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Sentinel node navigation surgery using near-infrared indocyanine green fluorescence in early gastric cancer

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Abstract

Background The aim of this study was to evaluate the feasibility of indocyanine green (ICG) fluorescent method for sentinel lymph node detection in early gastric cancer.

Methods Between December 2012 and December 2014, 28 cases of pilot examination were performed at Seoul National University Bundang Hospital. Advanced version of multispectral fluorescence organoscope was used to identify sentinel node by quantitative estimation of ICG fluorescent signal intensity. Sensitivity, specificity, false positive value were analyzed and compared with dual tracer method.

Results A total of 443 lymph nodes in 28 cases were examined and 184 sentinel nodes (41.5%) were identified by dual tracer method. The sensitivity using near-infrared ICG method was 98.9%. The specificity was 76.0% and false positive rate was 25.4% compared with dual tracer method. The adequate threshold for sentinel node detection was considered as 10% of maximum signal intensity.

Conclusion New near-infrared ICG fluorescent method could be a promising protocol for sentinel node navigation surgery in early gastric cancer.

Keywords Sentinel node navigation surgery · Early gastric cancer · ICG fluorescent signal intensity

Along with the advancement of diagnostic tools and spread of early screening system, the proportion of detecting early gastric cancer (EGC) now exceeds 60% in Korea and Japan [1, 2]. In gastric cancer, lymph node metastasis is the most important prognostic factor, and it is reported to be found in 2–18% of EGC [3, 4]. In order to predict lymph node metastasis in EGC with greater precision, the idea of sentinel lymph node is applicated in gastric cancer fields [5–9].

Sentinel node navigation surgery (SNNS) for gastric cancer is a surgery aiming to detect sentinel lymph node by means of injecting the tracer around the tumor and finding the lymph nodes with the earliest tracer spreading. SNNS has been adopted initially by using indocyanine green (ICG) as a sole tracer in the early days, resulting in low detection rate. Various studies introduced utilizing ICG with radioisotope (dual method) afterwards, making remarkable improvement in sensitivity and specificity [10]. This method, first introduced by Kitagawa et al., uses the blue dye which disseminates through lymphatic vessels and lymph node, making it grossly visible, while gamma probe is being used simultaneously for detecting radioactive lymph nodes [11].

Dual method, however, has some aspects which make it difficult to be used popularly for treating gastric cancer patients, even if it is established as a standard treatment. The particle size of radioisotope and ICG is different and exists as a simple mix-up without any chemical bonding

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or conjugation, making it difficult to determine the sentinel node accurately. Also, the patients need to suffer the fear of radiation exposure and the operation room should be a scale in which radiation devices could be accommodated [12, 13].

Various studies are ongoing in efforts to find sentinel lymph node without usage of radiation. Fluorescent imaging technology is a representative example, where near-infrared imaging system has been introduced many times as a method to increase sensitivity [14–16], while recently a newer approach of using blue light also reported high sensitivity and accuracy [17]. These studies, however, focused only on refraining the use of radiation and visibly identifying sentinel nodes with more precision. They could not substitute the radioisotope method which has greatest strength in numerically objectifying the sentinel node.

We introduce a SNNS utilizing an advanced version of multispectral fluorescence organoscope which can quantitatively estimate and objectify the ICG fluorescent signal intensity. We designed a method of using only fluorescence signal intensity of ICG, when sorting sentinel nodes and non-sentinel nodes in the back table after sentinel basin dissection. The purpose of this study is to verify whether the device can detect sentinel lymph node as much as dual method by using only dye method and finding out whether fluorescence signal intensity can be quantified.

Methods

Study design and participants

A pilot examination was performed in 28 patients diagnosed with gastric adenocarcinoma in Seoul National University Bundang Hospital from December 2012 to December 2014. The patients were fully informed of the study and filled out a written informed consent. This study was a single-arm, open-label, and prospective study. The study was approved by Institutional Review Board of Seoul National University Bundang Hospital (Registration Number: E-1208/167007) and the medical device used for the trial was approved by Korea Food and Drug Administration. In addition, this trial was approved as a clinical study (Registration Number: NCT01441310) by the Clinical Research Information Service (http://www.clinicaltrials.gov).

Eligibility criteria

The criteria for eligibility were histologically proven gastric adenocarcinoma; clinical stage of T1N0M0 according to the 7th edition of the American Joint Committee on Cancer System [18]; an age of 20–80 years; and tumor size less than 4 cm. Patients who did not understand or refuse to participate in the study were excluded. Patients with the following conditions were also excluded: serious concomitant illnesses; history of hypersensitivity to contrast media; and porphyria.

Multispectral fluorescence organoscope

Multispectral fluorescence organoscope (ANIMA scope) used in this study was first developed by Korea Electrotechnology Research Institute which was initially used as a preclinical fluorescence measurement device (Fig. 1A). This device has been originally employed for preclinical usage in recording multispectral fluorescence image and determining signal intensity of the fluorescent materials. For example, the course of cancer cell invasion or drug dissemination after injection has been traced by this device. The system is composed of a camera obtaining the fluorescent image, and a light source that irradiates the object, each of which is controlled by a computer. The light source is divided into three components: an intense pulse light component, a 635 nm laser component, and an 808 nm component. The intense pulse light component irradiates white light and intense pulse light within visible light range. The 635 nm laser component is used for excitation of self-fluorescence, and the 808 nm component for excitation of near-infrared fluorescence (Fig. 1B). The lymph node procured from the sentinel basin is put into the ANIMA scope in which it is subjected to excitation by 808 nm laser. Thereafter, the camera component measures the intensity of fluorescence and yields the value in numbers [19]. The distance between the specimen and the light source was set to 200 mm. The unit was expressed in AU (arbitrary unit), which is a relative value where normal tissue for each individual was set as a standard value.

Procedure for detecting sentinel lymph node

SNNS was conducted based on the prementioned standard dual method, while the sentinel node and non-sentinel node were separated in the back table, accordingly [5]. Sentinel node was defined conventionally, into blue node, hot node, and hot and blue node. These categorized lymph nodes were observed with ANIMA scope, and the intensity of ICG fluorescence was measured. The acquired lymph nodes were sent for frozen biopsy, and the pathologist carried out hematoxylin and eosin staining to check for micrometastasis. Once the lymph node was confirmed to be free from metastasis, stomach preserving surgery was performed. If sentinel lymph node metastasis was present, standard surgery was proceeded in accordance with the Japanese Gastric Cancer Treatment Guidelines 2010 (version 3) [20].

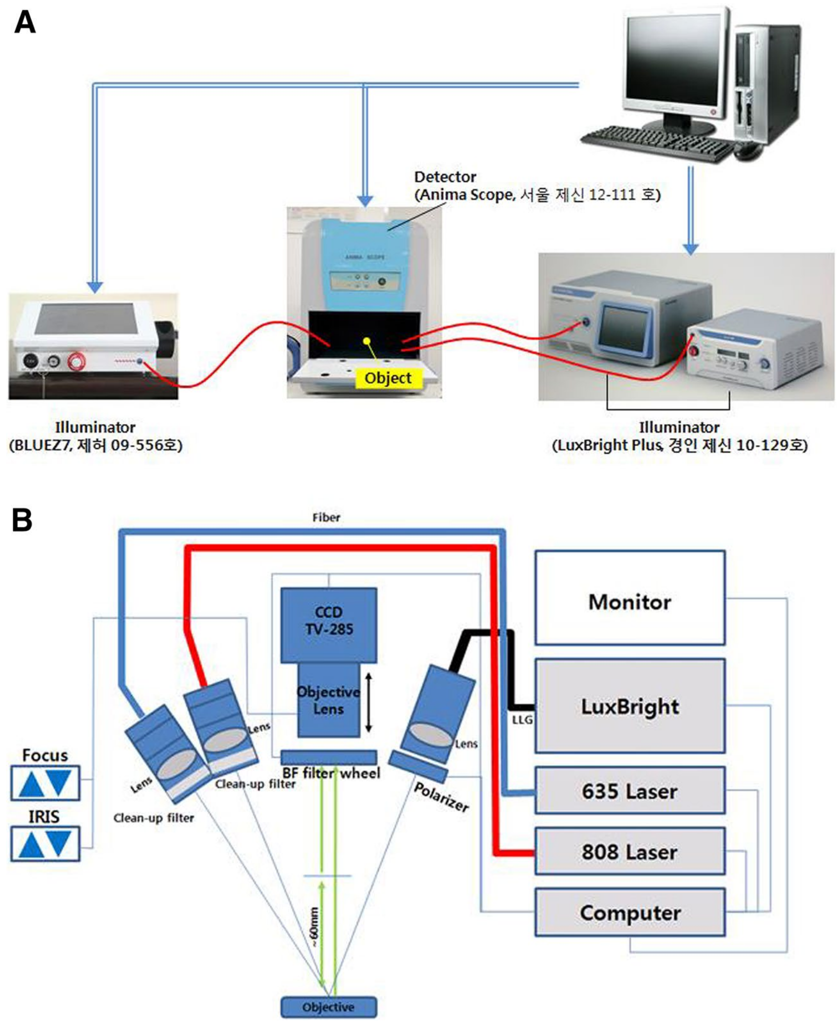

Fig. 1 Multispectral fluorescence organoscope (ANIMA scope). **A** Layout **B** schematic diagram

Data collection

The basic information of the enrolled patients concerning age and sex was collected, and the information on surgical outcome was analyzed. Fluorescence value was recorded for the nodes obtained from each patient, and a cut-off value was targeted for sensitivity that would reach 100% when compared with dual method. It was predictable that the absolute value of the signal intensity would not be a good parameter for cut-off value due to its variability between patients. Hence, we decided to define the cut-off value as the ratio of intensity for the minimum signal value of sentinel lymph node in each patient. The new sentinel lymph node detection method and initial dual method was compared based on this cut-off value to determine the sensitivity, specificity, and false positivity.

Results

Demographic data and surgical outcomes are shown in Table 1. Among the 28 patients enrolled, the mean (SD) age was 56.8 (14.6) years, while male-to-female ratio was 57–43%. Permanent biopsy result showed EGC for all except one patient, and sentinel lymph node metastasis was found in two patients. Complication occurred in two patients; 73-year-old male patient with delayed gastric emptying and 51-year-old male patient with hematoma in perigastric area, all of whom managed with conservative care. There was no mortality.

Table 2 shows an example of sentinel basin mapping from Patient Number 7 out of the 28 patients. In Patient 7, 1 hot and blue node and 10 hot nodes were detected, which were located in node station #6 and #8, while 4 non-sentinel nodes

Table 1 Profile of enrolled patients in pilot study (*N* = 28)

Age, mean (SD), year	56.8 (14.6)
Gender	
Male	16 (57%)
Female	12 (43%)
Tumor size, median (IQR), cm	1.6 (0.7–3.3)
Operation time, mean (SD), min	218.2 (47.4)
Depth of invasion	
Mucosa	20 (71%)
Submucosa	7 (25%)
Proper muscle	0 (0%)
Subserosa	1 (4%)
Operation	
Segmental resection	11 (39%)
Hemi-gastrectomy	6 (21%)
Distal gastrectomy	3 (11%)
Antrectomy	5 (18%)
Pylorus preserving gastrectomy	3 (11%)
Lymph node metastasis	
Yes	2 (7%)
No	26 (93%)
Complication[a]	2 (7%)

[a]Delayed gastric emptying and hematoma in perigastric area

Table 2 The value of ICG intensity of patient number 7

Node no.	Location[a]	Hot node	Blue node	ICG intensity (AU)
1	#6	+	+	3700
2	#6	+	−	2700
3	#6	+	−	2900
4	#6	+	−	5300
5	#6	+	−	3900
6	#6	+	−	1100
7	#6	+	−	3600
8	#6	+	−	2800
9	#6	+	−	3700
10	#6	+	−	4200
11	#8	+	−	4300
12	#3	−	−	342
13	#3	−	−	303
14	#3	−	−	1034
15	#3	−	−	315

ICG indocyanine green, *AU* arbitrary unit

[a]The station number was described according to the Japanese Classification of Gastric Carcinoma

were found in node #3. The maximum value of fluorescence emitted from sentinel lymph node was 5300 AU and minimum value was 1100 AU when measured with the ANIMA scope. The fluorescence value was also measured for all non-sentinel nodes.

The result of sentinel basin mapping for 28 patients is described in Table 3. There was no case of blue node found alone. As for the nodes defined as sentinel node by dual method, maximum and minimum fluorescence value and each of its ratio was calculated. Cut-off value for all 28 patients is shown in Fig. 2. The minimum fluorescence values for Patient 18 and 24 were 145 AU and 260 AU, respectively, which is an exceedingly low value with respect to the maximum value, resulting in a cut-off value of 0.02. No sentinel node metastasis was found in these two patients. Other 26 patients, excluding the former two patients, showed a minimum/maximum value above 0.1 including Patient 7 and 23 who were sentinel node positive in frozen biopsy. Thus, in order to minimize false positivity and reach 100% sensitivity, we defined the cut-off value as 10% of the maximum fluorescence value and regarded any value above this as sentinel lymph node. After establishing the definition, comparison was made with the dual method, concerning sensitivity, specificity, and false positive rate, which is recorded in Table 4. The new sentinel node detection method missed two nodes that were found positive by dual method (nodes that showed minimum value in Patient 18 and 24), while detecting 62 sentinel nodes that were non-sentinel nodes in dual method. Considering the dual method as a gold standard, sensitivity, specificity, and false positive rates were 98.9%, 76.0%, and 25.4%, respectively. Neither late complication nor tumor recurrence was found in any of the patients up until December, 2017 (follow-up loss in 3 patients).

Discussion

Sentinel lymph node is defined as first lymph node drained from the primary tumor. SNNS is referred as a procedure, in which the extent of the surgery is dependent upon the status of lymph node metastasis. The essential part of improving the accuracy of SNNS is the usage of the most efficient tracer with a detection system with an effective identification [21]. Most commonly used tracers are vital dye which can be traced by naked eye, and radioisotopes which can be traced in digits using gamma probes. Dual tracer method, using both of these tracers, possesses the most acceptable sensitivity and accuracy and is used in many clinical studies as a standard procedure [22–25].

Drawbacks exist, however, that the two tracers used in the dual method are not concomitant, making it less accurate, and also by the fact that it uses radiation. Usage of radiation is both burdensome for the patient and the operator due to radiologic hazard. The hospital also needs to be equipped with the radioisotope detecting device. Inconvenient annual curriculums are obliged to all participating members of the

Table 3 Result of sentinel basin mapping

Patient	SLN			NSLN	MAX	MIN	Cut-off[a]
	HBN	HN	Location				
1	2	3	#3,7	3	7538	3708	0.49
2	0	2	#3,7	8	5126	4117	0.80
3	1	5	#6,7	8	7749	850	0.11
4	2	0	#6,8	17	7713	5216	0.68
5	6	1	#3,7	4	7142	3000	0.42
6	3	3	#3,7	5	4300	2247	0.52
7[b]	1	10	#6,8	4	5300	1100	0.21
8	1	1	#4d	2	5100	2400	0.47
9	2	14	#1,3	6	5700	1300	0.23
10	1	2	#3,4d	21	3485	1900	0.55
11	2	4	#6,7	4	6637	3435	0.52
12	1	3	#1,3	7	4093	3039	0.74
13	2	0	#1,3	2	5364	3040	0.57
14	0	10	#3,4d,6,7	7	7756	1140	0.15
15	0	10	#3	8	4834	1444	0.30
16	2	0	#3	0	1980	1600	0.81
17	1	4	#4d	22	5408	1500	0.29
18[c]	3	8	#6,8	20	6710	145	0.02
19	1	7	#4d	15	3734	800	0.21
20	0	9	#3	17	7634	1362	0.18
21	1	10	#3,4d,7	21	14,000	4200	0.30
22	2	6	#4d,6	9	9000	3300	0.37
23[b]	3	8	#3,4d,6	12	29,509	8730	0.30
24[c]	2	4	#3,4d	12	14,000	260	0.02
25	0	4	#3	1	4100	1530	0.37
26	1	8	#3,7	16	35,000	19,000	0.54
27	0	2	#6	5	6800	4500	0.66
28	0	6	#4d	3	12,000	2200	0.18

SLN sentinel lymph node, *HBN* hot and blue node, *HN* hot node, *NSLN* non-sentinel lymph node, *MAX* maximum fluorescence intensity of sentinel node, *MIN* minimum fluorescence intensity of sentinel node

[a]The cut-off value was calculated from the ratio of the highest and lowest value of sentinel node fluorescence intensity

[b]Patient 7 and 23 showed sentinel node metastasis in frozen biopsy

[c]The minimum fluorescence values for Patient 18 and 24 were an exceedingly low value with respect to the maximum value (cut-off 0.02)

operation regarding radio hazard-proof protocols. There was a need to detect sentinel node without using radiation in order for SNNS to become more popular, pushing the researchers to discard radioisotope and to focus on developing techniques to discriminate the vital dye more clearly. The most commonly used technique is near-infrared light imaging, which by using ICG as a tracer along with fluorophore makes the sentinel basin more distinctly visible for resection [14, 15].

The advancement of fluorescent imaging technology will play an important role in popularizing SNNS. Patients will be able to receive surgery without feeling insecure if sentinel node can be found without using radiation. Subdivision of fluorescent imaging technology is differentiated by using different wave length, light, and vital dye, but the aforementioned techniques eventually depend on the human eye which detects the fluorescence in order to remove the sentinel basin. Decision making done only by the means of human eye is extremely subjective and poses a danger of false negativity which may result in losing a chance of cure in gastric cancer. Gamma probe reinforces the dual method by objectively measuring the radioisotope. The intensity of radioisotope is expressed in numbers to objectively check the sentinel node, which is the reason why dual method is currently adopted as a standard procedure. Then, would it be possible to objectively quantify the sentinel node with

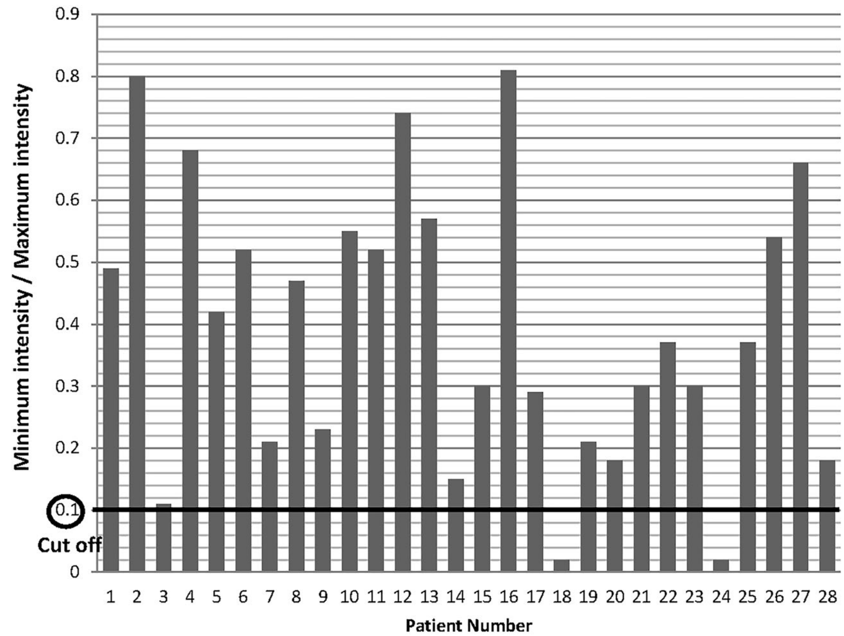

Fig. 2 Cut-off value

Table 4 Comparison of sentinel basin dissection between dual method and new sentinel node detection method (cut-off value 10%)

	Dual method	New sentinel node detection method
Number of sentinel nodes	184	244
Number of non-sentinel node	259	199
Total number of lymph node	443	443
Sensitivity (%)[a]		98.9 (182/184)
Specificity (%)		76.0 (197/259)
False positivity (%)[b]		25.4 (62/244)
False negativity (%)		1.0 (2/199)

[a]New sentinel node detection method missed two nodes that were found positive by dual method

[b]New sentinel node detection method detected 62 sentinel nodes that were non-sentinel nodes in dual method

sensitivity and specificity similar to dual method without using radioisotope? We initiated this pilot study in thoughts that if the fluorescence expression could be objectified in numbers in collaboration with fluorescent imaging technique; it could substitute the dual method completely and safely without using radiation.

Sentinel basin dissection was performed in 28 patients using the standard dual method, and all hot node, hot and blue node, and non-sentinel node were identified in the back table. Each and every node were picked and put in the ANIMA scope and their values were recorded. The ICG intensities checked in the sentinel nodes were generally higher than the parameters from non-sentinel nodes (Fig. 3). We needed to set a standard fluorescence value for each individual patient in order to detect all of the nodes confirmed to be sentinel node by dual method. The cut-off value was calculated from the ratio of the highest and lowest value of sentinel node fluorescence intensity. The result showed that it was most reasonable to exclude Patient 18 and 24, whose intensity in the sentinel node showed an exceptionally low value (confirmed to be free from metastasis), and to regard any value above 10% of the maximum fluorescence value to be sentinel nodes (Fig. 2). In Patient 7 and 23 who showed to have actual lymph node metastasis by pathologic finding, sentinel node was readily detectable from the 10% cut-off value.

We believe that this study will play a role in popularizing SNNS in gastric cancer. Although false positivity is 25.4% which is relatively high compared to the current standard of dual method, ANIMA scope was able to detect nearly 99% of sentinel nodes found by dual method. Also, our attempt marks the first prospective study to numerically objectify the sentinel node without using radiation, and the procedure was easily performed without using any sophisticated or dangerous devices. By using near-infrared imaging to detect sentinel nodes and checking the fluorescence intensity by ANIMA scope, a new kind of dual method may be adopted for SNNS as a standard procedure.

There are, however, some limitations in this study. First, the fluorescence intensity parameters had a wide variation between each individual. For example, the highest value for sentinel node is 35,000 AU in Patient 26, but Patient 25 showed 4100 AU, revealing a large gap existing between patients. Patients 18 and 24, who were excluded from the analysis, showed lowest sentinel lymph node value of 145 AU and 260 AU, which is a value lower than

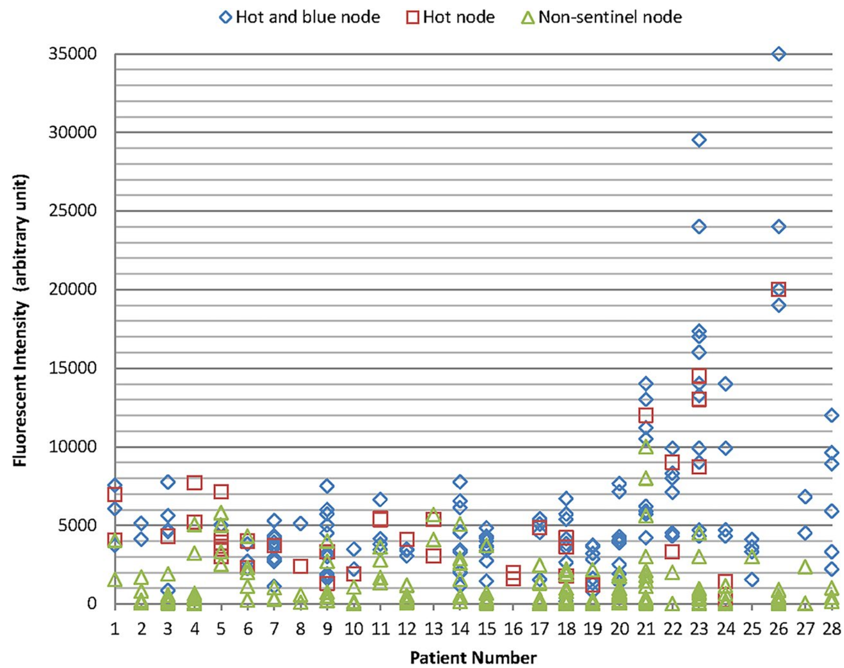

Fig. 3 The value of ICG intensity of all patients (scatter plot)

non-sentinel node (Table 3). Although no metastasis was observed in the frozen biopsy, these two lymph nodes deterred the achievement of zero false negativity in comparison with the dual method, which can be a potential threat to patients. Among many explanations for this phenomenon, the initial reason is due to a fundamental problem of ICG fluorescence inevitably showing individual discrepancy. The condition of lymphatic flow, body mass index, and the amount of visceral fat all differs between patients, and the accuracy of submucosal injection largely depends on the experience of the endoscopist, associated with the difference in fluorescence between individuals. More important factor is the depth of the measured signal. The measured depth indicates the depth of lymph node or any other target from the surface. If the target is deep under the surface, it may be measurable, but the signal weakens after passing through vessels, nerves, and connective tissues [26]. In this study, each node was picked in the back table and the fluorescence intensity was quantified through the ANIMA scope. Even if the nodes were cleanly dissected, the density and the component of the fat tissue surrounding the nodes differ for each patient, naturally resulting in discrepancy in fluorescence value. Blood or any other debris around the nodes or even electrocoagulation may affect the fluorescence value. Since these factors hinder an accurate comparison between individuals, it is preferable to search for sentinel nodes based on comparison between normal autologous tissues that are expected to lack fluorescence for each patient. Once technical advancement is achieved on data correction in relation to the depth, more accurate results can be drawn.

Second limitation is a high false positivity compared to dual method. While this study proposed a cut-off value of 10%, the applied calculation resulted in counting 62 nodes as a sentinel lymph node which the dual method sorted as a non-sentinel node. For example, node number 14 from Patient 7 showed 1034 AU, which is a non-sentinel node when using dual method. ANIMA scope, however, measured over 530 AU (10% of maximum value of 5300 AU), diagnosing it as sentinel node (Table 2). High false positivity degrades the efficiency of the procedure and delays the operation time, which could be an obstacle in popularization of ANIMA scope.

Third limitation is the need for the lymph node to be extracted for it to be measured. Dual method uses laparoscopic gamma radioisotope probe inside the inflated abdominal cavity where the sentinel basin dissection is performed for detection of sentinel lymph node. In this study, however, near-infrared image was used for the removal of sentinel basin, and the extracted node was put in the ANIMA scope outside of the body. Consequently, the process of sentinel basin dissection was performed by resecting nodes that were identified by naked eye, meaning that the procedure was carried out without any method of objectification. This is a common issue in all measuring devices, of the fact that difficulty exists in measuring substances under dynamic condition. The measurement of fluorescence is particularly sensitive, and the outcome may likely be inaccurate if measurement is not made in a fixed position. Further advancement of technology will be able to create ANIMA scope for laparoscopic usage, but it is doubtful that the laparoscopic environment surpasses the fluorescent measurement done by extracorporeal method. Lastly, this is a pilot study with limited sample size. Further evaluation is needed in regards to the validity of the method in detecting sentinel basin.

In conclusion, by using ANIMA scope, we were able to detect all sentinel nodes possible by dual method. Even though it is a small sampled pilot study, objectification by quantification of sentinel node was possible in EGC patients by using only vital dye. If supplemented by using ANIMA scope, we expect that the fluorescent imaging technology, which is currently in a rapidly developing pace, can become one of the methods which would be able to replace the initial dual method.

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Compliance with ethical standards

Disclosure Dong-Wook Kim, Bosu Jeong, Il-hyung Shin, Uk Kang, Yoontaek Lee, Young Suk Park, Sang-Hoon Ahn, Do Joong Park, and Hyung-Ho Kim have no conflicts of interest or financial ties to disclose.

Ethical approval The study was approved by Institutional Review Board of Seoul National University Bundang Hospital (registration number: E-1208/167007). The patients were fully informed of the study and filled out a written informed consent. This study was conducted according to the principles of the Declaration of Helsinki.

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