INTRODUCTION

The incidence and death rate from gastric cancer are second and third most common, respectively in Korea.\(^1\)\(^,\)\(^2\) The proportion of patients with early gastric cancer (EGC) is increasing annually due to the national screening program and frequent self-check endoscopy based on concerns about gastric cancer. The standard EGC treatment is gastric resection with radical lymph node dissection, depending on the preoperative evaluation, except the absolute indication for endoscopic resection (ER).\(^3\) The 5-year overall survival rate in patients with EGC is > 90% using this standard surgery, and patients are living as long-term survivors. However, this standard surgery for patients with EGC produces various short-term surgical complications and long-term impaired of quality of life (QOL) in terms of suboptimal diet, altered bowel habits, and poor nutrition. Thus, new concepts and trials have been discussed for long-term surviving patients after EGC.

After an increase in the use of minimally invasive surgery, such as laparoscopy and robotics for gastric cancer surgery, short-term QOL improved with similar morbidity to that of he conventional laparotomy but long-term oncological outcomes await prospective trials.\(^4\)\(^,\)\(^5\) However, long-term QOL after laparoscopic gastric cancer surgery is similar to that of conventional laparotomy due to the same gastric resection and lymph node dissection approach. Various surgical techniques,
such as proximal gastrectomy, pylorus preserving gastrectomy, and vagus nerve preserving surgery, have been used to improve long-term QOL but the results are not confirmative or encouraging. Injury to innervation and sphincters must be minimized to preserve gastric function and volume and improve long-term QOL. The type of minimal approach should not impair the oncologic outcomes in patients with EGC by removing the entire tumor burden from the primary tumor and metastatic lymph nodes. ER is a minimally invasive and organ-preserving procedure used only for absolute indicated patients with a very low possibility of lymph node metastasis. Many studies have been performed to expand the indications for ER, but the risk of recurrence due to lymph node metastasis has limited expansion. The sentinel node biopsy (SNB) concept was developed to minimize lymph node dissection if no metastasis are present in the SN. This approach minimizes damage to nerves and sphincters and preserves gastric volume by resecting small EGC lesions. This concept was postulated to preserve the gastric function and improve the troublesome long-term QOL in patients with EGC.

FEASIBILITY STUDIES AND META ANALYSES OF SENTINEL NODE BIOPSY IN PATIENTS WITH GASTRIC CANCER

Many SNB gastric cancer feasibility studies have been published in the last decade mainly from Korea and Japan (Table 1). However, most were performed by a single institution with small numbers of patients. The SNB indication and techniques, such as biopsy method, tracers, injection site, and pathological evaluations, were not standardized so procedural details differ. Several review articles and meta-analyses have been reported about this topic in gastric cancer. The pooled detection rate estimate was > 90% but sensitivity was 80%, with heterogeneity between studies. Several points have been suggested to improve SNB results, such as harvesting five or more SNs, preference for EGC rather than advanced gastric cancer, double tracers rather than a single tracer, submucosal rather than subserosal injection, and more precise pathological evaluations. The conclusion from all of these meta-analyses is that SNB is unsatisfactory for clinical application and should be used cautiously. Additional methods have been investigating recently to improve SNB results in patients with gastric cancer, particularly in terms of sensitivity.

PUBLISHED SENTINEL NODE BIOPSY CLINICAL TRIALS IN PATIENTS WITH GASTRIC CANCER

Two large-scale multicenter SNB feasibility studies in patients with gastric cancer have been performed in Japan. The first is the Japan Clinical Oncology Group trial (JCOG0302) and the other is the Japanese Society for Sentinel Node Navigation Surgery (SNNS) trial. Several of the protocols differed between the studies and the final published results were totally different. Miyashiro et al. reported that the JCOG0302 study was stopped before all patients were recruited due to the high false-negative rate. The cause of the high false-negative rate was the simple pathological evaluation and insufficient experience of the participating institutions. Kitagawa et al. reported promising results for clinical applicability from the SNNS trial. They reported 97.5% detection rate with a mean of 5.6 SNs and 93% sensitivity. Among the four false-negative cases, two were T2 lesions, and the location of missed metastatic nodes was at the same sentinel basin in three cases. These results suggested that the optimal indication is T1 lesions, and that sentinel basin dissection rather than a pick-up biopsy is an adequate biopsy method.

A small phase II trial was reported from a single institution of Japan. Ichikura et al. reported that limited gastrectomy with SNB was satisfactory for short-term outcomes and recurrence during the observation period. Another single-center phase II trial from Korea is closing patient recruitment and we are waiting for the final results.

ONGOING PHASE III TRIAL OF LAPAROSCOPIC SENTINEL NODE BIOPSY IN PATIENTS WITH GASTRIC CANCER

The controversial issue of SNB in gastric cancer has been investigated by many academic societies and institutional researchers. Several points were suggested to improve the SNB results. Moreover, most patients with EGC who will be long-term survivors want to save their stomach for improved QOL, and clinicians have the responsibility to solve this problem. A study group called SENORITA (SEntinel Node ORlented Tailored Approach) was launched by a Korean academic society that includes surgeons, gastroenterologists, pathologists, and nuclear medicine specialists to solve this problem in a phase III trial. The protocol for the SENORITA multicenter phase III trial has been developed and patient recruitment is ongoing. Briefly, the study is a non-inferior design of laparoscopic SNB with stomach preserving surgery compared to conventional standard laparoscopic gastrectomy (Fig. 1). The primary endpoint is 3-year disease free survival and the secondary endpoints are postoperative complications, QOL, 5-year disease free survival, and overall survival. The calculated sample size was 290 patients for each arm and the indication was cT1NO < 3 cm, regardless of the histological
### Table 1. Details of published feasibility studies on sentinel node biopsy

| Author      | Year | No. of Pts | Age | Sex | Indication | Approach | Method of biopsy | Tracer | Injection site | No. of SNs | LND | Histol. Eval. | No of positive LNs | Detection rate | Sensitivity | NPV | PPV |
|-------------|------|------------|-----|-----|------------|----------|-----------------|--------|----------------|------------|-----|--------------|------------------|----------------|-------------|-----|-----|
| Hiratuska   | 2001 | 74         | -   | -   | EGC,AGC    | Open     | Pick up         | Dye    | ss             | 2.6        | Radical | HE | 10              | 98.6%             | 90.0%         | 98.4%       | 66.7% |
| Aikou       | 2001 | 18         | -   | -   | EGC        | Open     | Basin           | Dye,Ri | sm             | 3.0        | Radical | RT-PCR | 6               | 94.4%             | 83.3%         | 91.7%       | 0%    |
| Ichikura    | 2002 | 62         | -   | -   | EGC        | Open     | Postgast        | Dye    | sm             | 7.3        | Radical | HE | 15              | 100%            | 86.7%         | 95.9%       | 0%    |
| Kitagawa    | 2002 | 145        | 57  | 107:38 | EGC,AGC    | Open     | Postgast        | RI     | sm             | 3.6        | Radical | HE | 24              | 95.2%            | 91.7%         | 98.3%       | 0%    |
| Hundley     | 2002 | 14         | 66  | 8:6 | -          | Open     | Pick up         | Dye    | ss             | 2.8        | Radical | IHC | 10              | 100%            | 70.0%         | 57.1%       | 85.7% |
| Miva        | 2003 | 211        | 62  | 136:67 | EGC | Open     | Basin           | Dye    | sm             | 6.0        | Radical, limited | HE | 35              | 96.2%             | 88.6%         | 97.7%       | 45.2% |
| Yasuda      | 2003 | 21         | -   | -   | -          | Open     | Postgast        | RI     | sm             | 3.9        | Radical | HE | 6               | 100%             | 100%         | 100%        | 0%    |
| Carlini     | 2002 | 40         | -   | -   | -          | Open     | Basin           | Dye    | -             | -          | Radical | RT-PCR | 24              | 100%             | 91.7%         | 88.9%       | 68.2% |
| Ajsaka      | 2003 | 35         | -   | -   | EGC        | Open     | Basin           | Dye    | sm             | 6.1        | - | RT-PCR | 6                  | 100%             | 100%         | 100%       | 50.0% |
| Uronosono   | 2003 | 36         | 66  | 27:9 | EGC        | Open     | Postgast        | RI     | sm             | 2.7        | Limited | IHC | 6               | 88.9%             | 100%         | 100%       | 50.0% |
| Ryu         | 2003 | 71         | 54  | 40:31 | EGC,AGC    | Open     | Pick up         | Dye    | ss             | 2.5        | Radical | HE | 18              | 91.5%            | 61.1%         | 87.0%       | 72.7% |
| Song        | 2004 | 27         | 50  | 19:8 | -          | Open     | Pick up         | Dye    | sm             | 2.7        | Radical | HE | 8               | 96.3%            | 100%         | 100%       | 100% |
| Kim         | 2004 | 46         | 53  | -   | EGC,AGC    | Open     | Pick up         | Dye    | sm             | 2.0        | Radical | IHC | 13              | 93.5%            | 84.6%         | 93.8%       | 45.5% |
| Nimura      | 2004 | 84         | -   | -   | EGC,AGC    | Open     | Pick up         | Dye    | sm             | 10.5       | Radical | IHC | 11              | 98.8%            | 100%         | 100%       | 100% |
| Karube      | 2004 | 41         | 59  | 31:10 | EGC,AGC    | Open     | Pick up         | Dye,Ri | sm             | 5.0        | Radical | IHC | 13              | 100%             | 92.3%         | 96.6%       | 33.3% |
| Isozaki     | 2004 | 99         | -   | -   | EGC,AGC    | Open     | Pick up         | Dye    | sm             | 3.3        | Radical | HE | 23              | 100%             | 65.2%        | 90.5%       | 0%    |
| Tenouchi    | 2005 | 37         | 64  | 26:11 | EGC,AGC    | Open,lapa| Pick up         | Dye    | sm             | 4.0        | Radical | IHC | 4               | 94.6%            | 75%           | 96.7%       | 0%    |
| Gretschel   | 2005 | 34         | -   | 19:15 | EGC,AGC    | Open     | Postgast        | Dye,Ri | sm             | 3.0        | Radical | IHC | 23              | 97.1%            | 95.7%         | 90.9%       | 100% |
| Uronosono   | 2005 | 104        | 64  | 81:23 | EGC,AGC    | Open     | Pick up         | RI     | sm             | 4.0        | Limited | IHC | 33              | 95.2%            | 81.8%         | 91.7%       | 29.6% |
| Park        | 2006 | 100        | 56  | 69:31 | EGC,AGC    | Open     | Pick up         | Dye    | ss             | 4.4        | Radical | IHC | 14              | 94.0%            | 78.6%         | 96.4%       | 54.6% |
| Zulfikaroqlu| 2005 | 32         | 58  | 26:6 | EGC,AGC    | Open     | Pick up         | RI     | sm             | 2.4        | Limited | IHC | 9               | 96.9%            | 100%         | 100%       | 88.9% |
| Ishizaki    | 2006 | 101        | 62  | 57:44 | EGC,AGC    | Open     | Pick up         | Dye    | sm             | 6.5        | Radical | IHC | 21              | 100%             | 85.7%        | 96.4%       | 0%    |
| Robin       | 2006 | 43         | 69  | 26:17 | -          | Open     | Pick up         | Dye    | ss             | 2.9        | - | IHC | 31              | 79.1%            | 90.3%        | 76.8%       | 71.4% |
| Arigami     | 2006 | 61         | 65  | 44:17 | EGC,AGC    | Open     | Postgast        | RI     | sm             | 4.6        | Limited | RT-PCR | 22              | 100%             | 95.5%        | 97.5%       | 0%    |

Pts = patients; SN = sentinel nodes; LND = lymph node dissection; Histol. Eval. = histological evaluation; LNs = lymph nodes; NPV = negative predictive value; PPV = positive predictive value; EGC = early gastric cancer; AGC = advanced gastric cancer; ss = subserosal; sm = submucosal; HE = Hematoxylin eosin; IHC = immunohistochemistry; RT-PCR = reverse transcriptase polymerase chain reaction.
Table 1. Continued

| Author   | Year | No. of Pts | Age | Sex | Indication | Approach | Method of biopsy | Tracer | Injection site | No. of SNs | LND | Histol. Eval. | No of positive LNs | Detection rate | Sensitivity | NPV | PPV |
|----------|------|------------|-----|-----|------------|----------|------------------|-------|----------------|------------|-----|--------------|------------------|----------------|-------------|-----|-----|
| Mura     | 2006 | 10         | 70  | 6:4 | EGC        | Open     | Pick up          | Dye,RI| sm             | 3.1        | Radical | IHC          | 2                | 100%          | 50.0%       | 88.9%| 100%|
| Mochiki  | 2006 | 59         | 60  | 41:18 | EGC, AGC   | Open     | Pick up          | RI    | sm             | 3.8        | Radical | HE           | 24               | 96.6%         | 83.3%       | 89.2%| 0%  |
| Ichikura | 2006 | 80         | 62  | 56:24| EGC        | Open     | Basin            | Dye,RI| ss, sm         | 4.9        | Radical, limited | HE           | 14             | 100%        | 92.9%       | 98.3%| 38.5%|
| Arima    | 2006 | 24         | 63  | 15:9 | -          | Open     | Postgast         | RI    | sm             | -          | -             | HE           | 24             | 100%        | 87.5%       | 0%  | -  |
| Lee      | 2006 | 64         | 60  | 52:12| EGC        | Open     | Pick up          | Dye,RI| sm             | 4.1        | Radical | IHC          | 17               | 96.9%         | 70.6%       | 90.0%| 41.7%|
| Rino     | 2006 | 38         | 62  | 29:9 | EGC        | Lapa     | Postgast         | Dye   | sm             | 2.5        | Radical | HE           | 4                | 92.1%         | 100%        | 100% | 50.0%|
| Saikawa  | 2006 | 35         | 62  | 25:10| EGC        | Lapa     | Basin            | Dye,RI| sm             | 3.9        | Radical | RT-PCR       | 2               | 94.3%         | 50.0%       | 96.9%| 0%  |
| Ishikawa | 2007 | 16         | 57  | 6:6  | EGC        | Lapa     | Pick up          | Dye   | sm             | 2.9        | Limited | HE           | 2                | 100%          | 50.0%       | 93.3%| 0%  |
| Gretschel| 2007 | 35         | 60  | 19:16| EGC, AGC   | Open     | Pick up          | Dye,RI| sm             | 3.0        | Radical | IHC          | 24              | 97.1%         | 91.7%       | 83.3%| 0%  |
| Orsenigo | 2008 | 34         | 62  | 19:15| EGC, AGC   | Lapa     | Pick up          | Dye   | sm             | 1.5        | Limited | IHC          | 14              | 79.4%         | 35.7%       | 59.1%| 0%  |
| Ohdaira  | 2007 | 52         | 60  | 37:15| EGC, AGC   | Open, Lapa| Basin          | Dye   | sm             | -          | -             | Radical | IHC | 2           | 100%        | 100%        | 100% | 0%  |
| Yanagita | 2008 | 133        | -   | -    | EGC, AGC   | Open     | Pick up          | Dye,RI| sm             | 4.3        | Limited | IHC          | 19              | 98.5%         | 100%        | 100% | 100%|
| Morita   | 2007 | 53         | 62  | 38:15| -          | Open     | Basin            | Dye,RI| sm             | 4.6        | Radical | IHC          | 11              | 100%          | 81.8%       | 95.5%| 33.3%|
| Rino     | 2007 | 43         | 63  | 26:17| EGC, AGC   | Open     | Pick up          | Dye,RI| sm             | 3.5        | Radical | HE           | 11              | 93.0%         | 81.8%       | 93.5%| 77.8%|
| Yanagita | 2008 | 160        | -   | 119:41| EGC, AGC   | Open     | Pick up          | RI    | sm             | 4.4        | Limited | IHC          | 30              | 98.8%         | 96.7%       | 99.2%| 31.0%|
| Wang     | 2008 | 23         | 51  | 14:9 | EGC        | Lapa     | Basin            | Dye   | sm             | 2.9        | Radical | IHC          | 4               | 100%          | 100%        | 100% | 50% |
| Kusano   | 2008 | 22         | 68  | 9:19 | -          | Open, Lapa| Basin          | Dye   | ss             | 3.6        | Limited | HE           | 10              | 90.1%         | 40.0%       | 62.5%| 100%|
| Lee      | 2008 | 42         | 58  | 26:16| EGC, AGC   | Lapa     | Pick up          | Dye,RI| sm             | 2.1        | Radical | IHC          | 6               | 54.8%         | 66.7%       | 89.5%| 100%|
| Lee      | 2008 | 50         | 60  | 32:18| EGC, AGC   | Lapa     | Basin            | Dye,RI| sm             | 3.4        | Radical | IHC          | 14              | 96.0%         | 85.7%       | 94.4%| 100%|
| Ishii    | 2008 | 35         | 62  | 23:12| EGC, AGC   | Open     | Basin            | Dye   | sm             | 7.2        | Limited | IHC          | 4               | 100%          | 100%        | 100% | 25.0%|
| Lee      | 2008 | 21         | 52  | 13:8 | EGC        | Lapa     | Basin            | Dye,RI| sm             | 7.0        | Radical | IHC          | 2               | 95.2%         | 100%        | 100% | 50% |
| Yaquchi  | 2008 | 43         | 63  | 28:15| EGC, AGC   | Open     | Basin            | Dye,RI| ss             | 8          | Limited | HE           | 7               | 100%          | 85.7%       | 97.3%| 0%  |
| Yaquchi  | 2008 | 20         | 61  | 15:5 | EGC, AGC   | Open     | Basin            | Dye,RI| ss             | 8          | Limited | HE           | 7               | 100%          | 100%        | 100% | 0%  |
| Tajima   | 2009 | 56         | 68  | 30:26| -          | Open, Lapa| Basin          | Dye   | ss, sm         | 7.2        | Limited | HE           | 17              | 96.4%         | 64.7%       | 86.0%| 0%  |

Pts = patients; SN = sentinel nodes; LND = lymph node dissection; Histol. Eval. = histological evaluation; LNs = lymph nodes; NPV = negative predictive value; PPV = positive predictive value; EGC = early gastric cancer; AGC = advanced gastric cancer; ss = subserosal; sm = submucosal; HE = Hematoxylin eosin; IHC = immunohistochemistry; RT-PCR = reverse transcriptase polymerase chain reaction.
Laparoscopic Sentinel Node Navigation Surgery for Gastric Cancer

result. Laparoscopic SNB will be done using basin dissection, and all harvested sentinel basin nodes will be examined by intraoperative frozen section with 2 mm slices. Primary tumor resection was proposed based on our previous publication but will be modified based on intraoperative findings (Fig. 2).

The most essential point for a SNB phase III surgical trial is to standardize and overcome the learning curve. The preceding quality control study of the participating institutions prior to the phase III trial is finished. This study was based on completing a checklist consisting of seven essential SNB steps associated with the endoscopic, surgical, and pathological procedures. If SNB was performed perfectly in 10 patients by completing these seven steps, that institution can participate in the phase III trial. The results showed 92.6% detection rate and 100% sensitivity.

CONCLUSION
Laparoscopic SNB with gastric organ and function-preserving surgery in patients with EGC may be a good surgical option to improve short- and long-term QOL without impairing the surgical or oncologic outcomes in selected patients with EGC after validation by the SENORITA phase III trial.

ACKNOWLEDGEMENTS
This study was supported by the National Cancer Center, Republic of Korea (Grant 1410140–2).

REFERENCES
1) Jung KW, Won YJ, Kong HJ, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2012. Cancer Res Treat 2015;47:127–141.
2) Shin A, Kim J, Park S. Gastric cancer epidemiology in Korea. J Gastric Cancer 2011;11:135–140.
3) Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113–123.
4) Kim YW, Baik YH, Yun YH, et al. Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. Ann Surg 2008;248:721-727.

5) Kim HH, Hwang WJ, Cho GS, et al. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report—a phase III multicenter, prospective, randomized Trial (KLASS Trial). Ann Surg 2010;251:417-420.

6) Suh YS, Han DS, Kong SH, et al. Laparoscopy-assisted pylorus-preserving gastrectomy is better than laparoscopy-assisted distal gastrectomy for middle-third early gastric cancer. Ann Surg 2014;259:485-493.

7) Ahn SH, Lee JH, Park do J, Kim HH. Comparative study of clinical outcomes between laparoscopy-assisted proximal gastrectomy (LAPG) and laparoscopy-assisted total gastrectomy (LATG) for proximal gastric cancer. Gastric Cancer 2013;16:282-289.

8) Son SY, Park JY, Ryu KW, et al. The risk factors for lymph node metastasis in early gastric cancer patients who underwent endoscopic resection: is the minimal lymph node dissection applicable? A retrospective study. Surg Endosc 2013;27:3247-3253.

9) Ryu KW, Choi IJ, Doh YW, et al. Surgical indication for non-curative endoscopic resection in early gastric cancer. Ann Surg Oncol 2007;14:3428-3434.

10) 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;104:578-584.

11) Lips DJ, Schutte HW, van der Linden RL, Dassen AE, Voogd AC, Bosscha K. Sentinel lymph node biopsy to direct treatment in gastric cancer. A systematic review of the literature. Eur J Surg Oncol 2011;37:655-661.

12) Wang Z, Dong ZY, Chen JQ, Liu JL. Diagnostic value of sentinel lymph node biopsy in gastric cancer: a meta-analysis. Ann Surg Oncol 2012;19:1541-1550.

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

14) Miyashiro I, Hiratsuka M, Sasaki 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;17:316-323.

15) Kitagawa Y, Takeuchi H, Takagi Y, et al. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. J Clin Oncol 2013;31:3704-3710.

16) Ichikura T, Sugasawa H, Sakamoto N, Yaguchi Y, Tsujimoto H, Ono S. Limited gastrectomy with dissection of sentinel node stations for early gastric cancer with negative sentinel node biopsy. Ann Surg 2009;249:942-947.

17) Kim HH. Laparoscopic Sentinel Node Navigation Surgery for Gastric Cancer [Internet]. Bethesda: U.S. National Institutes of Health; 2015 [cited 2015 August 20]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01441310.

18) Ryu KW. The future of sentinel node oriented tailored approach in patients with early gastric cancer. J Gastric Cancer 2012;12:1-2.

19) Ryu KW. Multicenter Phase III Trial of Laparoscopic Sentinel Node Biopsy [Internet]. Bethesda: U.S. National Institutes of Health; 2015 [cited 2015 August 20]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01804998.

20) 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;21:1123-1129.

21) Ryu KW. Quality Control Study of Laparoscopic Sentinel Node Biopsy in Early Gastric Cancer [Internet]. Bethesda: U.S. National Institutes of Health; 2015 [cited 2015 August 20]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01544413.

22) Ryu KW, Lee YJ, Jeong S-H, et al., editors. Prospective multicenter feasibility study of laparoscopic sentinel basin dissection for organ preserving surgery in gastric cancer: Quality control study for phase III trial. ASCO Annual Meeting Proceedings; 2015.