

Laparoscopic Sentinel Node Mapping for Colorectal Cancer Using Infrared Ray Laparoscopy

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Abstract. *Background:* Sentinel lymph node (SN) mapping by dye injection on conventional laparoscopy (CL) is often precluded by the presence of mesenteric adipose tissue in patients with colorectal cancer. SN mapping on CL was compared with that on infrared ray laparoscopy (IRL) during laparoscopy-assisted colectomy (LAC). *Patients and Methods:* Forty-eight patients with colorectal cancer who underwent LAC were enrolled. The tumor was identified by intra-operative fluoroscopy with marking clips. The tumor was stained intra-operatively by peritumoral injection of indocyanine green dye. SNs were observed by CL and by IRL. *Results:* In all 48 patients, dye injection and tumor localization during LAC were successful. The identification of SNs on IRL was approximately five times better than that on CL. There were no false-negative cases in T1 and T2 disease by IRL. *Conclusion:* SN mapping on IRL is superior to that on CL. SN mapping by IRL might be feasible for T1 and T2 tumors.

Sentinel node (SN) navigation is a new technology that has been clinically validated and used to evaluate malignant melanoma (1) and breast cancer (2). SNs are the lymph nodes that first receive drainage from a tumor and, therefore, have the highest likelihood of containing metastases. Whether SN navigation can optimize surgery for colorectal cancer (CRC) remains controversial, but SN mapping has been found to be diagnostically useful in patients with early CRC (3). Wood *et al.* (4) reported that the intra-operative peritumoral injection of blue dye consistently identified SNs during laparoscopy-assisted

colectomy (LAC). SNs were mapped by the submucosal injection of dye on intra-operative colonoscopy, or by the use of a spinal needle and percutaneous subserosal injection of dye at a premarked site (pre-operative tattooing of polypectomy site with carbon). However, our experience indicates that laparoscopic SN mapping by dye injection is technically difficult because injection of the dye into the colon wall during LAC is cumbersome. Submucosal injection of dye on intra-operative colonoscopy makes LAC difficult and problematic. Distension of the small intestine with air on colonoscopy interferes with the operative field and precludes laparoscopic procedures. Moreover, intra-operative colonoscopic examinations require considerable time, especially in patients with right-sided colon cancer. In contrast, percutaneous subserosal injection of dye into the thin colon wall is difficult and dye often leaks out of the colorectal wall (5, 6). Staining of SNs frequently cannot be accurately assessed in ordinary white light on conventional laparoscopy (CL) because of mesenteric adipose tissue. To solve these problems, infrared ray laparoscopy (IRL) (Olympus Corp., Tokyo, Japan) was used to map SNs during LAC in patients with CRC in whom saline was injected near the tumor before dye injection.

Patients and Methods

Patients. Between July 2002 and December 2004, a total of 48 patients (28 women and 20 men; age range, 40-88 years; mean age, 63.9 years \pm 12.6 [SD]; body mass index [BMI], 17-30; mean BMI, 22.5 \pm 2.9 [SD]) who underwent LAC for CRC or tumors *in situ* were enrolled. These patients were referred to our institution for treatment of CRC.

All patients had malignant polyps that were partially or completely removed during colonoscopy but required segmental colon resection, or large malignant tumors that could not be removed by colonoscopy. The tumor characteristics are shown in Table I. All the patients were specifically questioned about drug reactions and the absence of specific allergies was confirmed. Oral and written informed consent for LAC and SN mapping were obtained from all the patients before the procedures were performed.

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Key Words: Sentinel node navigation, lymphatic mapping, infrared ray, colorectal cancer, laparoscopic colon resection.

Table I. Tumor characteristics and number of successful sentinel node mapping on infrared ray laparoscopy without false negative.

	No. of patients	No. of successful mappings	P
Total no. of patients	48	42	
Tumor site			NS according to tumor site
Cecum	3	2 (67)	
Ascending colon	5	4 (80)	
Transverse colon	4	4 (100)	
Descending colon	1	1 (100)	
Sigmoid colon	24	22 (92)	
Upper rectum	11	9 (82)	
Tumor differentiation			NS according to tumor differentiation
Well	22	21 (95)	
Moderate	22	18 (82)	
Mucinous	4	3 (75)	
Depth of invasion			<0.0001, pT1-2 vs. pT3
pT1	25	25 (100)	
pT2	4	4 (100)	
pT3	19	13 (68)	
TNM stage ^a			<0.0001, stage I/II vs. III/IV
I	25	25 (100)	
II	12	11 (92)	
III	11	6 (55)	
IV	0	0	

NS = not significant; Values in parentheses are percentages.

^aHistopathological staging for lymph node metastasis according to standard hematoxylin and eosin staining. ^aTNM, tumor node metastasis.

Sentinel node mapping by IRL. Infrared rays have none of the undesirable effects of ultraviolet rays and only permeate tissue (7). Because infrared rays are absorbed by indocyanine green dye (ICG), lymph nodes and lymph vessels containing ICG can be visualized by infrared irradiation (8).

Examination techniques. Laparoscopic abdominal exploration was performed to rule out intra-abdominal metastasis. Intra-operative fluoroscopy was performed and the location of the tumor or polypectomy site was identified with marking clips set on pre-operative colonoscopy. Intra-operative colonoscopy was not performed in all patients. The location of the tumor was easily and accurately identified on laparoscopic images and fluoroscopic images at the same time. The involved segment of the colon was mobilized without disruption of the lymphatic vessels or blood vessels. ICG (25 mg) (Diagnogreen®; Dai-Ichi Pharmaceutical Co., Ltd., Tokyo, Japan) diluted with 5 ml of distilled water was used. First, 1 - 3 ml of saline was injected into the colon wall from the

Table II. Identification of sentinel nodes on conventional laparoscopy and on infrared ray laparoscopy in patients with colorectal cancer.

	CL	IRL	P
Number with sentinel nodes	32	169	
Mean sentinel nodes/patient	0.68±0.86	3.5±1.7	<0.001
Range of sentinel nodes/patient	0-3	0-7	<0.001

CL = conventional laparoscopy; IRL = infrared ray laparoscopy.

serosal side *via* a percutaneously inserted 25-G long needle to ensure correct placement of the needle into the colon wall, confirmed by mild resistance and bulging of the serosa. Then, the ICG solution was carefully injected just proximal and distal to the tumor, taking care not to puncture the tumor. The total amount of ICG solution injected was 5 ml, as described previously (9). After 5 min, green-enhanced SNs were observed on CL, and black-enhanced SNs were observed on IRL. Each SN had been marked with clips during laparoscopic surgery. Green-enhanced and black-enhanced SNs were confirmed by three surgeons. SN mapping added 20 - 25 min to the operating time. Mobilization of the colon was completed. The involved segment of the colon and the regional lymph nodes, including all black-enhanced SNs, were then extracorporeally resected *en bloc* through a minilaparotomy.

The specimen was processed in a standard fashion and stained with hematoxylin and eosin (H&E). The primary neoplasm and all lymph nodes underwent routine microscopic analysis.

Statistical analysis. The relationships between successful SN mapping on IRL and tumor characteristics were assessed by χ^2 test (Table I). The Mann-Whitney *U*-test was used to analyze the difference between the identification of SNs by IRL and that by CL (Table II). Differences with *p* values of less than 0.05 were considered statistically significant.

Results

Feasibility. In mesenteric adipose tissue, lymph nodes and lymph vessels not seen in ordinary white light were visualized by IRL (Figure 1). When IRL was compared with white light in the same region and at the same time, IRL was found to provide much better visualization of the lymph nodes and lymph vessels. The identification of SNs on IRL was approximately five times better than that on CL (Table II). There were no complications specifically related to either method. No patient had to be reverted to open surgery because of uncontrollable bleeding or trauma.

Sentinel node detection and location. In all 48 patients, the dye injection and tumor localization during LAC were precise and successful. No tumors were punctured during the dye injection. Black-enhanced nodes were identified in 47 out of the 48 patients (97.9%). In the one failed case, where the black enhanced nodes were negative, the tumor was pT3 stage. Metastases were found in the lymph nodes

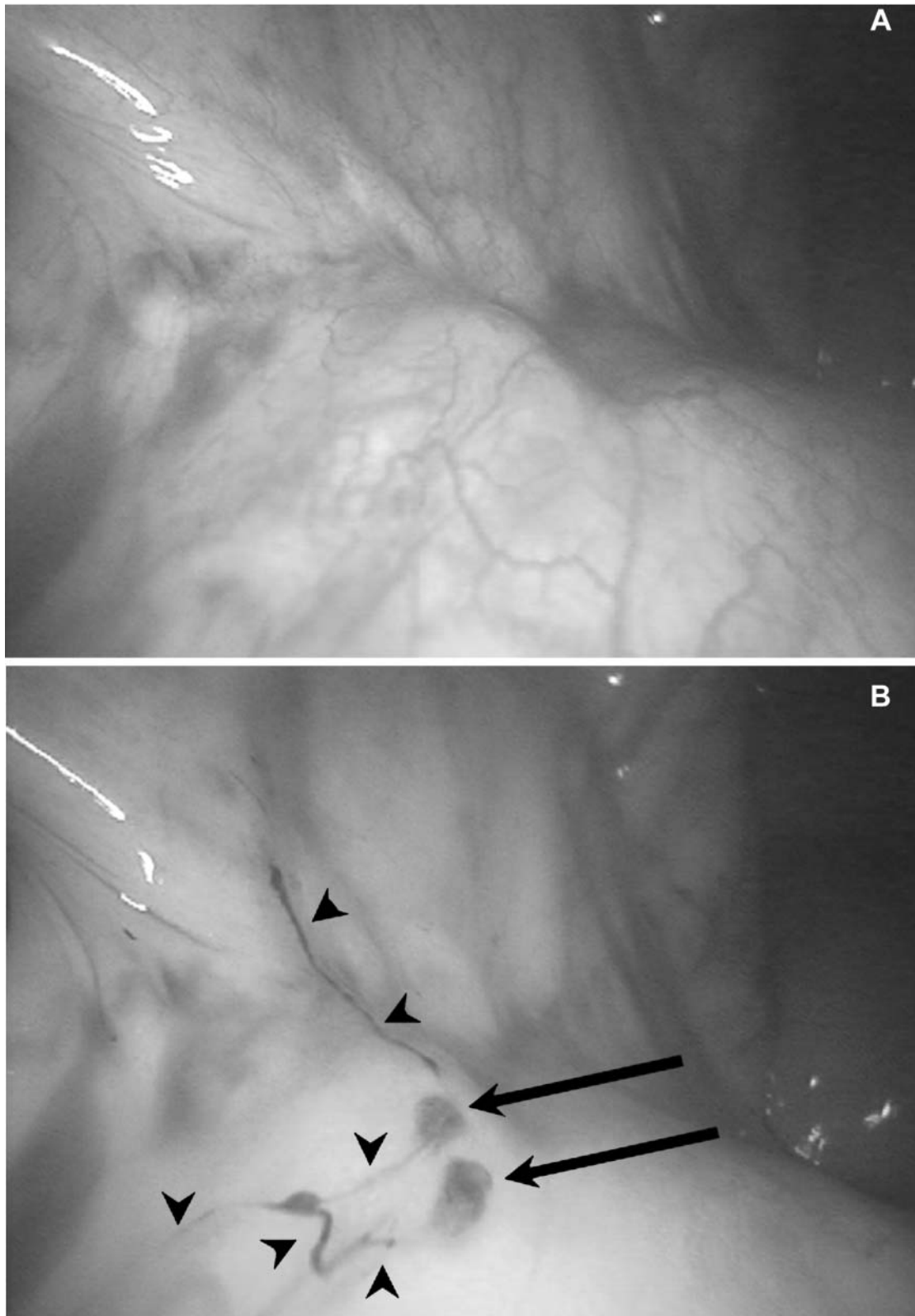


Figure 1. Laparoscopic sentinel node mapping for the sigmoid colon. (A) Regional lymph nodes and lymph vessels cannot be observed by conventional laparoscopy. (B) Black-enhanced regional lymph nodes (arrows) are clearly visualized by infrared ray laparoscopy. The path of the black-enhanced lymph vessels (arrowheads) can be clearly followed at the same time.

which were not stained even on IRL (non-SNs) for five patients. Of these five cases, all the tumors were of pT3 stage. Successful SN mappings on IRL without false negatives were achieved in 42 patients (Table I).

The number of patients in each pT category (histological extent of the primary tumor) of the TNM classification (10) is shown in Table I. The tumor site and differentiation were unrelated to the feasibility of SN mapping. The overall false-negative rate was 46.2% (66.7% in T3 disease) by IRL. There were no false-negative cases in T1 and T2 disease by IRL. In patients with stage pT3 CRC, laparoscopic SN mapping was not difficult, but resulted in a high number of false-negative (Table I) responses.

IRL detected additional SNs not identified on CL in 44 out of the 47 patients (93.6%). The average number of SNs identified on IRL was 3.5 per patient. From the resected specimens, the average number of lymph nodes was 21.0 ± 11.4 [SD] per patient (range 6-58). The total number of SNs identified was only 32 (0.68 ± 0.86 [SD] nodes/patient, range 0 - 3) on CL, as compared to 169 (3.5 ± 1.7 [SD] nodes/patient, range 0 - 7) on IRL (Table II). IRL detected SN, even in a patient with a BMI of 30. In this obese patient, seven SNs were detected on IRL as compared with none on CL.

Four out of the 29 patients with stage T1 and T2 CRC were found to have lymph node metastasis on histopathological examination (Table III). CL could not detect SNs that contained metastasis. Four metastatic lymph nodes were included among 17 lymph nodes identified by IRL to be SNs (positive). No metastatic lymph node was included among 53 lymph nodes identified by IRL as non-SNs (negative).

Discussion

Recent studies have indicated that LAC is a safe and feasible procedure for the treatment of CRC (11-13). Increasing evidence suggests that SN mapping is useful for the evaluation of CRC (3-6). Intra-operative SN mapping and SN biopsy can potentially be combined with minimally invasive surgery for CRC.

Our study led to three major findings. First, the observation of the ICG dye stain in SNs by IRL was far superior to that by CL. The identification of SNs on IRL was approximately five times better than that on CL (Table II). SN mapping on IRL might be useful in obese patients with large amounts of mesenteric adipose tissue and warrants further examination.

Second, the technique of saline injection before dye injection facilitated easy and precise SN mapping for CRC during LAC. In a previous study, most unsuccessful mappings in patients with CRC were due to incorrect dye injection technique (5). The technique of saline injection

Table III. Identification of lymph node metastasis on conventional laparoscopy and infrared ray laparoscopy (T1-T2).

Patient	No.	Proportion of nodes with metastasis			
		CL		IRL	
		Positive ^a	Negative ^b	Positive ^a	Negative ^b
1	15	0/1	1/14	1/5	0/10
2	13	0/0	1/13	1/2	0/11
3	16	0/2	1/14	1/6	0/10
4	26	0/1	1/25	1/4	0/22
Total	70	0/4	4/66	4/17	0/53

No. = number of resected lymph nodes, CL = conventional laparoscopy, IRL = infrared ray laparoscopy.

^aNumber of histologically confirmed lymph nodes as a proportion of number of resected lymph nodes stained on either CL or IRL. ^bNumber of histologically confirmed lymph nodes as a proportion of number of resected lymph nodes not stained on CL or not stained on IRL.

before dye injection resolves this technical problem and is not operator-dependent. The technique we developed uses readily available dye capable of being used in a wide range of patients, without interfering with surgical procedures or pathological diagnosis.

Our third major finding was that SN mapping on IRL might be feasible for stage T1 and T2 CRC (Table I, III). When obvious nodal metastases are present, the lymph flow through these nodes may be obstructed by tumor, leading to lymph drainage through alternative pathways (14). The route of lymph flow may also be affected by tumor growth into the bowel wall (5). A recent report has reported that locally advanced tumors and palpable nodes may partially account for a high false-negative rate (15). In our study, the overall false-negative rate was 46.2% (66.7% in T3 disease) by IRL. There were no false-negative cases in T1 and T2 disease by IRL. Therefore, SN mapping might be feasible for the evaluation of T1 and T2 stage CRC. This means that preoperative T-staging should be done before SN mapping.

Our procedure was easy to perform and had a high success rate. However, more experience is necessary before SN mapping can be routinely used during LAC in patients with CRC.

Acknowledgements

This study was supported in part by a Grant-in-aid (No.15790730) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We wish to thank Haruhiro Inoue, MD, Fumio Ishida, MD, Kishiko Tatsukawa, MD and Masahiko Hashimoto, MD, for their technical cooperation and Ms. Masako Kitatani for her secretarial assistance in preparing the manuscript.

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Received February 9, 2006

Accepted March 16, 2006