

## Sentinel node navigation surgery for gastric cancer: Overview and perspective

Masakazu Yashiro, Tasuku Matsuoka

Masakazu Yashiro, Tasuku Matsuoka, Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka 545-8585, Japan

Masakazu Yashiro, Oncology Institute of Geriatrics and Medical Science, Osaka City University Graduate School of Medicine, Osaka 545-8585, Japan

**Author contributions:** Yashiro M and Matsuoka T designed this review; Yashiro M wrote and edited the manuscript.

**Supported by** Partially funded by KAKENHI (Grant-in-Aid for Scientific Research), No. 23390329; by the National Cancer Center Research and Development Fund (23-A-9); and by Priority Research Fund of Osaka City University.

**Conflict-of-interest:** There are not any financial or other interests with regard to the submitted manuscript that might be construed as a conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Masakazu Yashiro, MD, Department of Surgical Oncology, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. [m9312510@med.osaka-cu.ac.jp](mailto:m9312510@med.osaka-cu.ac.jp)

Telephone: +81-6-66453838

Fax: +81-6-66466450

Received: October 3, 2014

Peer-review started: October 3, 2014

First decision: November 19, 2014

Revised: December 3, 2014

Accepted: December 29, 2014

Article in press: January 4, 2015

Published online: January 27, 2015

### Abstract

The sentinel node (SN) technique has been established for the treatment of some types of solid cancers to avoid unnecessary lymphadenectomy. If node disease

were diagnosed before surgery, minimal surgery with omission of lymph node dissection would be an option for patients with early gastric cancer. Although SN biopsy has been well ascertained in the treatment of breast cancer and melanoma, SN navigation surgery (SNNS) in gastric cancer has not been yet universal due to the complicated lymphatic flow from the stomach. Satisfactory establishment of SNNS will result in the possible indication of minimally invasive surgery of gastric cancer. However, the results reported in the literature on SN biopsy in gastric cancer are widely divergent and many issues are still to be resolved, such as the collection method of SN, detection of micrometastasis in SN, and clinical benefit. The difference in the procedural technique and learning phase of surgeons is also varied the accuracy of SN mapping. In this review, we outline the current status of application for SNNS in gastric cancer.

**Key words:** Sentinel node navigation surgery; Gastric cancer; Micrometastasis; Minimal surgery; Review

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The sentinel node (SN) technique has been established for the treatment of some types of malignancies to avoid over invasive surgery. However, SN navigation surgery in gastric cancer has not been yet universal due to the complicated lymphatic flow from the stomach. The results reported in the literature on SN biopsy in gastric cancer are widely divergent and many issues are still to be resolved, such as the collection method of SN, the accuracy of SN mapping, detection of micrometastasis in SN, and clinical benefit. SN mapping should be promising tool for indicating minimally invasive surgery of gastric cancer.

Yashiro M, Matsuoka T. Sentinel node navigation surgery for gastric cancer: Overview and perspective. *World J Gastrointest*

*Surg* 2015; 7(1): 1-9 Available from: URL: <http://www.wjg-net.com/1948-9366/full/v7/i1/1.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v7.i1.1>

## INTRODUCTION

Gastric cancer is the fourth most common cancer in the world, accounting for approximately 989600 new cases each year and 738000 deaths in the world<sup>[1,2]</sup>. Recently the proportion of gastric cancer at an early stage has been increasing because of the advances in the screening system, such as endoscopic investigation<sup>[2]</sup>. In fact, almost half of the patients in Japan who undergo surgery for Depth of tumor invasion (T) 1 gastric cancer<sup>[3]</sup>. Patients with T1 or T2 gastric cancer have superior prognosis when curative resection was carried out, due to the low rate of node involvement and distant metastasis compared with patients with advanced stage. Thus, in contrast with standard radical gastrectomy with Extent of lymph node dissection (D) 2 lymphadenectomy for gastric cancer, limited lymph node dissection, such as D1+ was often selected for patients with early gastric cancer. Theoretically, lymphadenectomy is unnecessary for patients without nodal metastases. Thus, early and accurate identification of lymph node metastasis is pivotal in making the subsequent surgical decisions. Considering the problem of postoperative morbidity and mortality after gastrectomy with extended lymphadenectomy, D2 lymph node resection is considered to be an over invasive surgery for patients with Lymph node metastasis (N) 0 gastric cancer in Western countries<sup>[4]</sup>. However, to date, the effective tools to diagnose pre- or intra-operatively the N0 status remains undefined.

The sentinel node (SN) technique has been established in the management of some types of cancers to avoid unnecessary lymphadenectomy<sup>[5-7]</sup>. SN is defined as the first lymph node to receive cancer cell drainage from the primary tumor, and the lymph node to which cancer cells metastasize initially. In 1992, Morton *et al*<sup>[8]</sup> reported that the SN was successfully detected by dye injection into cutaneous melanoma. Since then, SN biopsy has been well ascertained in the treatment of breast cancer and melanoma<sup>[8]</sup>. Minimally invasive surgery such as limited lymph node dissection and reduced the extent of resection based on SN mapping is termed SN navigation surgery (SNNS). This surgery may prevent the complications of the patient and serve as a useful tool for avoiding an over invasive surgery. However, SNNS of gastric carcinoma has not been universal due to the complicated lymphatic flow from the stomach and skip metastasis, which are sometimes recognized in gastric cancer<sup>[9-11]</sup>. In this review, we outline the current status of SNNS in gastric cancer and provide the future perspective.

## STUDY STRATEGY

### Data source and search strategy

Literature searches of electronic PubMed, Embase,

and the Cochrane Library were performed in English-language articles to identify articles published until September 2014 that described SNNS in gastric cancer. The terms “gastric carcinoma”, “gastric cancer”, “sentinel”, “mapping”, “navigation surgery” were utilized. The abstracts were reviewed, and articles that were not associated with to the specific topic were excluded. Duplicate references as well as repeated publications were discarded. All of the studies that were considered to be eligible were retrieved and the final selection was based on the full article.

### Study selection

We included randomized and controlled clinical trials or experimental studies (excluding case reports). Studies were considered without restrictions on duration of follow-up. First, the titles were screened and appropriate studies were selected. Of these studies, the full text was acquired. A total of 108 articles meeting this criteria were identified.

## CONCEPT AND INDICATION OF SNNS FOR GASTRIC CANCER

The SN technique is derived from the concept that the tumor-bearing status of the SN reflects that of the remaining nodes. If this theory is established, negative metastasis in the SN indicate no other lymph node metastasis. Patients who undergo standard gastrectomy with D2 lymphadenectomy often suffer a variety of complications, such as diarrhea, reflux, dumping syndrome, termed postoperative syndrome. Extended lymph node removal also shows a significantly higher rate of mortality and a longer hospital stay than those underwent D1 lymphadenectomy in Western countries<sup>[12]</sup>. Thus, redundant extended lymph node dissection should be prevented to keep the patient's quality of life. The proportion of lymph node metastasis in gastric cancer relies on the depth of cancer infiltration across the layers of the stomach (termed TNM staging): it is found in 2%-18% of T1 and in about 20% of T2 tumors. On the other hand, the majority (more than 90%) of the patients with early gastric cancer survive 5-year and pathological data have suggested that the greater part of lymph nodes resected do not show nodal involvement<sup>[13]</sup>.

The SN concept for gastric cancer surgery was first suggested by Japanese studies at the beginning of the 21<sup>st</sup> century<sup>[14-16]</sup>. The preliminary data showing a high degree of sensitivity and diagnostic accuracy by the use of an intraoperative radiation technique with a gamma probe was reported in 2002<sup>[17]</sup>. Another study presented that SN biopsy using indocyanine green (ICG) can predict the lymph node status with a high degree of accuracy<sup>[15]</sup>. In general, SN mapping and biopsy is performed in patients with clinical T1 or T2 tumors, primary lesions less than 4 cm in diameter, and clinical N0 gastric cancer. A recent study demonstrated 90.9% of patients with T1 tumors and 88.2% with T2 tumors had stained SLNs

as compared to only 68.8% of patients with T3 tumors, sentinel node mapping in T1 and T2 gastric cancers may be useful in the decision-making process with regard to the extent of lymphadenectomy<sup>[18]</sup>. As well as other type of malignancies, SN mapping would exclude in the cases with positive lymph node metastasis ascertained by preoperative image including ultrasonography and computed tomography<sup>[11,19]</sup>.

## RESEARCH

### **Surgical techniques for SN mapping in gastric cancer**

**Tracer:** As a means of identifying the SN, a dye-guided or radio-guided method has been conducted mainly for SN mapping. Dye or radioisotope colloid was usually injected around the primary tumor, and subsequently, the stained lymph node or lymph node uptake of RI was identified, respectively. Patent blue, lymphazurin, and the ICG are preferably selected in intraoperative time. Dye-guided method has been widely used due to the cost effectiveness and has benefit to detect the lymphatic vessels as well as lymph nodes. However, it has been reported that the dye-guided method is not suitable for patients with a dense adipose tissue, which would cause a high false-negative rate<sup>[20]</sup>. Recent studies described ICG dye is more suitable for SN due to its high accuracy rate<sup>[21]</sup>. But meanwhile, its disadvantage of poor visibility compared with blue node was often pointed out<sup>[22]</sup>.

To overcome this problem, a noble attempt to use infrared ray electronic endoscopy (IREE) combined with ICG has been studied and developed<sup>[23]</sup>. IREE (Olympus Optical, Tokyo, Japan) can illuminate not only SLNs but lymphatic vessels that were not found by ICG injection alone. As compared to visual observation of ICG, lymph nodes identified as SNs by IREE combined with ICG showed higher sensitivity and accuracy. ICG fluorescence imaging has been reported to be innovative in that SN can be identified through a dense adipose tissue<sup>[24]</sup>. In the meanwhile, in order to observe the ICG infrared or fluorescence of the lymph nodes and lymph vessels, dark operating room is indispensable.

On the other hand, in the case of the radio-guided method, technetium-99m tin colloid, technetium-99m sulfur colloid, and technetium-99m antimony sulfur colloid is generally used as radioactive tracers<sup>[20]</sup>. It has been detected using a gamma probe during surgery by injecting through endoscopy so far. The radio-guided method has several benefits over the dye-guided method such as objectivity to see from its quantity, and identification of SLNs, even in patients with a dense adipose tissue. Furthermore, it is suitable for laparoscopic surgery due to the longer time of its stay in the lymph nodes. However, it has several subjects such as requirement of special facilities and high cost of radioactive substances. Consequently, considering of the advantages and disadvantages in both methods, a dual-tracer method is currently regarded as the most reliable to obtain a more precise identification rate of true SN and avoid confusion<sup>[20,25,26]</sup>. Recently, a hybrid single-photon

emission computed tomography/computed tomography (SPECT/CT) was established to enable gamma cameras to capture precise anatomical structures in CT images for SN mapping in various types of malignancies<sup>[27,28]</sup>. Application of SPECT/CT may develop the identification and the localization of SNs before gastric cancer surgery.

**Injection site of the tracer:** To conduct SN mapping by using a tracer, two kinds of methods have been mainly chosen; a method of injecting dye to the submucosal layer around the tumors under endoscopic examination, and a method of injecting to the serosal membrane at the site of primary tumor during surgical procedures. In fact, the dye is injected into the submucosa or serosa with 0.5 mL into the four quadrants around the tumor and 2.0 mL (150 MBq) of technetium-99m colloid solution is generally injected the day before surgery into four quadrants of the submucosal layer of the tumor using an endoscopic puncture needle<sup>[17]</sup>. Several studies have reported that there is no difference in the SN number and identification rate between the serosal and submucosal injection method<sup>[29,30]</sup>. In the meanwhile, the submucosal layer injection method has been predominantly used due to the reliability and rationality of a submucosal injection using an endoscope. This method may also be useful in laparoscopic surgery, because tumor cannot be palpable during an operation.

**Collection method of SN:** In general, there have been two types of methods to collect the SN sampling procedures for gastric cancer. One is the picked-up method to remove only hot node or staining lymph nodes that is currently used to assess breast cancer and melanoma. Another method is a lymphatic basin dissection (LBD)<sup>[31]</sup>. The gastric LBs were deemed to be distributed in the subsequent five directions along the main arteries: left gastric, right gastric, left gastroepiploic, right gastroepiploic, and posterior gastric artery area<sup>[32]</sup>. LBD is recognized as a sort of focused lymph node dissection involving stained lymphatic vessels and lymph nodes for early gastric cancer with keeping a safety area to avoid recurrence<sup>[33]</sup>. There is the possibility that SN basins contain true-positive nodes, even in the false-negative case. A recent report described that the accuracy rate of LN metastasis in LBD group was 92.3%, whereas that in the pick-up method group was 50%<sup>[34]</sup>. The fact that identified lymph node metastasis was completely involved into the lymphatic basin suggests that there is a limit to the sensitivity of the pickup method currently. Given the complexity of this procedure in laparoscopic surgery, it would be unsuitable for clinical applications. Considering the concept of SN biopsy, the picked-up method is more suitable rather than LBD. However, high accuracy rate of lymph node metastasis in LBD would cause an idea that LBD may be the first choice for the patients with early gastric cancer<sup>[10,35]</sup>.

### **Detection of cancer cells in lymph nodes**

It has been reported that reverse transcriptase polymerase chain reaction (RT-PCR) is the most sensitive method for determination of micrometastasis, while Morton *et al*<sup>[5]</sup>

**Table 1** Clinical trials that validated the importance of sentinel lymph node surgery for gastric cancer in a current decade

Ref.	Year	n	Detection rate (%)	Sensitivity (%)	Main results
Kitagawa <i>et al</i> <sup>[19]</sup>	2014	397	97.50	93.00	The proportion of false negatives was 46% (13/28) after a learning period. False negatives remained at 14% (4/28) even by examining additional sections of GNs by paraffin section
Stojanovic <i>et al</i> <sup>[60]</sup>	2013	137	98.20	100	Highly successful mapping and biopsy of SLNs, as well as highest sensitivity was demonstrated and IHC study might enable "ultra staging"
Dong <i>et al</i> <sup>[61]</sup>	2012	23	100	100	SLN-guided minimally invasive surgery could be safely performed in EGC according to feasible criteria
Park do <i>et al</i> <sup>[62]</sup>	2011	68	91.20	100	Simultaneous ICG and (99m)Tc-ASC-guided laparoscopic sentinel basin dissection is an effective tool for gastric cancer SN mapping
Kelder <i>et al</i> <sup>[34]</sup>	2010	212	99.50	97.00	LBD dissection based on IREE is a safe method of nodal dissection in patients with T1 or limited T2 tumors
Tajima <i>et al</i> <sup>[22]</sup>	2009	56	96.40	T1; 97.2 T2 or T3; 72.2	SN mapping guided by ICG fluorescence imaging is useful for predicting the metastasis in lymph nodes in gastric cancer with cT1-stage cancer
Rino <i>et al</i> <sup>[63]</sup>	2007	43	93.00	100	SN mapping seems sufficient in T1 or T2 gastric cancer
Morita <i>et al</i> <sup>[66]</sup>	2007	53	100	82	The accuracy of the SNNS procedure for detecting SNs in patients with early gastric cancer was 96% at the occult metastasis level
Ichikura <i>et al</i> <sup>[67]</sup>	2006	80	100	93	Dissecting the lymph node stations only where the tracers are distributed is recommended for patients with no metastatic SNs
Zulfikaroglu <i>et al</i> <sup>[64]</sup>	2005	32	97	100	SLN biopsy using gamma probe in gastric cancer is a feasible procedure with high sensitivity and accuracy

SLN: Sentinel lymph node; EGC: Early gastric cancer; ICG: Indocyanine green; LBD: Lymphatic basin dissection; IREE: Infrared ray electronic endoscopy; SNNS: Sentinel node navigation surgery.

examined lymph node metastasis by routine hematoxylin and eosin (HE) staining or immunohistochemical staining. It is important to prove the first lymph node detected by the dye-guided or radio-guided method is the true SN to which cancer cells metastasize initially. Osaka *et al*<sup>[61]</sup> reported that a lymph node detected by the dye-guided method should be the true SN by RT-PCR analysis of micrometastasis, and concluded that an appropriate minimal surgery with SN navigation using this dye-guided method would be made available for patients with early gastric cancer. Another study presented that RT-PCR using carcinoembryonic antigen (CEA) mRNA showed higher sensitive rate compared with immunohistochemistry for identifying micrometastasis of LN<sup>[37]</sup>. They also indicated minimally invasive surgery would be acceptable if SNNS is conducted for cT1 and cN0 gastric cancer. Shimizu *et al*<sup>[38]</sup> described that a newly established RT-PCR for the expression of cytokeratin (CK) 19, CK20 and CEA was acceptable for the intraoperative identification of micrometastasis, compared with HE staining and immunohistochemistry with anti-cytokeratin antibody in lymph nodes in patients with cT1 or cT2N0 gastric cancer. In the meanwhile, they also mentioned, if a false-negative finding was not entirely excluded, selective lymph node dissection with LBD was ideal even in patients with negative SN by RT-PCR.

#### Validation of SNNS for patients with gastric cancer

Despite the development of SNNS, there is still controversy with respect to the application of SN mapping in gastric cancer. Some investigators have reported the usefulness of SNNS in gastric cancer, while some studies report the limitation of SNNS. To date, a large number of single-institutional studies have demonstrated satisfactory

results of SN detection. In these reports, the SN detection rate was 90%-100%, and metastasis detection sensitivity was 85%-100% (Table 1). In accordance with these results, two prospective multicenter trials to verify the SN theory in early gastric cancer were conducted. A study group of the Japan Society of SNNS conducted a multicenter prospective trial of SN mapping and analyzes the validity of SNNS using the dual-tracer method with a radioactive colloid and isosulfan blue dye<sup>[19]</sup>. Twelve institutions with established SN mapping protocol and experienced surgical staffs participated. Three-hundred and ninety-seven patients with clinical cT1N0M0 or cT2N0M0 single tumor with the diameter of the primary lesion less than 4 cm, were enrolled. The SN detection rate was 97.5% and sensitivity of detection of regional lymph node metastasis was 93.0%, which were comparable to previously reported data of SN mapping<sup>[39]</sup>. The accuracy of metastatic status based on SN evaluation was 99.0%. The plan on the future SNNS study group, clinical study of reduction surgery for negative cases is initiated intraoperative SN for early gastric cancer from this result. On the basis of these findings, randomized controlled trial to compare individualized gastrectomy based on intraoperative SN biopsy data with conventional distal/total gastrectomy is under construction. In future studies, appropriate indications for function-preserving gastrectomy might be individually determined according to the SN mapping concept.

On the other hand, to verify the feasibility and accuracy of diagnosis utilizing SN, Japan Clinical Oncology Group (JCOG) carried out a multicenter clinical trial, JCOG0302<sup>[40]</sup>. Patients with T1 gastric cancer and less 4 cm tumor size were enrolled. Injection

**Table 2** Clinical trials that served to focus on the limitation of sentinel lymph node surgery for gastric cancer in a current decade

Ref.	Year	n	Detection rate (%)	Sensitivity (%)	Main results
Miyashiro <i>et al</i> <sup>[40]</sup>	2014	440	97.80	46% of false negative rate	The proportion of false negatives was 46% (13/28) after a learning period. False negatives remained at 14% (4/28) even by examining additional sections of GNs by paraffin section
Ryu <i>et al</i> <sup>[41]</sup>	2011	2684	87.80	97.50	A meta-analysis of feasibility studies showed SNB in gastric cancer may not be clinically applicable due to the unsatisfactory sensitivity and heterogeneity among practicing surgeons
Wang <i>et al</i> <sup>[11]</sup>	2011	2128	93.70	76.90	The reliability of SNLB in EGC is currently not comparable to SNLB in breast cancer or melanoma
Becher <i>et al</i> <sup>[8]</sup>	2009	27	100.00	83.00	The negative predictive value is 75% and clinical use of SN mapping for gastric cancer was not recommended
Yanagita <i>et al</i> <sup>[56]</sup>	2008	133	98.50	100.00	Micrometastasis and ITCs should be removed, especially during SN navigation surgery
Tonouchi <i>et al</i> <sup>[65]</sup>	2005	37	94.60	75.00	During laparoscopic SN mapping there is a high risk of false negativity with SNs located in the right pericardial region

GN: Green node; EGC: Early gastric cancer; ITCs: Isolated tumor cells; SNB: Sentinel node biopsy; SNLB: Sentinel lymph node biopsy; ITCs: Isolated tumor cells.

of 4-5 mL indocyanine green dye was conducted from the serosal side of the stomach around the initial tumor. The detection rate of green nodes was 97.8%. But the rate of false-negative was 46.4%, which was unexpectedly high, and 7 of 13 false-negative cases were diagnosed positively metastasized beyond the lymphatic basin. Recently, the study of meta-analysis studies was performed examining the sensitivity of SN biopsy for patients with gastric cancer<sup>[41]</sup>. Two thousand six hundred and eighty-four cases of 46 papers of SN biopsy-related gastric cancer were reported for 2001 and 2009. SN identification rate and sensitivity were 87.8% and 97.5%. Negative and positive predictive values were 91.8% and 38.0% respectively. By subgroup analysis, sensitivity of SN was shown to rely on the number of picked-up SN. They concluded SN mapping in gastric cancer is not clinically applicable for limited lymph node dissection due to its insufficient sensitivity and practical differences between surgeons. In the meanwhile, as a result of the examination of the 2128 cases paper of 38 study has been carried out<sup>[11]</sup>. SN detection rate, sensitivity, negative predictive value and accuracy was 93.7%, 76.9%, 90.3%, and 92.0%, respectively. Combined tracer, submucosal injection method, laparotomy, and immunohistochemical staining revealed a significantly better sensitivity and detection rate. Although the SN mapping is feasible, they concluded that further examinations are necessary for investigating the best technique and standard protocol. These studies that served to refer the limitation of sentinel lymph node surgery in gastric cancer are summarized in Table 2.

As described previously, the results reported in the literature on SN biopsy in gastric cancer are widely divergent. Many authors from Asia reported an accuracy of more than 98%<sup>[17,31]</sup>, in particular in early stages (T1-T2), whereas in Western countries the accuracy was about 80%, with the false negative SLN rate ranging from 15% to 20%<sup>[8,42,43]</sup>. This extreme variance in results may be explained by the difference in the procedural technique and learning phase of surgeons in these

studies. The accurate detection in the case of skip metastases is inadequate even using the LBD method, and the SN jumped the first lymph node level in about 20% of cases, in accordance with the results of the larger Eastern series<sup>[44]</sup>. Regarding the utility of SLN navigation in an attempt to detect the nodal basin, many issues are still to be resolved and further studies are recommended before this method can be introduced into daily practice.

In order to evaluate whether SN concept is suitable for clinical use, the study regarding the follow-up results including recurrence and survival is essential. In the case of breast cancer, meta-analysis of the literature for studies concerning clinically node-negative breast cancer patients presented the axillary recurrence rate was 0.3%-0.6%<sup>[45]</sup>. Patients with SN micrometastases or isolated tumor cells do not reveal a worse disease-free survival (DFS) or overall survival (OS) compared with SN negative cases. A significant shorter DFS and OS were shown in patients with macrometastatic disease in the SN<sup>[46]</sup>. A large, nonrandomized cohort study demonstrated SN biopsy in patients with melanoma more than 1.0 to 4.0 mm in thickness demonstrated improved DFS and regional recurrence-free survival<sup>[47]</sup>. Despite the advancement of follow-up findings in the prospective randomized studies for precise assessment of SNNS in breast cancer and melanoma, there are small amount of studies in the individual institute referring the recurrence or survival in patients with gastric cancer who underwent SNNS. The majority of reports presented no cases of postoperative metastasis or recurrence was found<sup>[33,48-50]</sup>. Yano *et al*<sup>[51]</sup> reported the one of 180 patients (0.8%) developed recurrence at the anastomosis, not at lymph node. A study examined additional RT-PCR analysis for patients with gastric cancer who were determined node-negative intraoperatively. The 3-year survival in group showing positive by RT-PCR (66.7%) is shorter than that showing negative (90%). They concluded the focused SN protocol by using RT-PCR can be applied for an intraoperative approach to determine the extent of lymphadenectomy. To acquire the clinical benefit

of SNNS in gastric cancer, prospective multicenter randomized trial to assess outcome and survival of SN biopsy is necessary.

## CONCLUSION

In the near future, preserving the function of a residual digestive organ and quality of life in postoperative patients will be more highlighted. SNNS is one of the most attractive tools to detect the clinical undetectable lymph node metastasis of gastric cancer, which may lead to individualized less invasive surgical approach. Despite a large number of studies have made an attempt to validate the feasibility and accuracy of SLN in gastric cancer, the results are still varied, which may due to the different protocol and surgical technique. Thus, for the confirmation of clinical applicability of SNB in early gastric cancer, multicenter phase III trial considering these issues should be urgently needed. Recently, SENORITA trial, which comparing the conventional laparoscopic gastrectomy versus laparoscopic SN biopsy with the organ and function preserving surgery of early gastric cancer is ongoing (NIH study trial registration number NCT01804998; ClinicalTrials.gov). Another Multicenter phase III trial is also in progress (NIH study trial registration number NCT01544413; ClinicalTrials.gov). All things to do the laparoscopic sentinel lymph node biopsy are ascertained by checklist and evaluated the performance complement. Accumulation of these recent clinical trials (NIH study trial registration number NCT00489515, NCT01926743; ClinicalTrials.gov) may contribute the application of SNNS in gastric cancer in practice.

For the clinical use of the SNNS in gastric cancer to avoid unnecessary lymph node dissection, negative diagnosis of metastatic lymph node should be confirmed intra-operatively before resection of the stomach. Accordingly, highly accurate intraoperative diagnostic techniques are to be explored<sup>[52]</sup>. To apply SNNS as a practically acceptable method in the same manner as breast cancer and melanoma, there are many issues to be resolved. To begin with, the protocol of SN biopsy should be generally valid. Although SN biopsy has the high accuracy to detect metastatic lymph node, a technique of surgical procedure and pathologic evaluation has been performed in a specialized center and could not be standardized in a wider range of clinical institutions. Subsequently, extensive experience is necessary for developing the technical skill to attain a high accurate degree, which means that the accuracy of the technique relies on the individual surgeon<sup>[53]</sup>. To overcome these obstacles, standardization of SN mapping technique, using improved tracer, and guideline to evaluate the positiveness of SN specimen should be planned to incorporate SNNS in routine practice.

One possible strategy to validate the conception of SNNS in gastric cancer would be the advancement of rapid intra-operative histopathology. Commonly, frozen lymph node specimen divided into two or four sections

is examined using HE staining. The JCOG0302 trial showed the unreliability of frozen section investigation with only one plane and intraoperative diagnosis using SN biopsy could be applied with requirement of multiple planes of specimen<sup>[40]</sup>. The diagnostic accuracy will increase depending on the number of slices. On the contrary, an enlarged sample number also causes several problems such as a time consuming, increasing workload of the surgeons and pathologists and economic burden. As previously described, in order to reduce the false-negative rate, the usefulness of the diagnostic tools to detect micrometastases using molecular-based diagnostic methods, including RT-PCR method has been reported<sup>[37,54,55]</sup>. Because of time consuming to obtain the finding of micrometastases by conventional RT-PCR method, conventional RT-PCR procedure has reported to be unpractical for rapid diagnosis during surgery<sup>[37,38]</sup>. Thus, new method reducing the time required to obtain results of micrometastasis may facilitate the practical use of this technique in the future<sup>[56]</sup>. One-step nucleic acid amplification assay, an automated system that uses the reverse-transcription loop-mediated isothermal amplification method for gene amplification, may be an ideal to replace the histological examination with a quick and simple molecular approach<sup>[57]</sup>. Since RT-PCR is not necessary for this assay, results are obtained within 30 min for one LN.

Another strategy to validate the conception of SNNS in gastric cancer would be an enhancement of sensitivity and accuracy of the dye-method to the degree of the combined method. Dye-method is a simple method that can be performed in a general hospital without the approved area for injection of radioactive colloid and special equipment. IREE and ICG fluorescence imaging may contribute to the achievement of this scheme. However, there is one problem that these detection systems have gray scale imaging and require a darkroom. Therefore, it is difficult to perform SN biopsy under the view of SN in the same time. Recent studies presented Hyper Eye Medical System can be used under room light with the ability to detect color and near-infrared rays simultaneously<sup>[58,59]</sup>. By using this system, surgery can be continued concurrently under the guidance of ICG fluorescence because this system is acceptable under room light. Such novel diagnostic examination and technologies could conquer the current problems of practical application of the SNNS.

In conclusion, there remain many issues to be defined to use SNNS in clinical practice. If these obstacles would successfully be settled, SN mapping should be promising tool for indicating minimally invasive surgery of gastric cancer.

## REFERENCES

- 1 Shimada Y. JGCA (The Japan Gastric Cancer Association). Gastric cancer treatment guidelines. *Jpn J Clin Oncol* 2004; **34**: 58 [PMID: 15061149]
- 2 Piazuelo MB, Correa P. Gastric cancer: Overview. *Colomb Med (Cali)* 2013; **44**: 192-201 [PMID: 24892619]

- 3 **Tanaka H.** Advances in cancer epidemiology in Japan. *Int J Cancer* 2014; **134**: 747-754 [PMID: 24105756 DOI: 10.1002/ijc.28519]
- 4 **Songun I,** Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11**: 439-449 [PMID: 20409751 DOI: 10.1016/S1470-2045(10)70070-X]
- 5 **Morton DL,** Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127**: 392-399 [PMID: 1558490 DOI: 10.1001/archsurg.1992.01420040034005]
- 6 **Giuliano AE,** Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; **220**: 391-398; discussion 391-398 [PMID: 8092905 DOI: 10.1097/00000658-199409000-00015]
- 7 **Bilchik AJ,** Saha S, Wiese D, Stonecypher JA, Wood TF, Sostrin S, Turner RR, Wang HJ, Morton DL, Hoon DS. Molecular staging of early colon cancer on the basis of sentinel node analysis: a multicenter phase II trial. *J Clin Oncol* 2001; **19**: 1128-1136 [PMID: 11181678]
- 8 **Becher RD,** Shen P, Stewart JH, Geisinger KR, McCarthy LP, Levine EA. Sentinel lymph node mapping for gastric adenocarcinoma. *Am Surg* 2009; **75**: 710-714 [PMID: 19725295]
- 9 **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 [PMID: 21636243 DOI: 10.1016/j.ejso.2011.05.001]
- 10 **Ryu KW.** The future of sentinel node oriented tailored approach in patients with early gastric cancer. *J Gastric Cancer* 2012; **12**: 1-2 [PMID: 22500256 DOI: 10.5230/jgc.2012.12.1.1]
- 11 **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 [PMID: 22048632 DOI: 10.1245/s10434-011-2124-2]
- 12 **Bonenkamp JJ,** Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999; **340**: 908-914 [PMID: 10089184 DOI: 10.1056/NEJM199903253401202]
- 13 **Gotoda T,** Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739 DOI: 10.1007/PL00011720]
- 14 **Kitagawa Y,** Fujii H, Mukai M, Kubota T, Ando N, Watanabe M, Ohgami M, Otani Y, Ozawa S, Hasegawa H, Furukawa T, Kumai K, Ikeda T, Nakahara T, Kubo A, Kitajima M. The role of the sentinel lymph node in gastrointestinal cancer. *Surg Clin North Am* 2000; **80**: 1799-1809 [PMID: 11140874 DOI: 10.1016/S0039-6109(05)70262-0]
- 15 **Hiratsuka M,** Miyashiro I, Ishikawa O, Furukawa H, Motomura K, Ohigashi H, Kameyama M, Sasaki Y, Kabuto T, Ishiguro S, Imaoka S, Koyama H. Application of sentinel node biopsy to gastric cancer surgery. *Surgery* 2001; **129**: 335-340 [PMID: 11231462 DOI: 10.1067/msy.2001.111699]
- 16 **Aikou T,** Higashi H, Natsugoe S, Hokita S, Baba M, Tako S. Can sentinel node navigation surgery reduce the extent of lymph node dissection in gastric cancer? *Ann Surg Oncol* 2001; **8**: 90S-93S [PMID: 11599911]
- 17 **Kitagawa Y,** Fujii H, Mukai M, Kubota T, Otani Y, Kitajima M. Radio-guided sentinel node detection for gastric cancer. *Br J Surg* 2002; **89**: 604-608 [PMID: 11972551 DOI: 10.1046/j.1365-2168.2002.02065.x]
- 18 **Rabin I,** Chikman B, Lavy R, Poluksht N, Halpern Z, Wassermann I, Gold-Deutch R, Sandbank J, Halevy A. The accuracy of sentinel node mapping according to T stage in patients with gastric cancer. *Gastric Cancer* 2010; **13**: 30-35 [PMID: 20373073 DOI: 10.1007/s10120-009-0532-9]
- 19 **Kitagawa Y,** Takeuchi H, Takagi Y, Natsugoe S, Terashima M, Murakami N, Fujimura T, Tsujimoto H, Hayashi H, Yoshimizu N, Takagane A, Mohri Y, Nabeshima K, Uenosono Y, Kinami S, Sakamoto J, Morita S, Aikou T, Miwa K, Kitajima M. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. *J Clin Oncol* 2013; **31**: 3704-3710 [PMID: 24019550 DOI: 10.1200/JCO.2013.50.3789]
- 20 **Kitagawa Y,** Fujii H, Kumai K, Kubota T, Otani Y, Saikawa Y, Yoshida M, Kubo A, Kitajima M. Recent advances in sentinel node navigation for gastric cancer: a paradigm shift of surgical management. *J Surg Oncol* 2005; **90**: 147-151; discussion 151-152 [PMID: 15895450]
- 21 **Kusano M,** Tajima Y, Yamazaki K, Kato M, Watanabe M, Miwa M. Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation surgery in gastrointestinal cancer. *Dig Surg* 2008; **25**: 103-108 [PMID: 18379188 DOI: 10.1159/000121905]
- 22 **Tajima Y,** Yamazaki K, Masuda Y, Kato M, Yasuda D, Aoki T, Kato T, Murakami M, Miwa M, Kusano M. Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer. *Ann Surg* 2009; **249**: 58-62 [PMID: 19106676 DOI: 10.1097/SLA.0b013e3181927267]
- 23 **Nimura H,** Narimiya N, Mitsumori N, Yamazaki Y, Yanaga K, Urashima M. Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer. *Br J Surg* 2004; **91**: 575-579 [PMID: 15122608 DOI: 10.1002/bjs.4470]
- 24 **Takeuchi H,** Kitagawa Y. Sentinel node navigation surgery in patients with early gastric cancer. *Dig Surg* 2013; **30**: 104-111 [PMID: 23867586 DOI: 10.1159/000350875]
- 25 **Gretschel S,** Bembenek A, Hünerbein M, Dresel S, Schneider W, Schlag PM. Efficacy of different technical procedures for sentinel lymph node biopsy in gastric cancer staging. *Ann Surg Oncol* 2007; **14**: 2028-2035 [PMID: 17453300 DOI: 10.1245/s10434-007-9367-y]
- 26 **Gretschel S,** Bembenek A, Ulmer Ch, Hünerbein M, Markwardt J, Schneider U, Schlag PM. Prediction of gastric cancer lymph node status by sentinel lymph node biopsy and the Maruyama computer model. *Eur J Surg Oncol* 2005; **31**: 393-400 [PMID: 15837046 DOI: 10.1016/j.ejso.2004.11.014]
- 27 **Ruf J,** Lehmkuhl L, Bertram H, Sandrock D, Amthauer H, Humprik B, Ludwig Munz D, Felix R. Impact of SPECT and integrated low-dose CT after radioiodine therapy on the management of patients with thyroid carcinoma. *Nucl Med Commun* 2004; **25**: 1177-1182 [PMID: 15640775 DOI: 10.1097/00006231-200412000-00004]
- 28 **Borbón-Arce M,** Brouwer OR, van den Berg NS, Mathéron H, Klop WM, Balm AJ, van Leeuwen FW, Valdés-Olmos RA. An innovative multimodality approach for sentinel node mapping and biopsy in head and neck malignancies. *Rev Esp Med Nucl Imagen Mol* 2014; **33**: 274-279 [PMID: 24842707]
- 29 **Lee JH,** Ryu KW, Kim CG, Kim SK, Choi IJ, Kim YW, Chang HJ, Bae JM, Hong EK. Comparative study of the subserosal versus submucosal dye injection method for sentinel node biopsy in gastric cancer. *Eur J Surg Oncol* 2005; **31**: 965-968 [PMID: 15908163 DOI: 10.1016/j.ejso.2005.03.006]
- 30 **Yaguchi Y,** Ichikura T, Ono S, Tsujimoto H, Sugawara H, Sakamoto N, Matsumoto Y, Yoshida K, Kosuda S, Hase K. How should tracers be injected to detect for sentinel nodes in gastric cancer—submucosally from inside or subserosally from outside of the stomach? *J Exp Clin Cancer Res* 2008; **27**: 79 [PMID: 19055749 DOI: 10.1186/1756-9966-27-79]
- 31 **Miwa K,** Kinami S, Taniguchi K, Fushida S, Fujimura T, Nonomura A. Mapping sentinel nodes in patients with early-stage gastric carcinoma. *Br J Surg* 2003; **90**: 178-182 [PMID: 12555293 DOI: 10.1002/bjs.4031]

- 32 **Kinami S**, Fujimura T, Ojima E, Fushida S, Ojima T, Funaki H, Fujita H, Takamura H, Ninomiya I, Nishimura G, Kayahara M, Ohta T, Yoh Z. PTD classification: proposal for a new classification of gastric cancer location based on physiological lymphatic flow. *Int J Clin Oncol* 2008; **13**: 320-329 [PMID: 18704632 DOI: 10.1007/s10147-007-0755-x]
- 33 **Takeuchi H**, Oyama T, Kamiya S, Nakamura R, Takahashi T, Wada N, Saikawa Y, Kitagawa Y. Laparoscopy-assisted proximal gastrectomy with sentinel node mapping for early gastric cancer. *World J Surg* 2011; **35**: 2463-2471 [PMID: 21882026 DOI: 10.1007/s00268-011-1223-3]
- 34 **Kelder W**, Nimura H, Takahashi N, Mitsumori N, van Dam GM, Yanaga K. Sentinel node mapping with indocyanine green (ICG) and infrared ray detection in early gastric cancer: an accurate method that enables a limited lymphadenectomy. *Eur J Surg Oncol* 2010; **36**: 552-558 [PMID: 20452171 DOI: 10.1016/j.ejso.2010.04.007]
- 35 **Lee YJ**, Ha WS, Park ST, Choi SK, Hong SC, Park JW. Which biopsy method is more suitable between a basin dissection and pick-up biopsy for sentinel nodes in laparoscopic sentinel-node navigation surgery (LSNNS) for gastric cancer? *J Laparoendosc Adv Surg Tech A* 2008; **18**: 357-363 [PMID: 18503367 DOI: 10.1089/lap.2007.0024]
- 36 **Osaka H**, Yashiro M, Sawada T, Katsuragi K, Hirakawa K. Is a lymph node detected by the dye-guided method a true sentinel node in gastric cancer? *Clin Cancer Res* 2004; **10**: 6912-6918 [PMID: 15501969 DOI: 10.1158/1078-0432.CCR-04-0476]
- 37 **Arigami T**, Natsugoe S, Uenosono Y, Mataka Y, Ehi K, Higashi H, Arima H, Yanagida S, Ishigami S, Hokita S, Aikou T. Evaluation of sentinel node concept in gastric cancer based on lymph node micrometastasis determined by reverse transcription-polymerase chain reaction. *Ann Surg* 2006; **243**: 341-347 [PMID: 16495698 DOI: 10.1097/01.sla.0000201453.65534.f1]
- 38 **Shimizu Y**, Takeuchi H, Sakakura Y, Saikawa Y, Nakahara T, Mukai M, Kitajima M, Kitagawa Y. Molecular detection of sentinel node micrometastases in patients with clinical N0 gastric carcinoma with real-time multiplex reverse transcription-polymerase chain reaction assay. *Ann Surg Oncol* 2012; **19**: 469-477 [PMID: 22065193 DOI: 10.1245/s10434-011-2122-4]
- 39 **Can MF**, Yagci G, Cetiner S. Sentinel lymph node biopsy for gastric cancer: Where do we stand? *World J Gastrointest Surg* 2011; **3**: 131-137 [PMID: 22007282 DOI: 10.4240/wjgs.v3.i9.131]
- 40 **Miyashiro I**, Hiratsuka M, Sasako M, Sano T, Mizusawa J, Nakamura K, Nashimoto A, Tsuburaya A, Fukushima N. 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 [PMID: 23933782 DOI: 10.1007/s10120-013-0285-3]
- 41 **Ryu KW**, Eom BW, Nam BH, Lee JH, Kook MC, Choi IJ, Kim YW. 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 [PMID: 21695700 DOI: 10.1002/jso.21995]
- 42 **Rabin I**, Chikman B, Halpern Z, Wassermann I, Lavy R, Gold-Deutch R, Sandbank J, Halevy A. Sentinel node mapping for gastric cancer. *Isr Med Assoc J* 2006; **8**: 40-43 [PMID: 16450751]
- 43 **Orsenigo E**, Tomajer V, Di Palo S, Albarello L, Doglioni C, Masci E, Viale E, Staudacher C. Sentinel node mapping during laparoscopic distal gastrectomy for gastric cancer. *Surg Endosc* 2008; **22**: 118-121 [PMID: 17483992 DOI: 10.1007/s00464-007-9385-7]
- 44 **Li C**, Kim S, Lai JF, Oh SJ, Hyung WJ, Choi WH, Choi SH, Noh SH. Solitary lymph node metastasis in gastric cancer. *J Gastrointest Surg* 2008; **12**: 550-554 [PMID: 17786527 DOI: 10.1007/s11605-007-0285-x]
- 45 **van der Ploeg IM**, Nieweg OE, van Rijk MC, Valdés Olmos RA, Kroon BB. Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: A systematic review and meta-analysis of the literature. *Eur J Surg Oncol* 2008; **34**: 1277-1284 [PMID: 18406100 DOI: 10.1016/j.ejso.2008.01.034]
- 46 **Meattini I**, Desideri I, Saieva C, Francolini G, Scotti V, Bonomo P, Greto D, Mangoni M, Nori J, Orzalesi L, Fambrini M, Bianchi S, Livi L. Impact of sentinel node tumor burden on outcome of invasive breast cancer patients. *Eur J Surg Oncol* 2014; **40**: 1195-1202 [PMID: 25179162 DOI: 10.1016/j.ejso.2014.08.471]
- 47 **van der Ploeg AP**, Haydu LE, Spillane AJ, Quinn MJ, Saw RP, Shannon KF, Stretch JR, Uren RF, Scolyer RA, Thompson JF. Outcome following sentinel node biopsy plus wide local excision versus wide local excision only for primary cutaneous melanoma: analysis of 5840 patients treated at a single institution. *Ann Surg* 2014; **260**: 149-157 [PMID: 24633018 DOI: 10.1097/SLA.0000000000000500]
- 48 **Bravo Neto GP**, Dos Santos EG, Loja CA, Victor FC, Neves MS, Pinto MF, Carvalho CE. Minor gastric resections with modified lymphadenectomy in early gastric cancer with negative sentinel node. *Rev Col Bras Cir* 2012; **39**: 183-188 [PMID: 22836565 DOI: 10.1590/S0100-69912012000300004]
- 49 **Ohdaira H**, Nimura H, Takahashi N, Mitsumori N, Kashiwagi H, Narimiya N, Yanaga K. The possibility of performing a limited resection and a lymphadenectomy for proximal gastric carcinoma based on sentinel node navigation. *Surg Today* 2009; **39**: 1026-1031 [PMID: 19997796 DOI: 10.1007/s00595-009-3993-x]
- 50 **Ichikura T**, Sugawara 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 [PMID: 19474686 DOI: 10.1097/SLA.0b013e3181a77e7e]
- 51 **Yano K**, Nimura H, Mitsumori N, Takahashi N, Kashiwagi H, Yanaga K. The efficiency of micrometastasis by sentinel node navigation surgery using indocyanine green and infrared ray laparoscopy system for gastric cancer. *Gastric Cancer* 2012; **15**: 287-291 [PMID: 22041868 DOI: 10.1007/s10120-011-0105-6]
- 52 **Miyashiro I**. What is the problem in clinical application of sentinel node concept to gastric cancer surgery? *J Gastric Cancer* 2012; **12**: 7-12 [PMID: 22500258 DOI: 10.5230/jgc.2012.12.1.7]
- 53 **Miyashiro I**, Hiratsuka M, Kishi K, Takachi K, Yano M, Takenaka A, Tomita Y, Ishiguro S. Intraoperative diagnosis using sentinel node biopsy with indocyanine green dye in gastric cancer surgery: an institutional trial by experienced surgeons. *Ann Surg Oncol* 2013; **20**: 542-546 [PMID: 22941164 DOI: 10.1245/s10434-012-2608-8]
- 54 **Ishii K**, Kinami S, Funaki H, Fujita H, Ninomiya I, Fushida S, Fujimura T, Nishimura G, Kayahara M. Detection of sentinel and non-sentinel lymph node micrometastases by complete serial sectioning and immunohistochemical analysis for gastric cancer. *J Exp Clin Cancer Res* 2008; **27**: 7 [PMID: 18577253 DOI: 10.1186/1756-9966-27-7]
- 55 **Kumagai K**, Yamamoto N, Miyashiro I, Tomita Y, Katai H, Kushima R, Tsuda H, Kitagawa Y, Takeuchi H, Mukai M, Mano M, Mochizuki H, Kato Y, Matsuura N, Sano T. 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**: 273-280 [PMID: 23743877 DOI: 10.1007/s10120-013-0271-9]
- 56 **Yanagita S**, Natsugoe S, Uenosono Y, Kozono T, Ehi K, Arigami T, Arima H, Ishigami S, Aikou T. Sentinel node micrometastases have high proliferative potential in gastric cancer. *J Surg Res* 2008; **145**: 238-243 [PMID: 17603078 DOI: 10.1007/s11605-007-0285-x]



- 10.1016/j.jss.2007.04.037]
- 57 **Visser M**, Jiwa M, Horstman A, Brink AA, Pol RP, van Diest P, Snijders PJ, Meijer CJ. Intra-operative rapid diagnostic method based on CK19 mRNA expression for the detection of lymph node metastases in breast cancer. *Int J Cancer* 2008; **122**: 2562-2567 [PMID: 18324628 DOI: 10.1002/ijc.23451]
- 58 **Kubota K**, Yoshida M, Kuroda J, Okada A, Ohta K, Kitajima M. Application of the HyperEye Medical System for esophageal cancer surgery: a preliminary report. *Surg Today* 2013; **43**: 215-220 [PMID: 22782594 DOI: 10.1007/s00595-012-0251-4]
- 59 **Yoshida M**, Kubota K, Kuroda J, Ohta K, Nakamura T, Saito J, Kobayashi M, Sato T, Beck Y, Kitagawa Y, Kitajima M. Indocyanine green injection for detecting sentinel nodes using color fluorescence camera in the laparoscopy-assisted gastrectomy. *J Gastroenterol Hepatol* 2012; **27** Suppl 3: 29-33 [PMID: 22486868 DOI: 10.1111/j.1440-1746.2012.07067.x]
- 60 **Stojanovic D**, Milenkovic SM, Mitrovic N, Marinkovic D, Stevanovic D, Radovanovic D. The feasibility of sentinel lymph node biopsy for gastric cancer: the experience from Serbia. *J BUON* 2013; **18**: 162-168 [PMID: 23613402]
- 61 **Dong LF**, Wang LB, Shen JG, Xu CY. Sentinel lymph node biopsy predicts lymph node metastasis in early gastric cancer: a retrospective analysis. *Dig Surg* 2012; **29**: 124-129 [PMID: 22538386 DOI: 10.1159/000336210]
- 62 **Park do J**, Kim HH, Park YS, Lee HS, Lee WW, Lee HJ, Yang HK. Simultaneous indocyanine green and (99m)Tc-antimony sulfur colloid-guided laparoscopic sentinel basin dissection for gastric cancer. *Ann Surg Oncol* 2011; **18**: 160-165 [PMID: 20652640 DOI: 10.1245/s10434-010-1221-y]
- 63 **Rino Y**, Takanashi Y, Hasuo K, Kawamoto M, Ashida A, Harada H, Inagaki D, Hatori S, Ohshima T, Yamada R, Imada T. The validity of sentinel lymph node biopsy using dye technique alone in patients with gastric cancer. *Hepatogastroenterology* 2007; **54**: 1882-1886 [PMID: 18019740]
- 64 **Zulfikaroglu B**, Koc M, Ozmen MM, Kucuk NO, Ozalp N, Aras G. Intraoperative lymphatic mapping and sentinel lymph node biopsy using radioactive tracer in gastric cancer. *Surgery* 2005; **138**: 899-904 [PMID: 16291391 DOI: 10.1016/j.surg.2005.04.014]
- 65 **Tonouchi H**, Mohri Y, Tanaka K, Kobayashi M, Ohmori Y, Kusunoki M. Laparoscopic lymphatic mapping and sentinel node biopsies for early-stage gastric cancer: the cause of false negativity. *World J Surg* 2005; **29**: 418-421 [PMID: 15770372 DOI: 10.1007/s00268-004-7732-6]
- 66 **Morita D**, Tsuda H, Ichikura T, Kimura M, Aida S, Kosuda S, Inazawa J, Mochizuki H, Matsubara O. Analysis of sentinel node involvement in gastric cancer. *Clin Gastroenterol Hepatol* 2007; **5**: 1046-1052 [PMID: 17632042]
- 67 **Ichikura T**, Chochi K, Sugasawa H, Yaguchi Y, Sakamoto N, Takahata R, Kosuda S, Mochizuki H. Individualized surgery for early gastric cancer guided by sentinel node biopsy. *Surgery* 2006; **139**: 501-507 [PMID: 16627059]

**P- Reviewer:** Shimi SM **S- Editor:** Song XX **L- Editor:** A  
**E- Editor:** Lu YJ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

