

Laparoscopic sentinel node navigation surgery for early gastric cancer: a prospective multicenter trial

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Abstract

Background Prospective multicenter trials have shown the feasibility of sentinel node (SN) navigation surgery using a dual tracer of dye and radioisotope for early gastric cancer. However, comparable trials using the indocyanine green (ICG) and the infrared ray laparoscopic system (IRLS) have not been reported. On the basis of our cohort studies, we assumed that the ICG imaging with the IRLS is as effective as the dual tracer in detecting SNs. Therefore, we conducted a prospective multicenter trial to assess the effectiveness and generalizability of the infrared ICG technique in patients with early gastric cancer.

Patients and methods Patients with previously untreated cT1 gastric adenocarcinomas less than 4 cm in gross diameter were eligible for inclusion in this study. SN mapping was performed by using ICG combined with IRLS technique. Following biopsy of the identified SNs, D2 or modified D2 laparoscopic gastrectomy was performed according to the current Japanese Gastric Cancer Association guidelines.

Results Among the 47 patients who gave written informed consent, 44 were eligible from the surgical findings, for whom

SN biopsy was performed. The detection rate of the lymphatic basin by the ICG with IRLS was 100% (44/44). The accuracy was also 100% (7/7) for detecting metastatic lymph node, which was verified on the permanent pathologic examination. Following the median follow-up of 114 months (range, 60 to 120 months), no recurrence (0/40) was observed. Although the number of patients was unequally distributed among the hospitals participating in the trial, the detection rates of SNs in low-volume hospitals were comparable to those in high-volume hospitals. Consequently, there was no learning curve in this trial.

Conclusion The infrared ICG imaging accurately detected the lymphatic basin and SNs with occult metastasis in SN-navigated gastrectomy for gastric cancer. This method was feasible even for low-volume surgeons and hospitals.

Keywords Sentinel node navigation surgery · Gastric cancer · Infrared indocyanine green

Abbreviations

ICG	Indocyanine green
SN	Sentinel node
SNNS	Sentinel node navigation surgery
IRLS	Infrared ray laparoscopic system

Introduction

Sentinel node (SN) navigation surgery has been well investigated and adopted in melanoma and breast cancer, allowing a reduction in the extent of surgical intervention with limited lymph node dissection [1, 2]. However, the clinical application of SN biopsy in early gastric cancer has long been debated due to the complicated lymphatic flow around the stomach

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and the inconsistent results. Some studies suggested the limitation of SN navigation surgery for early gastric cancer, because it could overlook a number of positive SNs [3, 4]. For the past decade, clinical trials using a dual tracer with dye and radioisotope [5] revealed that the dual tracer is better than the single tracer [6, 7] in detecting SNs in early gastric cancer. For instance, in a study using a dual tracer by Kitagawa et al. [8], the detection rate was 96%, the mean number of retrieved SNs was 4.1, sensitivity was 93%, and accuracy was 99%. In a retrospective study not using the radioisotope, we demonstrated that high detection and accuracy rates could be achieved with the indocyanine green (ICG) and infrared ray laparoscopic system (IRLS) in patients with early gastric cancer [9, 10]. In general, the use of radioactive substances was associated with high costs and potential biohazard, restricting its clinical application. ICG plus infrared ray method seems safer, more convenient, and less expensive compared with the method using radioisotope as a tracer. As far as we know, prospective multicenter studies using the infrared ICG imaging have not been published. Therefore, we conducted a trial to evaluate the clinical significance of SN mapping with the ICG and IRLS. The primary aim of this study was to assess the effectiveness of the infrared ICG technique across the hospitals with different experiences in SN navigation surgery for early gastric cancer. The secondary aim was to clarify the long-term outcome of the participants.

Patients and methods

Indication for sentinel node biopsy

Patients with previously untreated cT1N0M0 gastric adenocarcinomas less than 4 cm in gross diameter were eligible for inclusion in this study. Clinical staging was determined by routine preoperative endoscopy and computed tomography, while endoscopic ultrasound was not routinely performed. Patients with apparent T3/T4 tumors, nodal or distant metastasis diagnosed intraoperatively, and extensive abdominal adhesion were excluded from the study. Four institutions participated in this multicenter prospective study. Prior to entry in the trial, all surgeons were trained to be a surgeon for SN navigation surgery for early gastric cancer, but there were considerable differences in surgical volume among them. From July 2005 to June 2007, 47 patients were enrolled onto this study, all of whom were preoperatively registered in a central data center after obtaining written informed consent. This study was approved by all local institutional review boards and conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Sentinel node mapping, pathological evaluation, and learning curve

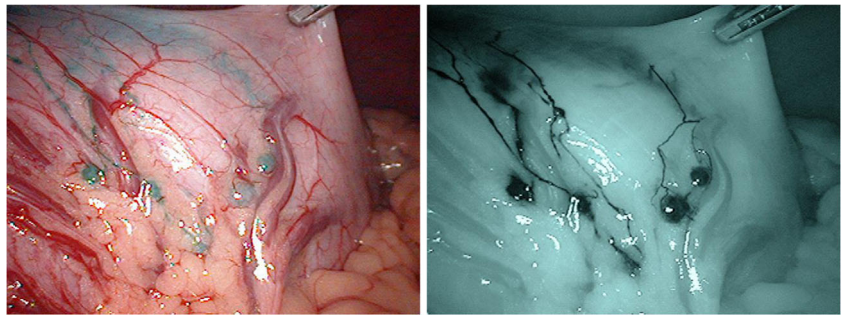
SN navigation surgery was performed as previously described [9]. Briefly, prior to ICG injection, the stomach was mobilized by dissecting through the gastrocolic ligament without disrupting the gastroepiploic vessels. ICG (5 mg/ml; Diagnogreen™, Daiichi Pharmaceutical, Tokyo, Japan) of 0.5 ml was injected endoscopically in four quadrants of the submucosa surrounding the tumor with an endoscopic puncture needle. At 20 min after the injection, SNs stained with ICG were observed with the naked eye (ordinary light observation) followed by the IRLS (Olympus Optical, Tokyo, Japan) (infrared light observation). Positive or negative staining was judged in concordance with at least two surgeons and one endoscopist. The lymphatic vessels and lymph nodes were dyed green by the ordinary light observation and they were seen in black by IRLS (Fig. 1). The detected lymphatic basin including SNs were resected laparoscopically and recorded according to the lymph node station numbers as described in The Japanese Classification of Gastric Carcinoma. Suspected SNs were then histologically examined intraoperatively in one plane (with the largest dimension) by frozen section with H&E staining. Laparoscopic gastrectomy with lymphadenectomy was performed regardless of the metastatic status of SNs on the frozen section examination. Postoperatively, permanent pathological examination was performed by the experienced pathologist, who was blinded to the SN status and detection methods. Both SNs and non-SNs were diagnosed by one plane (with the largest dimension).

To evaluate the presence of a learning curve, we analyzed the primary outcome for each surgeon. We attempted to follow up all patients on the outpatient basis for a long-term survival analysis.

Results

As shown in Fig. 2, one patient was preoperatively excluded and two others were excluded because of intraoperative findings ineligible for the trial. Finally, 44 patients underwent SN biopsies (Table 1). Adverse events associated with the SN biopsy did not occur during the study period. The detection rate of the lymphatic basin by the infrared light observation was much higher than that by the ordinary light observation (100 vs. 57%). At the back-table, the detection rate of the SN by the infrared light was 100%, while the SN detection rate determined by the ordinary light observation alone was 80% (35/44). Lymph node metastasis was pathologically confirmed in 16% of patients (7/44). The proportion of false negatives by the ordinary light observation was 57% (4/7); however, that by the infrared light observation was 0% (0/7) (Table 2). In five of these seven patients (71%), metastatic

Fig. 1 Lymphatic ducts and lymph nodes, which are difficult to see under ordinary light (*left*), can be clearly visualized under infrared light (*right*)



spread was limited to the SNs, and in the remaining two patients, metastases were limited to the area within the SN basins.

The number of patients enrolled in the trial were unevenly distributed among the surgeons and institutions (Table 3). There was no learning curve, although the sample size was too small to obtain a sufficient statistical power (Table 3). Four patients were lost to follow-up. Following the median follow-up of 114 months (range, 60 to 120 months), no recurrence was observed.

Discussion

In the present study, SNs were detected by the infrared light observation in all the patients during laparoscopic gastrectomy for early gastric cancer, while the SN detection rate was 80% in the ordinary light alone. In addition, the sensitivity of the infrared ICG for detecting SNs was 100%, which was much

higher than the 43% achieved by naked eye observation. There was no learning curve in the trial.

In the clinical trials using a dual tracer, efficacy of SN biopsy for early gastric cancer has been reported [11, 12]. Kitagawa et al. [11] suggested that SN mapping for gastric cancer with the dual tracer method was a feasible and safe procedure, because the detection rate of SNs was 97.5% and the false negative rate was 7% in their trial. In a more recent study, sentinel basins were detected in 100 of the 108 patients (92.6%), and all patients with nodal metastasis (10/10), which was confirmed on permanent section, were identified during surgery [12]. Oppositely, in a multicenter trial using the non-infrared ICG as a single tracer by Miyashiro et al. [13], a high false negative rate (46%) on interim analysis stopped patient accrual. The present study also revealed the suboptimal ability of the non-infrared ICG to detect SN and predict nodal metastasis, whereas the infrared ICG did not miss the SNs and nodal metastasis (Table 2).

Tonouchi et al. [14] conducted a literature review to determine the cause of false negative SN biopsies in gastric cancer

Fig. 2 Trial profile
abbreviations: SN sentinel node,
IRLS infrared ray laparoscopic
system

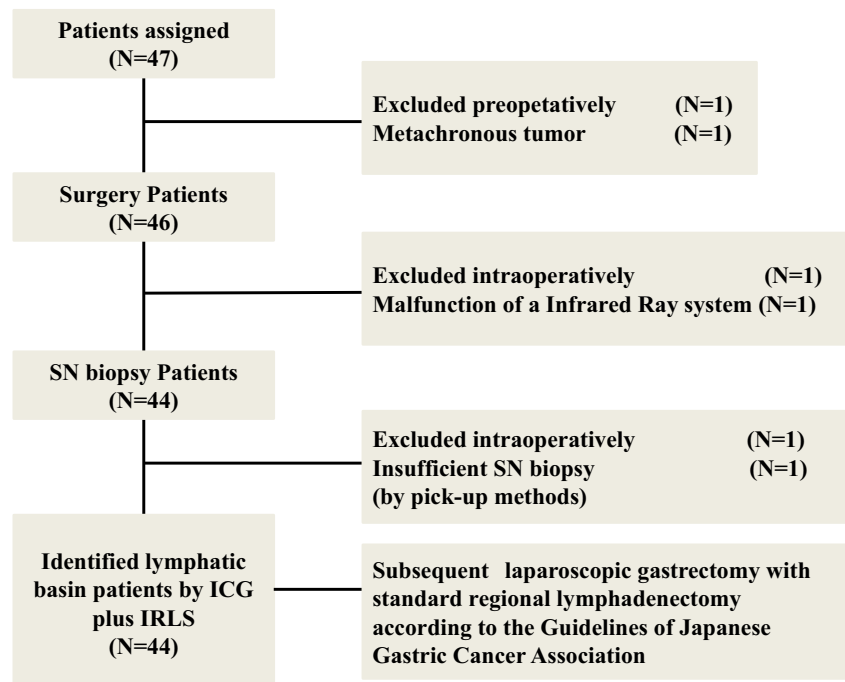


Table 1 Patients characteristics ($N = 44$)

Characteristics	No.	Percent
Age	60.9	
Mean	39–79	
Range		
Gender	35	80
Male	9	20
Female		
cT factor	24	53
M	9	21
SM1	11	26
SM2		
Tumor size (mm)	24.8	
(measured after gastrectomy)	6–68	
Mean		
Range		
Location of tumor	6	14
Upper third	25	57
Middle third	13	29
Lower third		

No. number, *M* mucosa, *SM* submucosa

and concluded that the common cause was lymphatic occlusion due to massive lymph node metastasis. Careful attention should be paid to the preoperative diagnosis of the T factor. Notably, the diagnostic accuracy of SN mapping for cT2 tumors is currently suboptimal; therefore, we believe that the clinical application of SN mapping should be limited to cT1 tumors. In a single-center study including 16 patients with early gastric cancer, the feasibility and usefulness of SN mapping with the infrared ICG was shown [15]. In our retrospective cohort study of 84 patients, SNs detected by ICG injection alone did not include metastases in 4 of 11 patients, whereas the infrared ICG imaging detected SNs containing lymph

node metastases in all 11 patients [9]. Therefore, we conducted this multicenter trial, assuming that outcomes of SN mapping by ICG combined with IRLS would be comparable to those of the dual tracer method.

Lee et al. [16] speculated that the learning period for identification of sentinel nodes in gastric cancer would be 26 cases, and the learning curve should be considered to minimize bias due to surgical factors in clinical trials for gastric cancer with SN mapping. In the present trial, the lymphatic basin was detected in all 44 cases, which was achieved by a combined team of well- and less-experienced surgeons. Although firm conclusion cannot be drawn from our study with a small sample size, it could be assumed that infrared ICG is feasible for less-experienced surgeons to perform SN navigation surgery under supervision after a short period of training. We acknowledge that the current study does not completely erase the concern about a considerable learning time required for achieving better and sustainable outcomes of SN-navigated gastrectomy with the infrared ICG imaging. There are a number of factors which may shorten the learning curve, including patient selection, the site of injection of ICG (submucosal or subserosal), and the observation timing after injection. Long-term outcomes of SN navigation surgery for early gastric cancer have been poorly studied. In 40 patients who could be followed-up for the median period of 114 months in the trial, no recurrence was observed. The use of infrared ICG imaging is being extended particularly to SN navigation surgery for early breast cancer [17] and early endometrial cancer [18] with high detection and accuracy rates. Since the first description of ICG fluorescence imaging with a charge-coupled device detecting fluorescence signals from SNs in

Table 2 Results of SN biopsy by ICG plus IRLS ($N = 44$)

Variable	No. (%)	Ordinary light No. (%)	Infrared light No. (%)
Intraoperative identification of lymphatic basin		25 (57)	44 (100)
Detected		19 (43)	0 (0)
Undetected			
SNs identification at the back table		35 (80)	44 (100)
Detected		9 (20)	0 (0)
Undetected			
No. of identified SNs		3.7 ± 4.0	7.9 ± 5.6
Mean ± SD			
pN factor	7 (16)		
Positive	37 (84)		
Negative			
LN metastasis in SNs		4/7 (57)	7/7 (100)
Positive		3/7 (43)	0/7 (0)
Negative (false negative)			

No. number, *SN* sentinel node, *IRLS* infrared ray laparoscopy system, *ICG* indocyanine green

Table 3 SN detection and false negative rates stratified by surgeons

Surgeon (experience)	No. of patients	Sentinel node visualization by ICG plus IRLS		
		No. of patients (%)		
A (>30)	26	Intraoperative SN basin detection 26 (100)	No. of pN+ 3 (11)	False negative 0 (0)
B (<30)	7	7 (100)	2 (29)	0 (0)
C (<10)	6	6 (100)	1 (17)	0 (0)
D (<10)	2	2 (100)	0 (0)	0 (0)
E (<10)	1	1 (100)	0 (0)	0 (0)
F (<10)	1	1 (100)	0 (0)	0 (0)
G (<10)	1	1 (100)	1 (100)	0 (0)

No. number, SN sentinel node, IRLS infrared ray laparoscopy system, ICG indocyanine green, pN+ positive lymph node metastasis

gastric cancer and colorectal cancer by Kusano et al. in 2008. [19], the scope of fluorescence-based SN mapping has expanded from the stomach, breast, skin, and lower digestive tract to the lung, head and neck, aerodigestive tract, and genitourinary system [20]. The present findings suggest that infrared ICG imaging is feasible for SN mapping in minimally invasive surgery for early gastric cancer, as is ICG fluorescence imaging.

In conclusion, the infrared ICG observation was much superior to ICG observation with naked eyes in detection of SNs, irrespective of the surgeon's experience. These findings suggest that SN biopsy using the infrared ICG is an effective and useful procedure to identify patients with cT1 N0 gastric cancer who have occult nodal metastasis.

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Compliance with ethical standards

Ethics and consent The study protocol and publication of the study results including the personal details were approved by the Institutional Review Board of the Jikei University School of Medicine (Reference No.15-53) and all local institutional review boards. Written informed consent was obtained from all patients.

Conflict of interest All authors declare that they have no conflict of interest.

Author's contributions Naoto Takahashi, Hiroshi Nimura, Seigo Kitano, and Katsuhiko Yanaga conceived the study and analyzed the data. Norio Mitsumori, Norio Shiraishi, and Hitoshi Satodate helped collect the clinical data. Naoto Takahashi, Hiroshi Nimura, and Tetsuji Fujita drafted and revised the manuscript on behalf of all authors. All authors read and approved the final manuscript.

Availability of data and materials We clarified that the datasets supporting the conclusions of this article are included within the article.

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