Near-Infrared Fluorescence Lymph Node Navigation Using Indocyanine Green for Gastric Cancer Surgery

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Near-infrared (NIR) fluorescence imaging is a promising method for image-guided surgery, providing robust functional images with relatively good cost-effectiveness. A cyanine vital dye indocyanine green (ICG) is a safe NIR fluorophore emitting 800~840 nm of light and has been used in numerous surgical procedures. The technique has been applied to lymph node navigation of gastric cancer surgery with an expectation of better visualization of lymphatic structures without any risk of radio-hazard compared with a “dual method” using both vital dyes and radioisotopes. Given the characteristics of ICG, such as fast distribution and quenching effect, diluted concentrations, such as 0.05~0.1 mg/ml, are thought to be optimal for sentinel node navigation. Injection into the subserosal layer is feasible; however, endoscopic submucosal injection has advantages of improved accuracy of the injection site and feasibility of injection one day prior to surgery; these advantages are preferred by some investigators due to a smaller number of sentinel nodes compared with injection in the operation theatre. The technology requires evaluation of the sensitivity and specificity, as well as the non-inferiority, compared with the dual method in a large cohort for justification as a safe node navigation method.

Keywords: Near-infrared, Indocyanine green, Sentinel lymph node biopsy, Stomach neoplasms

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INTRODUCTION

According to the increasing needs and interest in precision surgery, which is characterized by individual tailored surgical strategies, image-guided surgery is receiving increased attention as the most intuitive and strong methodology to implement precision surgery.¹ Computer-based augmented reality, which overlays the virtual images reconstructed from preoperative CT scan or MRI on the operative visual field, is a technology used to optically navigate the surgical view, and its applications are expanding, especially to surgeries of rigid organs, such as orthopedic surgery, neurosurgery, and dental surgery.^{2,3} Its practical usage in abdominal surgery has not been as rapidly implemented compared with rigid organ

surgery given the increased complexity of non-rigid registration between the virtual images and optical images due to numerous factors, resulting in deformities of the organ during the surgery. In addition, the need for additional time, human power, and resources to construct virtual images and overlaying procedures has been limiting.

In contrast, near-infrared (NIR) imaging using indocyanine green (ICG) has been independently developed for functional imaging of location and patency of vascular structures in neuro-, ophthalmologic, and vascular surgeries since 1980s.⁴⁻⁶ The wavelength of NIR light is approximately 700~1,000 nm. This range is the least absorbed by blood or water; thus, this “optical window” has been regarded as the best wavelength of imaging to provide the deepest penetration of the signal.^{7,8} Indocyanine

green is an FDA-approved vital dye for liver function tests and exhibits good characteristics as a fluorophore for NIR images. NIR imaging has been applied to various procedures in general surgery, providing functional information of the perfusion of the organs, visualization of the biliary tract and hepatic tumors, and margins of the anatomic segments of the liver.⁹⁻¹³

ICG has been used as a vital dye to visualize sentinel lymph nodes, which are observed by the naked eye.¹⁴ ICG can provide better sensitivity and depth penetration when used together with NIR imaging systems, which are composed of excitation light sources and special filters and cameras optimized for the NIR wavelength of light.^{15,16} Compared with radioisotopes, which are additional tools used for sentinel node navigation, ICG has advantages that can avoid special safety protocols necessary for the use of radioactive dyes. Therefore, NIR imaging using ICG is under active investigation as an effective and safe tool for lymph node navigation in oncologic surgeries, including cancers of the stomach, esophagus, colon, and gynecologic organs.¹⁷⁻¹⁹

This article is intended to review previous studies of NIR fluorescent imaging using ICG in lymph node navigation in gastric cancer surgery with a special focus on when and how to inject the ICG.

ICG AND NIR FLUORESCENT OPTICAL SYSTEMS

ICG was approved by the Food and Drug Administration (FDA) for liver function tests in 1958 given its almost exclusive metabolism by the liver. It is one of the safest vital dyes with only very rare reports of hypersensitivity reactions.⁷ ICG belongs to cyanine dyes, which structurally contain two rings and double bonds between them. The length of the double bonds determines the wavelength of the emitted signal. ICG is excited at 700~800 nm, and the emitted maximal signal is 800~840 nm.²⁰

Previously, tracers with high photon yields, such as quantum dots, were suggested as tracer fluorophores for NIR imaging. Strong excitation light and the usage of quantum dots can result in very deep penetration signal depths; however, possible harmful effects of excessive excitation light and heavy metals in quantum dots have limited their application in human surgeries. In contrast, ICG exhibits a great safety profile. However, the quantum yield is relatively low, thus the penetration depth for practical usage seems to be a maximum of 0.5 cm.

Of note, ICG has not been approved for NIR imaging by the FDA until recently, and most of the studies used ICG for off-labeled indications.

Initial studies used NIR imaging systems designed for open

surgeries. Many gastric surgery researchers used a prototype system based on the photodynamic eye (PDE) system (Hamamatsu Photonics, Hamamatsu, Japan).²¹⁻²⁶ This system only shows NIR imaging.

Yoshida et al. used the Hyper Eye Medical System (HEMS; Mizuho Ikakogyo Co., Ltd, Tokyo, Japan), which simultaneously provides both NIR images and white light images,²⁷ and Frangioni and Tummer et al. developed systems for open surgeries, including the Mini-Fluorescence-Assisted Resection and Exploration (Mini-FLARETM) image-guided surgery system.²⁸

The Novadaq company commercialized the laparoscopic NIR imaging system PinpointTM and its DaVinci version FireflyTM system.²⁹ Both systems provide fused images from white light and NIR imaging.³⁰

Other companies have reported prototypes of laparoscopic systems from other companies,³¹ and several laparoscopic systems, including the D-lightTM system (Karl-Storz, Tuttlingen, Germany), AIM ENVTM system (Stryker, San Jose, CA, USA), and IRTM system (Olympus, Tokyo, Japan), are currently available in the market (Fig. 1).

INJECTION OF ICG INTO THE STOMACH

Most of the locations of the injection for sentinel lymph node navigation involve the four quadrants adjacent to the gastric cancer: proximal, distal, and two lateral areas. For small tumors, which are usually indicated for sentinel lymph node navigation, 4 injection sites are regarded as sufficient to cover the entire lymphatic flow from primary tumors because ICG spreads greater than 1 cm when injected into the gastric wall. However, additive injection may be required for larger tumors when the ICG injection cannot cover entire margin of the tumor (Fig. 2).²⁵

ICG can be injected either into the subserosal layer by the surgeon or into the submucosal layer via endoscopic needle. Ryu et al. compared submucosal injection and subserosal injection using the vital dye isosulfan blue and reported no differences in the detection rate, number of sentinel lymph nodes, and sensitivity.³² No study has compared two access routes in the NIR system, and both methods have been used.

Subserosal injection seems to be beneficial given that the surgeon can control the injection by her/himself.^{21,23-27,30,31} Additionally, in my personal opinion, ICG injected into the subserosal layer reaches to the lymphatic pathway more quickly compared with ICG injected into the submucosal layer. However, the location of the primary tumor is frequently difficult to identify using the external view unless the tumor is too advanced to be easily visualized. Some areas may be technically demanding to inject, especially in laparoscopic surgery.

Fig. 1. Examples of lymph node navigation using various imaging systems. Yellow arrowhead: lymph node. Yellow arrow: lymphatic channel. White arrow: injection site. After an injection of 2.5 mg/ml of indocyanine green, only one green lymphatic channel is observed by white light view (A), however, multiple lymphatic channels as well as a lymph node are visualized by AIM system ENV™ mode (Stryker, San Jose, CA, USA) (B). After injection of 0.1 mg/ml of indocyanine, lymphatic channels and lymph nodes are visualized in the D-light™ system (Karl-Storz, Tuttlingen, Germany) (C, D), Pinpoint fluorescence mode (E) and color segmented fluorescence mode (F) in Pinpoint™ system (Novadaq, Canada), and IR™ system (Olympus, Tokyo, Japan) (G, H).

Fig. 2. Endoscopic injection of indocyanine green. (A) Submucosal injection of indocyanine green using endoscopic injection needle around the tumor. (B) Blockage of proximal jejunum using atraumatic forceps or clamps can prevent accidental inflation of the small bowels, which may interrupt operation, during endoscopic injection.

Furthermore, if the injected ICG leaks from the injection site, it can stain the operation field. The identification of the lymphatic structures and lymph nodes can be disturbed because the NIR signal of ICG is very strong and ICG is very difficult to be removed from stained tissues.

In contrast, submucosal injection via an endoscopic needle has more advantages given accurate localization of the tumor and less technical difficulties of injection depending on the location.^{21,23–27,30,31} Endoscopic injection has a risk of penetration of the gastric wall and spillage of the ICG into the peritoneal space, so some a learning period may be required for beginners.

Lymph node navigation is used for sentinel node navigation surgery, but it can also be used to evaluate and/or ensure complete wide lymph node dissection. Some clinical trials to evaluate new laparoscopic gastrectomy technologies tried to ensure adequate and complete lymph node dissection and opt to collect photographs of the operative field after completion of the lymph node dissection.³³ NIR imaging may provide further information regarding whether ICG-stained lymph

nodes were completely removed from the field. In this context, ICG injection does not have to be limited to peritumoral area but can be widely performed at multiple areas, i.e., several spots along the lesser curvature side and several spots along the greater curvature side, to cover all the main perigastric lymphatic pathways.

Injection methods and results are summarized in Table 1.

ICG INJECTION AMOUNT

NIR imaging is very sensitive to small amounts of ICG, and the NIR signal is not linearly correlated to the amount of ICG. A special characteristic of ICG is the “quenching effect”, which refers to the phenomenon whereby the signal decreases with increasing concentrations of ICG because closely crowded ICG molecules absorb the NIR signal from nearby ICG molecules. Consequently, the NIR signal of ICG is the strongest at a concentration of 0.001–0.01 mg/ml and decreases as the concentration either increases or decreases (Fig. 3).^{34,35} The default concentration obtained from commercially available ICG is

Table 1. Studies of near-infrared fluorescence image-guided sentinel lymph node navigation using indocyanine green

Author (year)	Procedure	N.	Indication	Device	Concentration, volume, site	Injection route	Observation starting time (intraop. injection)	No. of LNs	Results
Miyashiro (2008) ²¹	SN biopsy→distal gastrectomy and lymphadenectomy	3	cT1	PDE system (Hamamatsu Photonics, Hamamatsu, Japan)	NA, total 2 ~ 4 ml, around the tumor	Endoscopic, Intraop./1 day before surgery	Immediately after injection	Intraop. 4, 1/ preop. 4	SNs were identified by both methods No LN metastasis
Kusano (2008) ²²	SN biopsy→standard gastrectomy and lymphadenectomy	22	NA	PDE system	5 mg/ml, 0.5 ml, 4 sites around the tumor	Subserosa, Intraop.	Immediately after injection	Mean 3.6±4.5	At least one SN was found: 90.9% (20/22) All cases: accuracy 70.0% (14/20), false-negative 60.0% (6/10), positive predictive value 100% (4/4), negative predictive value 62.5% (10/16) T1 cases: accuracy 88.9% (8/9), false-negative 33.3% (1/3), positive predictive value 100% (2/2), negative predictive value 85.7% (6/7)
Tajima (2009) ²³	SN biopsy→standard gastrectomy and lymphadenectomy	56	Without pre-op chemotherapy	PDE system	5 mg/ml, 0.5 ml, 4 sites around the tumor	Endoscopic 1 ~ 3 days before surgery (n = 31)/ subserosa intraop. (n = 25)	Immediately after injection	Mean 7.2±7.0 (pre-op 9.9±7.5 vs intraop. 4.1±5.0)	At least one SN was found: 96.4% (54/56) Accuracy: 88.9% (48/54), false-negative 35.3% (6/17) Accuracy: cT1 97.2% vs cT2,3 72.2% (p = 0.0127) False negative: cT1 14.3% vs cT2,3 50.0 (p = NS) Accuracy: preop 100% vs intraop 73.9% (p = 0.0039) False negative: preop 100% vs intraop 60.0% (p = 0.0345) Frequently ICG fluorescence leakage from injured lymphatic vessels in patients with intraoperative ICG injection (and only a few patients with preoperative ICG injection)

Table 1. Continued 1

Author (year)	Procedure	N.	Indication	Device	Concentration, volume, site	Injection route	Observation starting time (intraop. injection)	No. of LNs	Results
Tajima (2010) ²⁴	SN biopsy → laparoscopic or open gastrectomy and lymphadenectomy	77	cT1 or cT2, <6 cm	PDE-2 system	5 mg/ml, 0.5 ml, 4 sites around the tumor	Endoscopic 1 ~ 3 days before surgery/subserosa intraop.	Immediately after injection	Mean no. of SN 7.5 ± 6.5 , mean no. of lymphatic basin 1.9 ± 0.8	Accuracy 94.5% (69/73), false-negative 23.5% (4/17), positive predictive value 100% (13/13), negative predictive value 93.3% (56/60) Metastasis in LN outside the lymphatic basins: without metastasis in SNs: 0% (0/60) with metastasis in SNs: 23.1% (3/13)
Miyashiro (2011) ²⁵	SN biopsy → laparoscopic gastrectomy and lymphadenectomy	10	cT1	A prototype laparoscopic detection system based on the PDE system	0.25 ~ 1.25 mg/0.5 ml, total 2 ~ 4 ml, 4 ~ 8 sites around the tumor	Endoscopic intraop.	5 min	Median 3.0, mean 3.1 ± 1.5 (min 1 ~ max 6)	Metastasis only in SNs: 2/10 Metastasis both in SNs and non-SNs: 1/10
Yoshida (2012) ²⁷	SN biopsy → laparoscopic or open gastrectomy and lymphadenectomy	13	cT1, T2 N0	HEMS (Mizuho Ikakogyo Co., Ltd, Tokyo, Japan)	0.05 mg/ml, 0.5 ml, 4 sites just below the tumor	Endoscopic 1 day before op.		Mean 3.6 ± 2.1	Only 1 case of LN metastasis (12 out of 37 LNs) Preliminary trial: 0.1 mg/ml injected 1 day before: too intense and too many SNs 0.025 mg/ml injected 1 day before: too faint
Goto (2015) ³¹	NEWS with sentinel node basin dissection	1	cT1N0	NIR Laparoscopic System (Olympus, Tokyo, Japan)	5 mg/ml, 0.5 ml, 4 sites around the tumor	Endoscopic intraop.	10 min	2	No LN metastasis SN basin: #1, #3a/#7
Herrera-Almario (2016) ³⁰	Robotic gastrectomy (n = 29) or wedge resection (n = 2) with NIR LN navigation	31	Adenocarcinoma (n = 29), NET (n = 2)	Firefly Fluorescence Imaging Scope (Intuitive Surgical, Sunnyvale, CA, USA)	2.5 mg/ml, 2 ml, 4 sites around the tumor	Subserosa intraop.	10 min	Adenocarcinoma: mean 29 (min 17 ~ max 61)	≥5 ICG positive LNs along the main nodal basins found in all cases All ICG-positive LNs were included in the specimens

Table 1. Continued 2

Author (year)	Procedure	N.	Indication	Device	Concentration, volume, site	Injection route	Observation starting time (intraop. injection)	No. of LNs	Results
Kinami (2016) ²⁶	SN biopsy→ laparoscopic or open gastrectomy and lymphadenectomy (n=42)/function-preserving gastrectomy with basin dissection (n=30)	72	cT1N0	PDE or PDE neo	0.05 mg/ml, 0.5 ml or 0.2 ml, 4 sites around the tumor	Endoscopic 1 day before op.	Post-op. from specimen (n=14)/intra-op. and post-op. (n=54)	Post-op. only median 5 (4~11)/intra-op.: median 6 (2~9), post-op. (pickup failure): median 1 (0~4)	Sensitivity 90.1% (10/11), accuracy 98.6% (71/72) Total number of metastatic nodes: 35~22 (62.9%) in bright node, 12 (34.3%) in non-bright nodes within the basin, and 1 (2.9%) in non-bright node outside the basin median no. of SNs: 0.5 ml group 6 (3~11) vs 0.2 ml group 6 (2~7) Weak fluorescence at 0.005 mg/ml of ICG No difference between 0.5 ml and 0.2 ml→0.5 ml×4 points seems to be optimal due to its technical reliability
Ohdaira (2017) ²⁹	SN biopsy→ laparoscopic gastrectomy and lymphadenectomy	6	cT1N0 or cT2N0	PINPOINT® (NOVADAQ, Canada)	0.05 mg/ml (n=5)/0.0333 mg/ml (n=1)	Endoscopic 1 day before op.		Mean 7.0±4.7	Only 1 case of LN metastasis: one in #4 which is ICG positive
Turnmers (2016) ²⁸	SN biopsy→standard gastrectomy and lymphadenectomy	22	Most of patients underwent neoadjuvant chemotherapy	Intraop.: Mini-FLARE™ system/ Specimen: FLARE™ system	0.05 mg ICG+0.1 mg Nanocoll/1.6 ml	Subserosa intraop.	NA	Mean 3.1 (min 1~max 6)	At least one SN was found: 95% (21/22) Accuracy 90% (pTx, pT1, pT2 100%, pT3 90%, pT4 0%) LN metastasis-8 patients, 7 false negative LNs in 2 patient: all false negative LNs were completely effaced by tumor tissue and no lymphatic tissue could be identified By combining ICG with nanocolloid Nanocoll (GE Healthcare, Eindhoven, Netherlands), its hydro-dynamic diameter increases from ≤1 nm (ICG) to 20~80 nm (ICG:Nanocoll)

HEMS = hyper eye medical system; ICG = indocyanine green; Mini-Flare = mini-fluorescence-assisted resection and exploration; n. = number of cases; NEWS = non-exposed endoscopic wall-inversion surgery; NIR = near-infrared; Op. = operation; PDE = photodynamic eye; SN = sentinel node.

Fig. 3. Near-infrared fluorescence signal intensity of indocyanine green depending on the concentration of indocyanine green and albumin measure using the IVIS® spectrum in vivo imaging system (Xenogen Corporation, CA, USA).

either 5 mg/ml or 2.5 mg/ml, and this concentration cannot provide any NIR signal unless it is diluted numerous times. Theoretically, if a high concentration of ICG is injected, a nearby lymph node cannot be detected before the concentration is diluted. Therefore, the amount or the concentration of injected ICG should be decided such that the final concentration after dilution of injected ICG in the stomach can achieve the concentration of the highest signal. Because ICG is a free molecule and is rapidly and widely diffused, an excessive concentration of ICG can highlight too many lymph nodes for use in sentinel node biopsy. In addition, ICG can diffuse to adjacent soft tissues surrounding lymph nodes and stain the operative field via spillage from soft tissues during dissection. The timing of injection may also affect the decision regarding the injection dosage, but there are not a sufficient number of studies to clarify this effect to date. Yoshida et al. injected ICG via the endoscopic method one day before the operation. In this study, the ICG fluorescence of a patient injected 100 mg/ml was too intense and that of a patient injected 25 mg/mL was too faint.²⁷

In the human body, a significant proportion of ICG is attached to albumin. Albumin stabilizes and maintains the distance between the ICG molecules, and different albumin concentrations can affect the NIR signal intensity of ICG. Once ICG powder is mixed with the provided solution, it starts to lose the NIR signal via bleaching. The signal can be lost after 24 hours in vitro; however, the signal persists for a couple of days after injection into living organs by attaching to albumin or via phagocytosis by macrophages.³⁶

Regarding the volume of ICG solution, Kinami et al. injected 50 $\mu\text{g/ml}$ of ICG 4 quadrants of the primary tumor on the day prior to the surgery and compared 0.5 ml and 0.2 ml of injection at each site in terms of the number of bright nodes.²⁶

No differences in bright nodes were noted between the two groups [6 (range, 3~11) in the 0.5 ml group and 6 (range, 2~7) in the 0.2 ml group]. They determined that the adequate injection volume of ICG solution was 0.5 ml, and many other investigators used 0.5 ml given its technical reliability.

TIMING OF INJECTION

The injection is performed either at the time of initiation of the operation or 1 day before operation (Table 1). The advantage of the intraoperative injection is that the injection can be made under visual control in the operative view to minimize spillage and control spillage when it occurs regardless of whether a subserosal or submucosal injection is performed. The length of time is required for diffusion of ICG from the injection site to the lymph nodes has been not well established, but the lymphatic vessels are often visualized immediately after injection.^{22,23} Here, 10~20 minutes may be a sufficient waiting time.^{25,26,31}

Preoperative injection can be selected when endoscopy is not easily available in the operation theatre. Visualization of lymph nodes as well as lymphatic channels is regarded as an additional benefit compared with methods using radioisotopes. Although the lymphatic channels are more clearly visualized during the early period after intraoperative injection, it was also reported that lymphatic channels were visualized with an injection performed 1 day before operation.²³ Some authors reported that the intraoperative injection resulted in frequent fluorescence leakage from injured lymphatic vessels and too many false positive lymph nodes in case of intraoperative injection. These researchers preferred pre-operative injection.^{23,27}

Lymph nodes with NIR signals remaining one day after injection could be either sentinel lymph nodes or more distant

Fig. 4. Possible scenarios of ICG distribution at the injection site and the sequential lymph nodes. (A) Distribution of ICG immediately after injection. (B) A scenario of one day after injection, ICG at the injection site and the sentinel lymph node is washed out first, resulting in increased stain in the 2nd or distant tier's lymph nodes. (C) The other scenario of one day after injection, ICG is still continuously provided to the 1st lymph nodes, and ICG was washed out of the 2nd lymph nodes. This scenario results in more specific sentinel lymph node navigation.

lymph nodes from the injection site. If the ICG is washed out sequentially from the injection site to the 1st tier lymph node and more distant lymph nodes, it is more likely that the bright lymph nodes are 2nd or 3rd tier lymph nodes after sentinel lymph nodes (Fig. 4B). On the other hand, if ICG at the injection site continuously provides ICG to the 1st lymph nodes and the ICG at the distal lymph nodes is drained, the remaining bright lymph nodes are more likely sentinel nodes (Fig. 4C). To date, the second scenario seems to better explain the results of previous reports indicating that the bright lymph nodes were located near the ICG injection site.

NUMBER OF SENTINEL LYMPH NODES

There is no solid consensus about the ideal number of sentinel lymph nodes in gastric cancer surgery. Some examples of number of lymph nodes include 2~2.8 when using the dye method^{37,38} and 3.3~4.1 when using dual tracers.^{14,39} To increase the sensitivity of the identification of sentinel lymph nodes and reduce false negative nodes, which can be the most important value in terms of oncologic safety, an increased number of sentinel lymph nodes can be acceptable. However, there are practical limitations regarding the resection and evaluation of too many lymph nodes determine whether cancer cells are present inside those lymph nodes. Furthermore, basin dissection rather than node selection is recommended for gastric cancer considering the false negative lymph nodes in the same basin of false positive lymph nodes. If ICG spreads to too many basins, reducing the number of sentinel lymph nodes or tailoring the extent of the dissection can be meaningless. Ryu et al. performed a meta-analysis of the 46 studies which used dye, radioisotope or both tracer, and reported that a sen-

sitivity of the pooled estimate of studies became significantly improved when the number of the sentinel node is 5 or more compares to 4 or less number of the sentinel nodes (92.6% vs 82.3%) and there was no further improvement of sensitivity as the number of the sentinel node increases.⁴⁰ Based on this result, a Korean multicenter clinical trial (SENORITA) suggested an optimal number of sentinel lymph node as at least 5.⁴¹

Tajima et al. endoscopically injected 0.5% (5 mg/ml) of ICG at 4 sites around the tumor using a 0.5-ml injection volume at each site 1~3 days before operation, and 7.2 ± 7.0 (1~30) lymph nodes were brightened.²³ Miyashiro et al. injected 0.5~2.5 mg/ml of ICG at 4 sites around the tumor using a 0.5-ml of injection volume by intraoperative endoscopy, and 3.1 ± 1.5 lymph nodes were identified. Yoshida et al. injected 0.05 mg/ml of ICG using a 0.5-ml volume via endoscopy one day before surgery, and 3.6 ± 2.1 lymph nodes were identified. Kinami et al. injected ICG in a similar manner, and the median number of lymph nodes was 6 (3~11). These limited results suggest that the high concentration can affect many lymph nodes, and the 0.05 mg/ml concentration and 0.5-ml volume can serve as a reference dosage for further studies.

However, the optimal dosage depends on different factors, including timing of injection, amount of fat in the perigastric lymphatic basins, and different imaging devices with different sensitivities. These factors should be further studied.

FUTURE OF NODE NAVIGATION USING NIR IMAGING

A fundamental question about sentinel lymph node navigation is whether it can solve current concerns about false negative issues and can be established as a standard treatment of

gastric cancer.⁴²⁻⁴⁵ Further development of the basin dissection concept and strategies to chase the lymphatic pathway and lymph nodes with NIR signals may provide additional solutions.

In addition, the advantages of NIR imaging over current optimal options, such as a dual method with vital dye and radioisotope, include improved visualization and sensitivity compared with vital dyes and lack of radioactive concerns, supporting the possibility of replacing the dual method with single NIR imaging. Otherwise, NIR imaging could be justified if it can provide optimal safety for sentinel node navigation surgery when combined with radioisotopes. Skubleny et al. recently published a meta-analysis of sentinel lymph node biopsy using indocyanine green and infrared or fluorescent imaging of gastric cancer.⁴⁶ The sensitivity of this meta-analysis was relatively low as 87% (0.80~0.93) in pooled analysis. The study also reported sensitivity of the studies using infrared electronic endoscopic as 97% and that of the studies using NIR fluorescent imaging systems as 72%.^{24,28} However, only 2 studies with NIR imaging system were included in this study, and the studies included high proportion of cases with advanced gastric cancer. A large comparison study to compare ICG NIR imaging and the dual method is needed, too. Some small studies of breast cancer and gynecologic cancers suggested non-inferiority of NIR imaging compared with radioisotopes.⁴⁷⁻⁴⁹ Given the low incidence of lymph node metastasis from early gastric cancer, thousands of cases may be required to obtain sufficient statistical power to obtain a high level of evidence.

A tool for guidance or evaluation of wide radical lymph node dissection is another possible application of ICG NIR imaging technology more for advanced gastric cancer cases. In particular, the technology may help surgeons in Western countries who are not familiar with wide lymph node dissection. At the present time, this technique can be regarded as an additional tool for these purposes because false positive and false negative results are inferior in cases of advanced cancer compared with early gastric cancer cancers.^{22,23} This finding is probably due to blocking of lymphatic channels and lymph nodes by tumor cells. On the other hand, some researchers may be concerned about the possibility of unnecessary extensive surgery and subsequent complications, which could be caused by too sensitive and wide false positive ICG signals. Therefore, whether the area with ICG NIR signal can represent all the lymphatic structures within the area of standard lymph node dissection, whether further dissection of area with ICG signal outside the boundary of the standard lymph node dissection, and whether this technology can contribute the patients survival should be further studied in clinical trials.

Research is ongoing to overcome the limitations of ICG,

such as the rapid and wide distribution and non-specificity for the cancer. Some of examples include the use of modified cyanine dyes to increase the size to limit the diffusion of the tracer and monoclonal antibodies or affibodies tagged with NIR dye, which are specific to the molecular targets.^{16,28,36,50-53}

Multi-functional dyes, which can be detected by multiple diagnostic tools, including pre-operative CT or MRI, NIR imaging systems, and gamma-probe detectors for radioisotopes, may be helpful to plan and implement comprehensive planning and surgeries for gastric cancer.^{54,55}

CONCLUSIONS

NIR imaging investigations of lymph node navigation in gastric cancer surgery is a promising tool with possible advantages compared with vital dyes or radioisotopes. Given the characteristics of ICG, including quenching and fast diffusion, diluted concentrations are suggested for sentinel lymph node biopsy. A large-scale study is required to evaluate the accuracy of prediction of lymph node metastasis, and this technique should be compared with dual methods using vital dyes and radioisotopes.

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