goto O, Mitsui T, Fujishiro M, et al. New method of endoscopic full-thickness resection: a pilot study of...
non-exposed endoscopic wall-inversion surgery in an ex vivo porcine model. Gastric Cancer 2011;14:183-7.

44. Kim CG. Endoscopic full-thickness resection combined with laparoscopic surgery. Clin Endosc 2018;51:33-6.

45. Aoyama J, Goto O, Kawakubo H, et al. Clinical outcomes of non-exposed endoscopic wall-inversion surgery for gastric submucosal tumors: long-term follow-up and functional results. Gastric Cancer 2020;23:154-9.

46. Goto O, Takeuchi H, Kawakubo H, et al. First case of non-exposed endoscopic wall-inversion surgery with sentinel node basin dissection for early gastric cancer. Gastric Cancer 2015;18:434-9.

47. Kim CG, Yoon HM, Lee JY, et al. Nonexposure endolaparoscopic full-thickness resection with simple suturing technique. Endoscopy 2015;47:1171-4.

48. Eom BW, Kim CG, Kook MC, et al. Non-exposure simple suturing endoscopic full-thickness resection with sentinel basin dissection in patients with early gastric cancer: the SENORITA 3 pilot study. J Gastric Cancer 2020;20:245-55.

49. Park JY, Kook MC, Eom BW, et al. Practical intraoperative pathologic evaluation of sentinel lymph nodes during sentinel node navigation surgery in gastric cancer patients — proposal of the pathologic protocol for the upcoming SENORITA trial. Surg Oncol 2016;25:139-46.

50. Uenosono Y, Natsugoe S, Ehi K, et al. Detection of sentinel nodes and micrometastases using radioisotope navigation and immunohistochemistry in patients with gastric cancer. Br J Surg 2005;92:886-9.

51. Arigami T, Natsugoe S, Uenosono Y, et al. Evaluation of sentinel node concept in gastric cancer based on lymph node micrometastasis determined by reverse transcriptase-polymerase chain reaction. Ann Surg 2006;243:341-7.

52. Kumagai K, Yamamoto N, Miyashiro I, et al. Multicenter study evaluating the clinical performance of the OSNA assay for the molecular detection of lymph node metastases in gastric cancer patients. Gastric Cancer 2014;17:273-80.

53. Miyashiro I. What is the problem in clinical application of sentinel node concept to gastric cancer surgery? J Gastric Cancer 2012;12:7-12.

54. Lee JH, Ryu KW, Lee SE, et al. Learning curve for identification of sentinel lymph node based on a cumulative sum analysis in gastric cancer. Dig Surg 2009;26:465-70.

55. Park DJ, Park YS, Son SY, et al. Long-term oncologic outcomes of laparoscopic sentinel node navigation surgery in early gastric cancer: a single-center, single-arm, phase II trial. Ann Surg Oncol 2018;25:2357-65.

56. Park JY, Kim YW, Ryu KW, et al. Assessment of laparoscopic stomach preserving surgery with sentinel basin dissection versus standard gastrectomy with lymphadenectomy in early gastric cancer — A multicenter randomized phase III clinical trial (SENOrita trial) protocol. BMC Cancer 2016;16:340.

57. Ryu KW, Kim YW, Min JS, et al. Results of interim analysis of the multicenter randomized phase III SENORITA trial of laparoscopic sentinel node oriented, stomach-preserving surgery versus laparoscopic standard gastrectomy with lymph node dissection in early gastric cancer. J Clin Oncol 2017;35(15 suppl):4028.