Jikeikai Med J 2009 ; 56 : 57-62

Validity of the Infrared Ray Method for Sentinel Node Biopsy in Gastric Cancer

Tomoki KOYAMA[1], Hiroshi NIMURA[1], Norichika NARIMIYA[2], Yutaka MORI[3], Masahiro IKEGAMI[4], Norio MITSUMORI[1], and Katsuhiko YANAGA[1]

[1]*Departments of Surgery, The Jikei University School of Medicine*
[2]*Department of Endoscopy, The Jikei University School of Medicine*
[3]*Department of Radiology, The Jikei University School of Medicine*
[4]*Department of Pathology, The Jikei University School of Medicine*

ABSTRACT

Background. Conventional techniques for identifying sentinel nodes (SNs) include the dye method and the radioisotope method. Our infrared ray electronic endoscopy (IREE) method offers both the simplicity of the dye method and the high detectability of the radioisotope method. We studied the efficacy of combining the radioisotope and IREE methods in detecting SNs during gastric cancer surgery.

Methods. The subjects were 14 patients with gastric cancer diagnosed preoperatively as T1N0. Before surgery, ^{99m}Tc-phytate was injected submucosally at the margin of the tumor. During surgery, indocyanine green (ICG) was also injected endoscopically in the same fashion. SNs were identified with IREE and a gamma probe, and ICG-positive [ICG (+)] lymph nodes (LNs) and hot nodes (HNs) were mapped. The identified LNs were stained with hematoxylin and eosin, and LN metastasis was diagnosed with immunostaining.

Results. The identification rate of ICG (+) LNs was 100%, whereas that of HNs was 93%. The ICG (+) HNs comprised 40.8% of all detected LNs, ICG (+) cold nodes accounted for 55.3%, and ICG (−) HNs comprised the remaining 3.9%.

Conclusion. The IREE method makes the radioisotope method unnecessary. The IREE method is a useful technique for SN navigation surgery for gastric cancer.

(Jikeikai Med J 2009 ; 56 : 57-62)

Key words : gastric cancer, sentinel node navigation surgery, infrared ray electronic endoscopy, radioisotope

INTRODUCTION

The validity of the sentinel lymph node (SN) concept in melanoma and breast cancer was demonstrated by Morton et al. in 1992, and such a concept has since been employed clinically[1-6]. In recent years, studies of SN navigation surgery for gastric cancer have been reported, mostly from Japan[7-19]. SNs can be identified with the dye method[7,9,11,13,15,17] or radioisotope method[8,12,14,18,19]. One advantage of the dye method is that macroscopic observation allows lymphatic flow to be delineated through intraoperative injection. However, because the dye migrates with time, it cannot be followed macroscopically for a prolonged period. In addition, thick fat tissue hinders macroscopic dye observation. An advantage of the

Received for Publication, July 29, 2009
小山 友己，二村 浩史，成宮 徳親，森 豊，池上 雅博，三森 教雄，矢永 勝彦
Mailing address : Tomoki KOYAMA, Department of Surgery, The Jikei University School of Medicine, 3-25-8, Nishi-Shimbashi, Minato-ku, Tokyo, 105-8461, Japan.
E-mail : tomoki.8.31@jikei.ac.jp

radioisotope method is that because the colloid used is composed of large particles, it remains within the lymph nodes (LNs) to allow stable quantitative identification for some time after injection. Moreover, preoperative scintigraphy enables identification of LNs distant from the main lesion[20]. However, scintigraphy cannot identify SNs near primary cancers, including gastric cancer. Another disadvantage of the radioisotope method is that because a hand-held gamma probe is used for intraoperative identification, macroscopic observation is not possible, and the probe picks up lateral scattering from the radioactive source. In May 2000, we reported favorable results with our technique, infrared ray electronic endoscopy (IREE), in SN navigation surgery for gastric cancer[16]. Such a technique is as convenient as the dye method and has an identification rate comparable to that of the radioisotope method. In the present study, SNs were mapped by combining the IREE and radioisotope methods to compare these 2 methods in gastric cancer surgery.

PATIENTS AND METHODS

The protocol was approved by the Ethics Committee for Biomedical Research of the Jikei Institutional Review Board, and all patients provided informed consent. Subjects were 14 patients in whom T1N0 gastric cancer was diagnosed preoperatively. The 14 patients were 9 men and 5 women with an average age of 56.9±7.4 years. Five patients underwent open surgery, and 9 underwent laparoscopic surgery. The average tumor diameter was 17±5.9 mm in the 5 patients who underwent wedge resection and 31.7±20.5 mm in the 5 patients who underwent gastrectomy (Table 1).

As tracers, 5 mg/ml of indocyanine green (ICG) (Diagnogreen; Dai-Ichi Pharmaceutical Co. Ltd., Tokyo, Japan) was used for the IREE method, and 20 MBq (0.5 mCi) of ^{99m}Tc-phytate colloid (First Radioisotope Laboratories, Tokyo, Japan) was used for the radioisotope method. Ninety minutes before surgery, in the isotope room 0.2 ml of ^{99m}Tc-phytate colloid was injected submucosally at 4 quadrants at the margin of the tumor with a 23-gauge local-injection

Table 1. Clinicopathological findings

Patient	Age (yrs)	Sex	Location		Size (mm)	TNM	Depth	ly	v	Type of gastrectomy	LD
			UML	L, G, A, P							
1	48	F	M	L	55	T1N0M0	M	0	0	LADG	D1+α
2	58	M	U	P	23	T1N0M0	M	0	0	WR	LBD
3	63	M	M	L	8	T1N0M0	M	0	0	LWR	LBD
4	53	M	M	L	21	T1N0M0	SM	0	0	LWR	LBD
5	77	F	M	L	17	T1N1M0	SM	1	0	LADG	D1+α
6	54	F	M	L	39	T1N0M0	M	0	0	LADG	D1+α
7	56	M	L	P	11	T1N0M0	M	0	0	LADG	D1+α
8	58	M	U	P	67	T1N0M0	M	0	0	LATG	D1+α
9	59	M	M	G	33	T1N0M0	SM	0	0	PPG	D1+α
10	55	F	M	P	18	T1N0M0	SM	1	0	LWR	LBD
11	62	M	U	L	13	T1N0M0	SM	0	0	PG	D1+α
12	55	M	M	G	15	T1N0M0	SM	1	0	LWR	LBD
13	47	M	M	A	10	T1N0M0	M	0	0	DG	D1+α
14	51	F	M	L	40	T1N0M0	SM	1	0	DG	D1+α

UML, upper third, middle third, lower third of the stomach; L, lesser curvature; G, greater curvature; A, anterior wall; P, posterior wall; M, intramucosal cancer; SM, submucosal invasive cancer; ly, lymphatic involvement; v, vascular involvement; LADG, laparoscope-assisted distal gastrectomy; WR, open wedge resection; LWR, laparoscopic wedge resection; LATG, laparoscope-assisted total gastrectomy; PPG, open pylorus preserving gastrectomy; PG, open proximal gastrectomy; DG, open distal gastrectomy; LD, lymph node dissection; D1+α, dissection of the lymph nodes along the left gastric and common hepatic arteries in addition to D1 dissection; LBD, lymphatic basin dissection

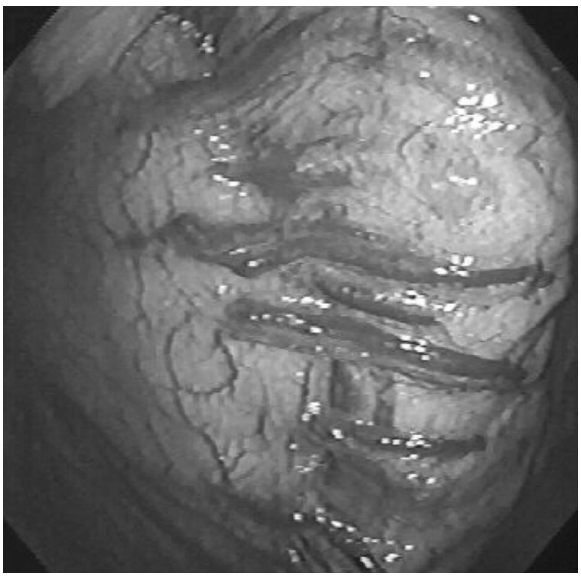

Fig. 1a.

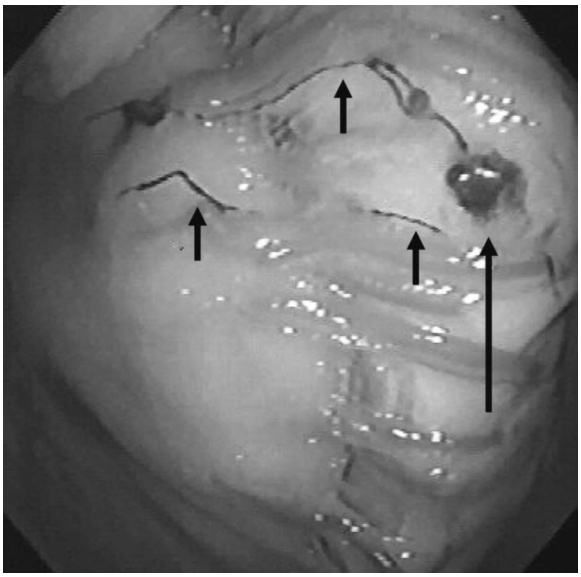

Fig. 1b.

Fig. 1. Serosal surface of the stomach during surgery, 20 minutes after endoscopic injection of ICG into the stomach.
a, White light. b, IREE.
a, Sentinel node staining with ICG alone is not clear to the naked eye. b, The same area observed under illumination by IREE. The long arrow indicates a positive LN (SN), and the short arrow indicates a lymphatic vessel. This node was identified as metastatic with pathological examination.

needle under endoscopic guidance. Lymphoscintigraphy was then performed to confirm that the radioisotope had migrated to the tumor, and the patient was taken to the operating room. During surgery, 0.5 ml of ICG (total dose, 2 ml) was injected submucosally at the same 4 quadrants at the margin of the tumor with a 23-gauge local-injection needle under endoscopic guidance.

Twenty minutes after ICG injection, IREE was used to observe the surrounding fat tissue from the serosal side to identify ICG-positive [ICG (+)] lymph vessels and ICG (+) LNs (Fig. 1a and 1b). At the same time, a gamma probe (Navigator GPS, Tyco Healthcare Japan, Tokyo, Japan) was used to identify SNs. The SNs were defined as hot nodes (HNs) with the gamma probe-guided technique. The cut-off value was =10 with 10-second cumulative counting. After observation, lymphatic basin dissection[11] was performed for patients undergoing wedge resection, and D1+α LN dissection was performed as a modified gastrectomy[21] according to the guidelines for patients undergoing gastrectomy. After specimen excision, LNs were removed on the side table to map ICG (+) LNs and HNs. Changes in the number of ICG (+) lymphatic basins during and after surgery were ascertained. The SNs were stored frozen, and LN metastasis was analyzed with hematoxylin and eosin staining and cytokeratin immunostaining (cytokeratin MNF116, DAKO, Glostrup, Denmark).

Results

Both during and after surgery, 8 patients had 1 ICG (+) lymphatic basin, and 6 patients had 2; the number of positive lymphatic basins was unchanged during and after surgery in all patients (Table 2). Table 3 shows SN identification rates in excised LNs. ICG (+) LNs were seen in all 14 patients (100%), whereas HNs were seen in 13 of the 14 patients (93%). The average number of SNs was 7.1±3.6 for IREE and 3.3±2.3 for the radioisotope method. Table 4 and 5 shows the details of identified SNs. There was a total of 103 SNs: 99 ICG (+) LNs and 46 ICG (+) HNs. The 10-second cumulative count for HNs ranged from 16 to 4,081 (median, 3,520.0).

Table 2. The ICG-positive lymphatic basin by IREE

Patient	ICG-positive lymphatic basins	
	Intraoperative	Postoperative
1	Lga, Rgea	Lga, Rgea
2	Lga	Lga
3	Lga	Lga
4	Lga	Lga
5	Lga	Lga
6	Lga	Lga
7	Lga, Rgea	Lga, Rgea
8	Lga	Lga
9	Lga, Rgea	Lga, Rgea
10	Lga, Rgea	Lga, Rgea
11	Lga	Lga
12	Lga	Lga
13	Lga, Rgea	Lga, Rgea
14	Lga, Rgea	Lga, Rgea

Lga=lymphatic basin around the left gastric artery; Rgea=the lymphatic basin around the right gastro epiploic artery; IREE=infrared ray electronic endoscopy; ICG=indocyanine green

Table 3. Detection rate of sentinel nodes by IREE or γ probe

	Methods of SN detection	
	IREE (n=14)	γ probe (n=14)
Patients of detected SNs	14 (100%)	13 (93%)
Number of SNs detected**	7.1±3.6* (1～14)***	3.3±2.3† (0～8)

*ICG-positive nodes †Hot nodes
**mean±SD ***range (minimum～maxmum)
IREE=infrared ray electronic endoscopy; SN=sentinel lymph node

Table 4. Comparison of IREE and RI methods (Number of SNs)

	Hot nodes	Cold nodes	total
ICG (+)	42 (41%)	57 (55%)	99 (96%)
ICG (−)	4 (4%)	0	4 (4%)

IREE=infrared ray electronic endoscopy; RI=radioisotope; SN=sentinel lymph node; ICG=indocyanine green

There were 42 ICG (+) HNs (41%), 57 ICG (+) cold nodes (55%), and 4 ICG (−) HNs (4%). Four patients demonstrated 1 ICG (−) HN (Fig. 2). In 1 patient (Table 1, patient 5), LN metastasis was found; 2 nodes, both ICG (+) LN-HN, were affected.

Table 5. Comparison of IREE and RI methods (Number of nodes)

	Number of mean±SD (range)
ICG (+) or Hot nodes	7.4±3.7 (1-14)
ICG (+) and Hot nodes	3.0±2.3 (0-8)
ICG (+) and Cold nodes	4.1±2.9 (0-9)
ICG (−) and Hot nodes	0.3±0.5 (0-1)

IREE=infrared ray electronic endoscopy; RI=radioisotope; ICG=indocyanine green

DISCUSSION

In SN navigation surgery for gastric cancer, the identification rate and sensitivity are less than 100% for both the dye method and the radioisotope method, and attempts have therefore been made to eliminate false negatives. Hayashi et al. combined the dye and radioisotope methods to enhance the advantages and to eliminate the disadvantages of each method and reported that the sensitivity for metastatic LNs was 100%[10]. In our previous report, with macroscopic ICG observation we identified LN metastasis in 7 of 11 patients, but with the IREE method we detected metastasis in all 30 LNs in 11 patients[16]. In this way, IREE is clearly more accurate than macroscopic ICG observation and yields results comparable with those of the combination of the dye and radioisotope methods reported by other institutions.

As a radioisotope tracer, ^{99m}Tc-tin colloid is often used because its particle size can be adjusted[12]. However, the present study used ^{99m}Tc-phytate colloid because it has a stable particle size and is easy to handle. Because the particle size of radioisotope colloid is larger than that of dyes, diffusion is less likely and imaging is stable. On the other hand, wash-out makes macroscopic identification more difficult with the dye method. However, the present study showed that, with IREE, ICG could be identified some time after injection. Moreover, there was no change in the number of ICG (+) lymphatic basins, because ICG binds with proteins inside lymph vessels after gastric wall injection and does not migrate far

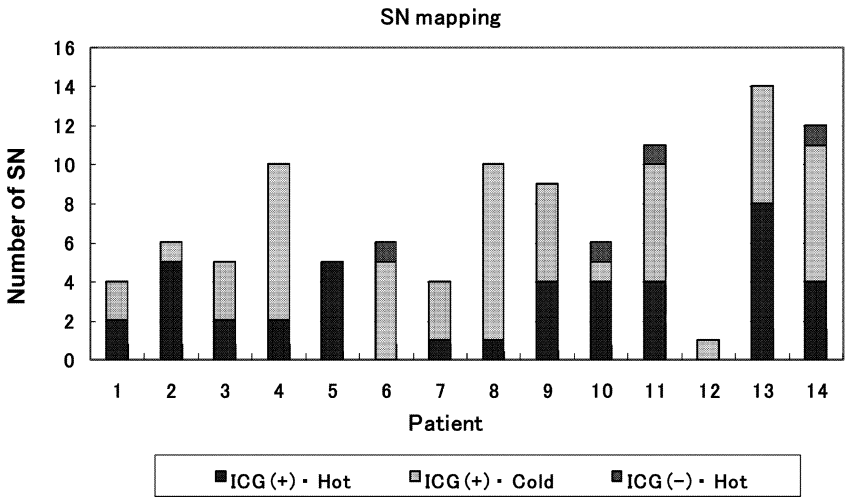

Fig. 2. LN mapping of SNs with the IREE and radioisotope methods
ICG (+) : ICG-positive LN as ascertained with infrared ray observation
ICG (−) : ICG-negative LN
Hot : LN judged positive with radioisotopes and a gamma probe
Cold : LN judged negative with radioisotopes and a gamma probe
SN was defined as ICG (+) LN as ascertained with IREE and HNs judged positive with the radioisotope method.

because of its large particle size[22]. However, the number of ICG (+) SNs identified with IREE was approximately twice that with the radioisotope method. Furthermore, whereas ICG (−) HNs were few, about half the SNs were ICG (+) cold nodes (Table 5). In the present study, SN identification was performed after gastrectomy, and the number of ICG (+) LNs was higher 4 hours after ICG injection. Intraoperative lymphatic basin dissection to identify ICG (+) LNs decreases the proportion of ICG (+) cold nodes but increases the proportion of ICG (+) HNs.

A few ICG (−) HNs were detected, presumably because ^{99m}Tc-phytate colloid clogged some LNs and draining lymph vessels, thus blocking ICG from entering the LNs.

Only one patient in this study had LN metastasis. This patient had 2 ICG (+) HNs ; hence, neither method yielded false-negative results.

In summary, if SNs are identified immediately with the IREE method after lymphatic basin dissection in intraoperative ICG (+) lymphatic basins, SN navigation surgery can be conveniently performed in a reliable manner without radioisotopes.

Acknowledgements : We thank Hiroshi Arakawa, Junko Fujisaki and Prof. Hisao Tajiri (Department of Endoscopy), Hiroto Narita, Shigeyuki Ogi and Enkichi Fukumitsu (Department of Radiology), and Misako Arima (Department of Pathology), all at The Jikei University School of Medicine, for their contributions to this study.

References

1. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992 ; 127 : 392-9.
2. van der Veen H, Hoekstra OS, Paul MA, Cuesta MA, Meijer S. Gamma probe-guided sentinel node biopsy to select patients with melanoma for lymphadenectomy. Br J Surg 1994 ; 81 : 1769-70.
3. Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg 1995 ; 222 : 394-401.
4. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet 1997 ; 349 : 1864-7.
5. Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, et al. The sentinel node in breast cancer : a

multicenter validation study. N Engl J Med 1998 ; 339 : 941–6.
6. Schrenk P, Wayand W. Sentinel-node biopsy in axillary lymph-node staging for patients with multicentric breast cancer. Lancet 2001 ; 357 : 122.
7. Hiratsuka M, Miyashiro I, Ishikawa O, Furukawa H, Motomura K, Ohigashi H, et al. Application of sentinel node biopsy to gastric cancer surgery. Surgery 2001 ; 129 : 335–40.
8. 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 : 604–8.
9. Ichikura T, Morita D, Uchida T, Okura E, Majima T, Ogawa T, et al. Sentinel node concept in gastric carcinoma. World J Surg 2002 ; 26 : 318–22.
10. Hayashi H, Ochiai T, Mori M, Karube T, Suzuki T, Gunji Y, et al. Sentinel lymph node mapping for gastric cancer using a dual procedure with dye- and gamma probe-guided techniques. J Am Coll Surg 2003 ; 196 : 68–74.
11. 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 : 178–82.
12. Uenosono Y, Natsugoe S, Higashi H, Ehi K, Miyazono F, Ishigami S, et al. Evaluation of colloid size for sentinel nodes detection using radioisotope in early gastric cancer. Cancer Lett 2003 ; 200 : 19–24.
13. Ryu KW, Lee JH, Kim HS, Kim YW, Choi IJ, Bae JM. Prediction of lymph nodes metastasis by sentinel node biopsy in gastric cancer. Eur J Surg Oncol 2003 ; 29 : 895–9.
14. Kim MC, Kim HH, Jung GJ, Lee JH, Choi SR, Kang DY, et al. Lymphatic mapping and sentinel node biopsy using 99mTc tin colloid in gastric cancer. Ann Surg 2004 ; 239 : 383–7.
15. Song X, Wang L, Chen W, Pan T, Zhu H, Xu J, et al. Lymphatic mapping and sentinel node biopsy in gastric cancer. Am J Surg 2004 ; 187 : 270–3.
16. Nimura H, Narimiya N, Mitsumori N, Yamazaki Y, Yanaga K, Urashima M. Infrared ray electronic endoscopy combined with indocyanine green injection of sentinel nodes of patients with gastric cancer. Br J Surg 2004 ; 91 : 575–9.
17. Isozaki H, Kimura T, Tanaka N, Satoh K, Matsumoto S, Ninomiya M, et al. An assessment of the feasibility of sentinel lymph node-guided surgery for gastric cancer. Gastric Cancer 2004 ; 7 : 149–53.
18. Kitagawa Y, Kitajima M. Diagnostic validity of radio-guided sentinel node mapping for gastric cancer : a review of current status and future direction. Surg Technol Int 2006 ; 15 : 32–6.
19. Aikou T, Kitagawa Y, Kitajima M, Uenosono Y, Bilchik AJ, Martinez SR, et al. Sentinel lymph node mapping with GI cancer. Cancer Metastasis Rev 2006 ; 25 : 269–77.
20. Kitagawa Y, Fujii H, Mukai M, Kubota T, Ando N, Watanabe M, et al. The role of the sentinel lymph node in gastrointestinal cancer. Surg Clin North Am 2000 ; 80 : 1799–809.
21. Nakajima T. Gastric cancer treatment guidelines in Japan. Gastric Cancer 2002 ; 5 : 1–5.
22. Cherrick GR, Stein SW, Leevy CM, Davidson CS. Indocyanine green ; observation on its physical properties, plasma decay and hepatic extraction. J Clin Invest 1960 ; 39 : 592–600.