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Validation Study of Radio-Guided Sentinel Lymph Node Navigation in Esophageal Cancer

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Background: Radio-guided detection of sentinel lymph nodes (SLN) has been used to predict regional lymph node metastasis in patients with melanoma and breast cancer. However, the validity of the SLN hypothesis is still controversial for esophageal cancer. The aim of this study is to evaluate the feasibility and accuracy of radio-guided SLN mapping for esophageal cancer.

Methods: Seventy-five consecutive patients who were diagnosed preoperatively with T1N0M0 or T2N0M0 primary esophageal cancer were enrolled. Endoscopic injection of technetium-99m tin colloid was performed before surgery and radioactive SLNs were identified with preoperative lymphoscintigraphy and gamma probe. Standard radical esophagectomy with lymphadenectomy was performed in all patients and all resected nodes were evaluated by routine pathologic examination.

Results: SLNs were identified successfully in 71 (95%) of 75 patients. The mean number of identified SLNs per case was 4.7. Twenty-nine (88%) of 33 cases with lymph node metastasis showed positive SLNs. The diagnostic accuracy based on SLN status was 94% (67/71). Distribution of identified SLNs was widely spread from the cervical to abdominal areas.

Conclusions: This study reveals that radio-guided SLN mapping is an accurate diagnostic procedure for detecting lymph node metastasis in patients with early-stage esophageal cancer.

(*Ann Surg* 2009;249: 757–763)

In the history of surgical oncology, survival benefit of extended lymphadenectomy has been a focus of debates in various organs.[1] The "fear" for the invisible micrometastasis prompted surgeons to perform more aggressive resections with lymphadenectomy to control the disease locally. However, the clinical significance of prophylactic lymph node dissection for patients without lymph node metastasis has been the subject of controversy over the past 10 years.[2–4]

Given this background, the concept of the sentinel lymph node (SLN), intraoperative lymphatic mapping and sentinel lymphadenectomy appeared attractive.[5] The SLN is defined as the lymph node(s) that is/are first to receive lymphatic drainage from a tumor site.[5] The SLN is thought to be the first possible sites of micrometastasis along the route of lymphatic drainage from the primary lesion. The pathologic status of the SLN is considered to predict the status of all regional lymph nodes. If the SLN is recognizable and negative for cancer metastasis, unnecessary radical lymph node dissection could be avoided. The SLN hypothesis was advanced to specifically address those patients at high risk of having lymph node metastasis based on the characteristics of their primary tumors, but who had no evidence of clinically detectable regional metastatic disease.

The histopathological status of tumor-draining regional lymph nodes is one of the most significant predictors of recurrence and overall survival for most clinical stage I/II solid tumors, and is often used to justify stratification of patients for adjuvant therapy.[6,7] More efficient and accurate diagnosis of lymph node metastasis and prognostic information can be obtained from a small number of lymph nodes, by intraoperative lymphatic mapping and sentinel lymphadenectomy.[5,8]

SLN mapping and biopsy was first applied to melanoma, and was subsequently extended to breast cancer and, more recently, to many other solid tumors including esophageal cancer.[9–12] The SLN concept has revolutionized the approach to the surgical staging of both melanoma and breast cancer, and these techniques can benefit patients by avoiding various complications that may result from unnecessary prophylactic radical lymph node dissection in cases of negative SLNs for cancer metastasis.

Esophageal cancer has one of the highest malignant potentials of any tumor. The postoperative, 5-year survival rate of American Joint Committee on Cancer (AJCC) stage I esophageal cancer is about 90%, and decreases to 45% for stage II, 20% for stage III, and only 10% for stage IV patients.[13] Lymph node metastasis has been recognized as one of the useful indicators for predicting the outcome of esophageal cancer. Lymph node metastasis is not a rare event in esophageal cancer, and the incidence of lymph node metastasis, even in pT1b tumors, reaches 45%.[13] The other specific characteristics of esophageal cancer is multidirectional lymphatic flow from the primary lesion, and the wide spread and random patterns of lymph node metastasis from cervical to abdominal areas. Actually, anatomic skip metastases to the second or third compartment of regional lymph nodes were found in 50% to 60% of esophageal cancer.[13] Based on these clinical observations, extended radical esophagectomy with 3-field lymph node dissection has become recognized as a standard procedure in Japan, even for clinically node-negative cases.[13,14] However, the esophagectomy with 3-field lymph node dissection is one of the most invasive procedures in gastrointestinal (GI) surgeries. A significant increase of morbidity and mortality after the invasive procedures has been reported.[15–17] To eliminate the necessity of uniform application of highly invasive surgery, SLN mapping may play a significant role by obtaining individual information to permit adjustments and modifications of the surgical procedure for that specific patient.

We previously developed a radio-guided method for SLN mapping in GI cancers and reported the procedure for the first time.[12] Although our preliminary study demonstrated that SLN mapping may be feasible in patients with early-stage esophageal cancer,[12,18] the earlier study was lacking in the number of patients studied. In this study, we hypothesized that the SLN concept for early esophageal cancer could be validated for future clinical application. This study demonstrates the results of SLN mapping in 75 patients with T1N0 or T2N0 esophageal cancer.

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PATIENTS AND METHODS

Patients

A total of 75 consecutive patients (64 men and 11 women; median age: 61 years; age range: 39–79), who were diagnosed preoperatively with T1N0M0 or T2N0M0 primary esophageal cancer at Keio University Hospital (Tokyo, Japan) between 1999 and 2007, were enrolled in this study. All patients underwent a standard radical esophagectomy with SLN mapping, followed by conventional lymph node dissection after signing an informed consent. A skillful surgical team has sequentially performed all esophagectomy and SLN mapping. Before treatments, patients were assessed via esophagography, esophagoscopy, bronchoscopy, computed tomography, ultrasonography, and endoscopic ultrasonography. Clinical staging and pathologic examination for resected specimens were performed according to the Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus of the Japan Esophageal Society[19] and the TNM classification as proposed by the AJCC.

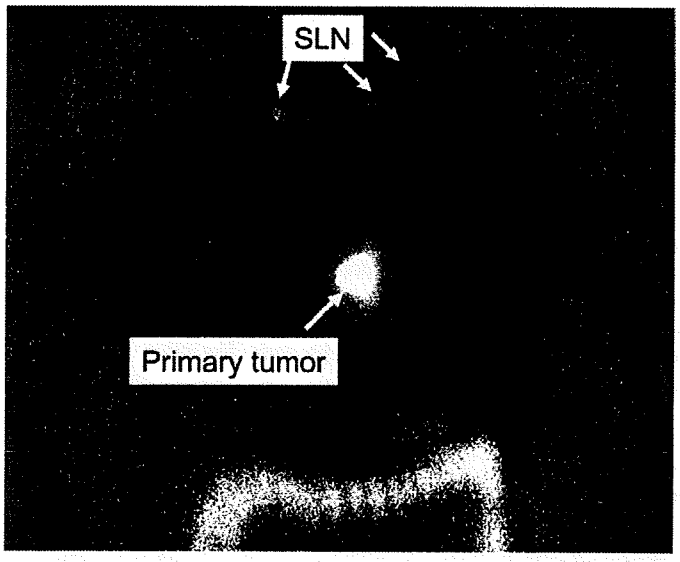

FIGURE 1. Preoperative lymphoscintigraphy for thoracic esophageal cancer.

SLN Mapping Procedures

To detect the SLN in esophageal cancer, we developed a radio-guided method, rather than the conventional blue-dye method, as previously described.[12,18] In brief, 1 day (within 16 hours) before the surgery, a 2.0-mL volume of technetium-99m tin colloid solution (150 MBq) was injected at 4 quadrants into the submucosal layer around the primary tumor using an endoscopic puncture needle. Preoperative lymphoscintigraphy was usually obtained 3 to 4 hours after the tracer injection. Distribution of SLN in the esophageal cancers was widely-spread from cervical to abdominal areas (Fig. 1).

Intraoperative SLN (ie, radio-labeled lymph nodes) sampling was performed using a handheld gamma probe (GPS Navigator, Tyco Healthcare, Tokyo, Japan). Gamma probing is also feasible in thoracoscopic or laparoscopic sampling of SLN using the special gamma detector, which is introducible from trocar ports (Figs. 2A–C). SLN located in the cervical area could be identified by percutaneous gamma probing. Intraoperative SLN sampling was subsequently followed by esophagectomy with extended regional lymph node dissection (at least D2 dissection on the Japanese Guidelines). On the back table, the residual SLN in the resected specimen was carefully investigated using the gamma probe, and all SLN were sent for intraoperative pathology examination. After lymph node dissection, the absence of SLN in the mediastinum or abdominal cavity was carefully confirmed by gamma probe from the incisional wound or thoracoscopic or laparoscopic ports.

For abdominal esophageal cancer or adenocarcinoma of gastroesophageal junction, a dual tracer method of the radioactive tracer and blue dye (1% isosulfan blue) was principally used for SLN detection. The blue-dye was injected into the submucosal layer of the primary lesion endoscopically right after surgery began. Subse-

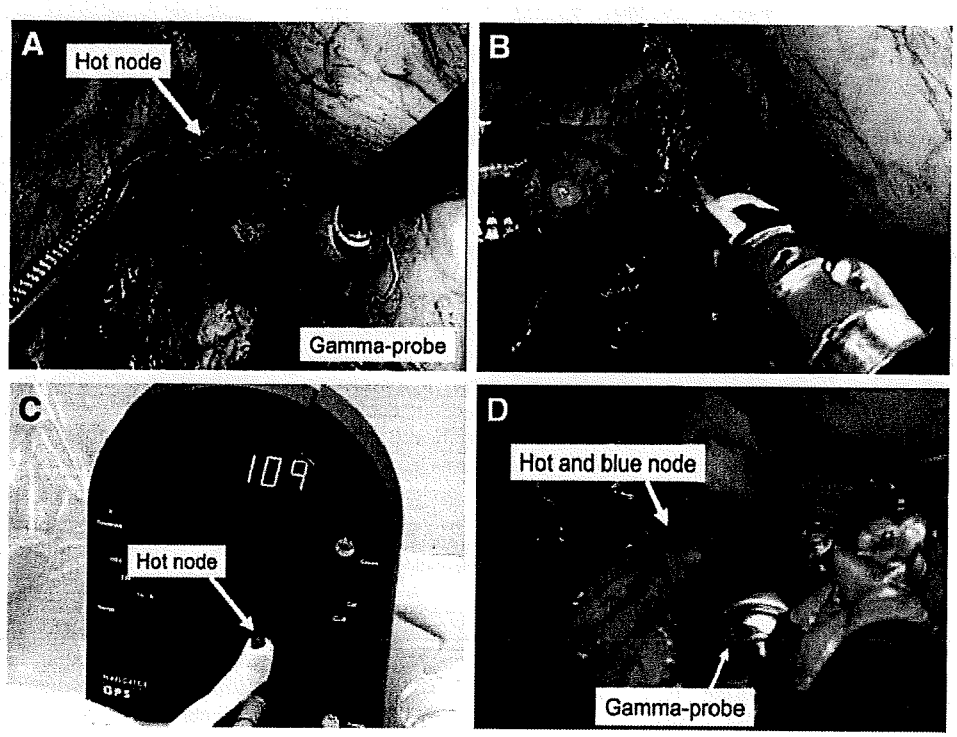

FIGURE 2. A, Intraoperative findings in the upper mediastinum during the thoracoscopic surgery. A radioactive (hot) node along the right recurrent laryngeal nerve regarded as SLN was identified using a handheld gamma probe. The sound of gamma probe is reflected by the radioactivity. B, The SLN was harvested using a vessel sealing device. C, The harvested SLN was placed on the gamma probe. The intensity of radioactivity in the SLN can be visualized by the scintillation counter. D, Dual tracer methods. A hot and blue-stained node along the left gastric artery was identified as the SLN.

quently, the tracer passed through the afferent lymphatics, and blue-stained nodes were identified as the SLN approximately 15 minutes after the injection (Fig. 2D).

Statistical analysis of the data was performed using the unpaired Student t test, the χ^2 test, Mann-Whitney U test, 1-way ANOVA, and Kruskal-Wallis test. All statistical analyses were performed using the StatView-J 5.0 (Abacus Concepts Inc., Berkeley, CA), and all P-values that were 2-sided at a value of <0.05 were considered to be statistically significant.

TABLE 1. Patients' Clinical Parameters

Parameter	n = 75 (%)
Age (yr) Mean ± SD	60.4 ± 7.7
Gender (M/F)	64/11
Tumor location	
Cervical esophagus	2 (3)
Upper thoracic esophagus	8 (11)
Middle thoracic esophagus	45 (60)
Lower thoracic esophagus	15 (20)
Abdominal esophagus or GEJ	5 (7)
Tumor length (cm), median (range)	3.0 (1.0–6.5)
Clinical TNM classification	
cT1N0M0	49 (65)
cT2N0M0	26 (35)
Neoadjuvant therapy	
Chemotherapy (Y/N)	4/71
Radiotherapy (Y/N)	0/75
Surgical procedures	
Right transthoracic total esophagectomy	26 (35)
Left transthoracic lower esophagectomy	5 (7)
Thoracoscopy-assisted total esophagectomy	41 (55)
Abdominal esophagectomy (and proximal gastrectomy)	2 (3)
Cervical esophagectomy	1 (1)
Number of dissected lymph nodes, M ± SE	49.2 ± 2.5
Pathological findings	
pT factor	
pT1	57 (76)
pT2	11 (15)
pT3	7 (9)
pN factor	
pN0	40 (53)
pN1	35 (47)
Histological stage	
Stage I	34 (45)
Stage IIA	6 (8)
Stage IIB	30 (40)
Stage III	5 (7)
Histological type	
Squamous cell carcinoma	67 (89)
Adenocarcinoma	5 (7)
Others	3 (4)
Lymphatic invasion	
+	40 (53)
−	32 (43)
Unknown	3 (6)
Vascular invasion	
+	20 (27)
−	51 (68)
Unknown	4 (5)

GEJ indicates gastroesophageal junction.

TABLE 2. Results of SLN Mapping for cT1N0M0 or cT2N0M0 Esophageal Cancer

Detection rate	95% (71/75)
SLN number per case (mean)	4.7
Sensitivity	88% (29/33)
Accuracy	94% (67/71)

RESULTS

Clinicopathological Background Factors

Patients' clinicopathological background factors are summarized in Table 1. Forty-nine (65%) of 75 patients showed cT1N0 esophageal cancer, and cT2N0 in 26 (35%) patients. Thoracoscopy-assisted total esophagectomy, which is a surgical approach less invasive than conventional esophagectomy with thoracotomy, was mainly performed for cT1N0 esophageal cancer. There were no significant differences in the number of dissected lymph nodes between thoracoscopy-assisted esophagectomy and conventional right-transthoracic esophagectomy (data not shown). In pathologic examination of resected specimens, 7 (9%) of 75 patients were diagnosed as T3 tumor, and 35 (47%) patients as pN1 cases.

Sentinel Lymph Node Mapping

SLN were detected successfully in 71 (95%) of 75 patients with cT1N0/cT2N0 esophageal cancer (Table 2). The mean number of dissected lymph nodes and identified SLN per case were 49.2 and 4.7, respectively. The mean number of identified SLN per case was 4.6 in thoracoscopic esophagectomy and 4.7 in conventional esophagectomy with right thoracotomy ($P = 0.88$). Twenty-nine (88%) of 33 cases with lymph node metastasis showed positive SLNs. Therefore the diagnostic accuracy based on SLN status was 94% (67/71).

Distribution of SLN in Esophageal Cancer

Distribution of identified SLN was widely spread from cervical to abdominal areas, as shown in Table 3. In upper thoracic esophageal cancer, the lymph nodes along bilateral recurrent laryngeal nerve chain (referred as station 106recR and 106recL in the Japanese Guidelines) were identified most frequently as SLN. SLN were also frequently identified in the cervical area. Surprisingly, 2 (25%) of 8 cases with upper thoracic esophageal cancer showed SLN along the left gastric artery (station 7). Middle thoracic esophageal cancer had a wide distribution of SLN with metastasis from cervical to abdominal areas. The station number 106rec, bifurcational and main bronchus lymph nodes (station 107 and 109), and middle thoracic paraesophageal lymph nodes (station 108) were all identified most frequently as SLN in middle thoracic esophageal cancer. However, more than 10% of the cases contain SLN in the area along the lesser curvature of stomach. Although SLN was mainly detected in the abdominal area of lower thoracic esophageal cancer, some cases revealed SLN in upper mediastinum, such as number 106rec and upper thoracic paraesophageal lymph nodes (station 105). In more than 85% of cases with thoracic esophageal cancer, at least 1 SLN was found to be located in the second or third compartment of regional lymph nodes. In general, the stations that were frequently identified as SLNs tended to have high incidence of metastasis pathologically.

TABLE 3. Distribution and Incidence of Metastasis in SLN

		Cervical Esophagus (n = 2)		Upper Thoracic Esophagus (n = 8)		Middle Thoracic Esophagus (n = 38)		Lower Thoracic Esophagus (n = 14)		Abdominal Esophagus to EGJ (n = 5)	
	Station	SLN	Metastasis	SLN	Metastasis	SLN	Metastasis	SLN	Metastasis	SLN	Metastasis
Cervical nodes	101	1 (50)	1 (50)	2 (25)	0	2 (5)	1 (3)	0	0	0	0
	102R	0	0	0	0	2 (5)	0	0	0	0	0
	102L	0	0	0	0	2 (5)	0	0	0	0	0
	103	0	0	0	0	0	0	0	0	0	0
	104R	1 (50)	0	3 (38)	0	2 (5)	1 (3)	0	0	0	0
	104L	0	0	2 (25)	0	6 (16)	1 (3)	1 (7)	0	0	0
Thoracic nodes	105	0	0	2 (25)	0	0	0	2 (14)	0	0	0
	106recR	2 (100)	1 (50)	5 (63)	2 (25)	13 (34)	4 (11)	3 (21)	2 (14)	0	0
	106recL	0	0	6 (75)	2 (25)	8 (21)	3 (8)	0	0	0	0
	106pre	0	0	0	0	0	0	0	0	0	0
	106tbL	0	0	0	0	5 (13)	0	0	0	0	0
	107	0	0	4 (50)	0	12 (32)	1 (3)	2 (14)	0	1 (20)	0
	108	0	0	0	0	12 (32)	3 (8)	4 (28)	1 (7)	0	0
	109R	0	0	0	0	10 (26)	0	2 (14)	0	0	0
	109L	0	0	0	0	11 (29)	1 (3)	1 (7)	0	0	0
	110	0	0	0	0	8 (21)	0	5 (36)	2 (14)	2 (40)	1 (20)
	111	0	0	0	0	1 (3)	0	2 (14)	0	0	0
	112	0	0	0	0	3 (8)	1 (3)	1 (7)	1 (7)	0	0
Abdominal nodes	1	0	0	0	0	5 (13)	1 (3)	5 (36)	3 (21)	2 (40)	0
	2	0	0	0	0	3 (8)	1 (3)	3 (21)	2 (14)	2 (40)	0
	3	0	0	0	0	5 (13)	0	3 (21)	0	3 (60)	0
	4sa	0	0	0	0	0	0	0	0	0	0
	4sb	0	0	0	0	0	0	0	0	0	0
	4d	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0	0	0
	7	0	0	2 (25)	0	4 (11)	1 (3)	5 (36)	2 (14)	3 (60)	0
	8a	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	1 (7)	0	0	0
	10	0	0	0	0	0	0	0	0	0	0
	11p	0	0	0	0	0	0	0	0	0	0
	20	0	0	1 (13)	0	2 (5)	0	0	0	0	0

The station number is described according to the Guidelines for the Clinical and Pathological Studies on Carcinoma of the Esophagus of the Japan Esophageal Society (19). 101 indicates Cervical paraesophageal lymph nodes (LN); 102R, Right deep cervical LN; 102L, Left deep cervical LN; 103, peripharyngeal LN; 104R, right supraclavicular LN; 104L, left supraclavicular LN; 105, upper thoracic paraesophageal LN; 106recR, right recurrent laryngeal nerve LN; 106recL, left recurrent laryngeal nerve LN; 106pre, pretracheal LN; 106tbL, left tracheobronchial LN; 107, subcarinal LN; 108, middle thoracic paraesophageal LN; 109R, right main bronchus LN; 109L, left main bronchus LN; 110, lower thoracic paraesophageal LN; 111, supradiaphragmatic LN; 112, posterior mediastinal LN; 1, right cardiac LN; 2, left cardiac LN; 3, LN along the lesser curvature; 4sa, LN along the short gastric vessels; 4sb, LN along the left gastroepiploic vessels; 4d, LN along the right gastroepiploic vessels; 5, Suprapyloric LN; 6, infrapyloric LN; 7, LN along the left gastric artery; 8a, LN along the common hepatic artery; 9, LN along the celiac artery; 10, LN at the splenic hilum; 11p, LN along the proximal splenic artery; 20, LN in the esophageal hiatus of diaphragm; GEJ, gastroesophageal junction. All data given as n (%).

Characteristics in Failure Cases of SLN Mapping

In this study, there were 4 of 75 cases in which SLN s were not detected (undetected case), and 4 of 33 cases with lymph node metastasis showed negative SLNs for metastasis (false-negative case). Next, the characteristics of these 8 "failed" cases of SLN mapping were assessed. If we categorized the 75 cases into the 4 groups as shown in Table 4, we could not find any difference on clinicopathological factors among the 4 groups. Interestingly, 7 (88%) of the 8 cases with undetected or false-negative SLNs were middle thoracic esophageal cancer, which may have wide-spread and complicated lymphatic drainage routes (Table 3). The SLN mapping was successful, even during thoracoscopic esophagectomy, compared with the conventional esophagectomy with thoracotomy. Ratio of the SLN mapping failure group in pathologically T1/T2, and T3 cases were 9% and 29%, respectively. In particular, pT3 cases were recognized in 2 (50%) of 4 false-negative cases. These results suggest that SLN mapping should not be applied to pT3 (or at least cT3) cases. The adverse effects of neoadjuvant chemotherapy, which consists of cisplatin and 5-FU on SLN mapping, were not observed in this study.

DISCUSSION

In this study, we have performed radio-guided SLN mapping for cT1N0 or cT2N0 esophageal cancer to verify the feasibility of the SLN mapping. Our data indicates successful SLN detection in 71 (95%) of 75 patients. The mean number of identified SLN per case

TABLE 4. Characteristics of Undetected or False-Negative Case

	SLN (−)/ Non-SLN (−) n = 38	SLN (+)/ Non-SLN (−) n = 20	SLN (+)/ Non-SLN (+) n = 9	Undetected or False-Negative Case n = 8	*P*
Age (yr) Mean ± SD	60.7 ± 6.9	60.8 ± 6.2	58.0 ± 11.5	60.4 ± 10.6	0.99
Gender M/F	29/9	19/1	9/0	7/1	0.14
Tumor length (cm) Mean ± SD	2.8 ± 1.4	3.3 ± 1.3	3.6 ± 1.3	2.9 ± 1.6	0.36
Tumor location					
Cervical esophagus	0 (0)	2 (10)	0 (0)	0 (0)	0.21
Upper thoracic esophagus	5 (13)	1 (5)	2 (22)	0 (0)	
Middle thoracic esophagus	24 (63)	9 (45)	5 (56)	7 (88)	
Lower thoracic esophagus	5 (13)	7 (35)	2 (22)	1 (13)	
Abdominal esophagus or GEJ	4 (11)	1 (5)	0 (0)	0 (0)	
pT					
pT1	32 (84)	14 (70)	5 (56)	6 (75)	0.17
pT2	4 (11)	5 (25)	2 (22)	0 (0)	
pT3	2 (5)	1 (5)	2 (22)	2 (25)	
Surgical procedures					
Thoracoscopic/others	25/13	8/12	3/6	5/3	0.14
Neoadjuvant chemotherapy (Y/N)	3/35	1/19	0/9	0/8	0.69

GEJ indicates gastrocsophageal junction. Data given as n (%) unless noted otherwise.

was 4.7, and the diagnostic accuracy based on SLN status was 94%. The SLN mapping was successful even during thoracoscopic esophagectomy, along with conventional surgical procedures.

To our knowledge, this study is the first report to convincingly demonstrate that radio-guided SLN mapping is an accurate diagnostic tool for detecting lymph node metastasis in patients with cN0 early esophageal cancer. Previous studies by our group or other groups demonstrated an acceptable accuracy with radio-guided SLN mapping for patients with esophageal cancer.[12,20,21] However, these earlier studies were lacking in the number of patients to validate the feasibility of the SLN mapping for future clinical applications.

Cases with clinically apparent lymph node metastasis were excluded from the study because the purpose of this technique is to identify clinically undetectable lymph node involvement. T1 and T2 esophageal cancers were suitable targets of the SLN mapping, as previously described.[12,18] On the other hand, T3 or T4 tumors, where the original lymphatic drainage routes might be obstructed and altered, result in a high incidence of false-negative cases. In this study, SLN mapping failure cases were recognized more frequently in pathologically T3 cases than that in pathologically T1/T2 cases. Failed cases of SLN mapping may be due to the technical errors such as the inaccurate tracer-injection and inadequate gamma probing. At least, however, our results suggest that SLN mapping should not be applied to cT3 or cT4 cases. Also care should be taken in case with middle thoracic esophageal cancer, which has wide-spread and complicated lymphatic drainage routes.

The total number of SLN in each patient was relatively higher than that which was previously reported in patients with breast cancer.[22] However, our previous study of SLN mapping for gastric cancer revealed a similar number of SLN (3.6 per patient) to the current study.[23] These studies suggest that the number of identified SLN may be organ-specific, owing the anatomy of the regional lymphatic network.

SLN mapping for esophageal cancer is generally more complicated than that for gastric cancer. Several factors are considered to answer the question. First, the dye-guided SLN mapping is not suitable for thoracic esophageal cancer, because regional lymph nodes of the thoracic esophagus are frequently pigmented by anthracosis. Therefore, it is difficult to identify blue-stained nodes in the mediastinum. Second, real-time observation of the lymphatic route using blue dye is impossible without operative mobilization of the esophagus; however, the mobilization itself may interfere with the active lymphatic flow from the primary lesion. On account of these factors, the radio-guided method for SLN mapping is employed in esophageal cancer.

Endoscopic submucosal injection is considered a reasonable and feasible route of administration of radioactive tracer for SLN mapping of esophageal cancer. The radioactive tracer, technetium-99m tin colloid, has a larger particle size (approximately 500 nm in diameter) than other tracers such as sulfur nanocolloid and blue dye, and may be useful to avoid excessive diffusion. The radioactive tracer injected using an endoscopy the day prior to surgery is known to migrate into the SLN within 2 hours, and is accumulated in the SLN. The radioactivity generally lasts at least for 20 hours, and is sufficient for detection during the surgery, as previously described.[23,24] In fact, our previous study for early gastric cancer demonstrated that the timing of tracer administration made no significant difference to the number of SLN identified between the patients with tracer injection 2 hours before surgery (n = 87) and the patients with tracer administered 16 hours before surgery (n = 58).[23] The other issue is that care should be taken not to send a lot of air into the stomach and small intestine when the radioactive tracer is injected using an endoscopy the same day as the surgery. For these reasons, we think that the radioactive tracer had better be injected 1 day (within 16 hours) prior to the surgery. Preoperative lymphoscintigraphy was very useful in predicting SLN in unexpected sites distant from the primary lesion of esophageal cancer before surgery. Shine-through effect from the primary lesion may interfere with accurate sampling of SLN by the gamma probe. However, our results demonstrated that intraoperative SLN sampling using gamma probe was considerably accurate and useful for prediction of lymph node metastasis in esophageal cancer. Gamma probing was feasible, even in thoracoscopic or laparoscopic sampling of SLN.

Transthoracic-extended esophagectomy with 3-field radical lymph node dissection has been recognized as an extensive and curative procedure for thoracic esophageal cancer in Japan.[13,14] In

this study, the distribution of SLN in thoracic esophageal cancer was widely spread from cervical to abdominal areas, especially in upper and middle thoracic esophageal cancer. Surprisingly, in more than 85% of the cases with thoracic esophageal cancer, at least 1 SLN was located in the second or third compartment of regional lymph nodes. Our findings suggest that the extended esophagectomy with 3-field lymphadenectomy may be a reasonable procedure for thoracic esophageal cancer on account of the wide SLN distribution and unpredictable metastatic patterns. However, the prognostic significance of 3-field lymphadenectomy is still controversial.[25] Moreover, uniform application of this highly-invasive procedure might increase the morbidity and markedly reduce the patient's quality of life (QOL) after surgery. SLN mapping would provide significant information to perform individualized selective lymphadenectomy that might reduce the morbidity without having a negative impact on the prognosis.[25] For instance, if the SLN were identified only in the mediastinum or abdominal area and all SLN were pathologically negative in patients with cT1N0 middle or lower thoracic esophageal cancer, the cervical lymph node dissection would be unnecessary.

On the other hand, subtotal esophagectomy with 2-field lymphadenectomy is widely performed in most countries. We think that the SLN mapping will have relevance even for 2-field lymphadenectomy, and provide significant information about the extent of intensive lymph node dissection. For instance, if the SLN is pathologically positive for metastasis, the lymph node dissection of the SLN basin should be performed carefully and intensively. In particular, if the SLN is identified along the recurrent laryngeal nerves in the upper mediastinum and positive for metastasis, extended lymphadenectomy for upper mediastinum and/or additional cervical lymphadenectomy might be considered. The other benefit of SLN mapping is that the absence of SLN in the mediastinum or abdominal cavity can be carefully confirmed by gamma probe after lymph node dissection even for the 2-field lymphadenectomy.

We think that the SLN mapping and biopsy will also be adaptable and reliable to adenocarcinomas of distal esophagus or GE junction. In addition to the current study, we have performed SLN mapping for 378 cases with early gastric cancer, and verified the accuracy of the SLN mapping.[23,24] Burian et al also demonstrated that SLN mapping is feasible and reliable in patients with adenocarcinoma of GE junction.[26] We think that the SLN mapping and biopsy for adenocarcinomas of distal esophagus or GE junction is useful to adjust and modify the surgical procedures. Hulscher et al[27] reported that there was no significant difference in postoperative survival between transhiatal and transthoracic esophagectomy in patients with adenocarcinoma of the mid-to-distal esophagus or adenocarcinoma of the gastric cardia involving the distal esophagus. Transthoracic esophagectomy with extended lymphadenectomy was associated with higher morbidity than transhiatal esophagectomy. However, their recent report after long-term follow-up demonstrated that patient with 1 to 8 positive lymph nodes significantly benefited from an extended transthoracic lymphadenectomy in 5-year locoregional disease-free survival and overall survival.[28] These results suggest that SLN mapping and intraoperative pathologic diagnosis of metastasis by SLN biopsy is reliable for the appropriate selection of the surgical procedures. For instance, if the SLN were identified only in the abdominal area and pathologically negative in the case with cT1N0 adenocarcionoma of distal esophagus, the patient would be treated with limited resection of distal esophagus by transhiatal approach without extensive mediastinal lymph node dissection.[26] On the other hand, if the SLN were positive for metastasis by intraoperative diagnosis, the patient should be treated with extended transthoracic lymphadenectomy. Prognostic benefit of modified lymphadenectomy based on SLN concept should be considered carefully. At least, however, the new surgical procedure might reduce the morbidity and mortality without having a negative impact on the QOL for early-stage esophageal cancer patients with pathologically negative SLN.

Metastatic status of regional lymph nodes is regarded as one of the most important prognostic factors in patients with esophageal cancer. Previous randomized trials showed that postoperative adjuvant chemotherapy with cisplatin and 5-FU for esophageal cancer had a significant preventive effect on relapse in patients with lymph node metastasis.[29] Therefore, accurate and sensitive detection of micrometastasis assessed by SLN mapping is very important clinically in aiding the performance of adequate adjuvant chemotherapy for cN0 esophageal cancer.

The incidence of lymph node metastasis cannot be ignored even in cN0 esophageal cancer. Therefore, the accuracy of SLN mapping has to be indispensable. Our results suggest that SLN concept seems to be valid and that radio-guided SLN mapping may be feasible in cT1N0 or cT2N0 esophageal cancer. Additional evidence based on multicenter clinical trials using standard protocol is needed. Nonetheless, SLN mapping and sentinel node navigation surgery has proven to be a promising strategy for a less invasive individualized surgery for early-stage esophageal cancer.

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REVIEW ARTICLE

Laparoscopic sentinel node navigation surgery for early gastric cancer

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Keywords
Gastric cancer; laparoscopic surgery; sentinel node

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Abstract

The sentinel node (SN) concept has revolutionized how the surgical staging of both melanoma and breast cancer are approached. Applying this concept can yield benefits for the patient by avoiding various complications relating to unnecessary prophylactic regional lymph node dissection in cases with negative SN for cancer metastasis. Clinical application of SN mapping for early gastric cancer had been controversial for years. However, single institutional results of laparoscopic SN mapping for early gastric cancer are considered acceptable in terms of detection rate and accuracy in determining lymph node status. For early stage gastric cancer such as cT1N0M0 – in which a better prognosis was generally achieved through conventional surgical approaches – an individualized, minimally invasive surgery that might retain the patient's quality of life should be established as the next surgical challenge. Although there are many issues still to resolve, laparoscopic minimized gastrectomy with SN navigation surgery or combined endoscopic mucosal resection and endoscopic submucosal dissection has the potential to achieve this goal.

Introduction

Every year in Japan, early gastric cancer (cT1) is detected in many asymptomatic patients as a result of the recent advances in endoscopic diagnosis. The population with early gastric cancer currently reaches in excess of 50% in our institution. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have already been accepted as the most minimally invasive procedures for the resection of early gastric cancer (1). Laparoscopic gastrectomy is an important intermediate option between EMR/ESD and open surgery for patients with gastric cancer (2). More recently, laparoscopic gastrectomy has shifted towards more radical procedures such as laparoscopy-assisted distal gastrectomy (LADG) or total gastrectomy with D1+β or D2 lymphadenectomy, which are comparable to conventional open surgery and can be applied to advanced cancer. In Japan, over 2000 cases per year are treated with advanced laparoscopic gastrectomy such as LADG.

Advanced laparoscopic gastrectomy is believed both to contribute to postoperative early phase recovery and to have cosmetic benefits. However, patients' quality of life (QOL) is mainly affected by late phase complications such as dumping syndromes and body weight loss resulting from oral intake disturbance. After gastric cancer surgery, attention should be paid to minimal invasiveness for early phase recovery and satisfied late phase function. Function-preserving surgery – including partial gastrectomy, segmental gastrectomy, pylorus-preserving distal gastrectomy and proximal gastrectomy – with limited extent of stomach resection and modified lymphadenectomy has been investigated. Although these limited gastrectomies with less lymph node dissection will help to improve functional results after surgery, a certain incidence of skip metastasis in the second (or third) compartment of regional lymph nodes remains an obstacle to these procedures' wider application. To overcome these issues, the sentinel node (SN) concept has attracted attention and is anticipated to become a novel diagnostic tool for identifying clinically undetectable lymph node metastasis in patients with early gastric cancer.

The SN is defined as the lymph node(s) first receiving lymphatic drainage from the primary site of a tumor (3).

The SN is thought to be the first possible site of micrometastasis along the route of lymphatic drainage from the primary lesion. Thus, the pathological status of the SN is thought to predict the status of all regional lymph nodes. If the SN is recognizable and negative for cancer metastasis, unnecessary radical lymph node dissection might be avoided. The SN hypothesis is applied to patients at high risk of having lymph node metastasis based on the characteristics of their primary tumors, but whose regional metastatic nodes were clinically undetectable by preoperative diagnostic imaging.

The histopathological status of regional lymph nodes is one of the most significant predictors of recurrence and overall survival for most early stage solid tumors; it is often used to justify risk stratification of patients for adjuvant therapy. A more efficient and accurate diagnosis of lymph node metastasis, as well as prognostic information, can be obtained from a small number of lymph nodes, through intraoperative SN mapping and sentinel lymphadenectomy (3,4). The SN navigation surgery is defined as a novel minimally invasive surgery without unnecessary lymph node dissection based on a SN biopsy and a diagnosis for nodal metastasis targeting SN.

SN mapping and biopsy were first applied to melanoma and breast cancer, and were subsequently extended to many other solid tumors (3–6). The SN concept has revolutionized the approach to the surgical staging of both melanoma and breast cancer. Applying this concept can yield benefits for the patient by avoiding various complications relating to unnecessary prophylactic radical lymphadenectomy, even in cases with negative SN for cancer metastasis.

Clinical application of SN mapping for early gastric cancer was controversial for years. However, single institutional results, including ours, of SN mapping for early gastric cancer are considered acceptable in terms of detection rate (90%–100%) and accuracy (85%–100%) in determining lymph node status (7). Based on these results, we are endeavoring to develop a novel laparoscopic minimally invasive gastrectomy with SN navigation.

Current procedures for laparoscopic SN biopsy

Japan Society of Sentinel Node Navigation Surgery has designed the standard protocol for SN mapping for gastric cancer (Table 1). A dual-tracer method using radioactive colloids and blue dye is the most reliable method as this moment for the stable detection of SN in early gastric cancer (8,9). An accumulation of radioactive colloids allows us to identify the SN even in resected specimens, on the back table and blue dye is effective for intraoperative visualization of lymphatic flows even in laparoscopic surgery.

Table 1 Current standard protocols for sentinel node (SN) mapping for gastric cancer (Keio University Hospital, Tokyo, Japan)

Indication
cT1/T2 N0M0 (single lesion, no previous treatments)
Diameter of primary lesion < 4.0 cm
Radio-guided method
Tracer: 99 m Technetium tin colloid (0.3 mCi at the time of surgery)
Administration: Endoscopic submucosal injection (0.5 × 4 points)
Timing of administration: The day before surgery
SN detection: Gamma probing (GPS Navigator, TycoHealth Care, Japan)
Dye-guided method
Tracer: 1% Isosulfan blue (Lymphazurin, TycoHealth Care, Japan)
Administration: Endoscopic submucosal injection (0.5 × 4 points)
Timing of administration: The day before surgery
SN detection: Identification of blue stained nodes within 15 min

Patients with clinical T1 or T2 tumors with primary lesions less than 4cm diameter and clinical N0 gastric cancer were included in the study and underwent SN mapping and biopsy. Patients with clinical T3 or T4 tumors and with clinically apparent nodal metastasis, in which original lymphatic drainage routes might be obstructed and altered, were excluded from the study.

After local administration, technetium-99m-labeled tin colloid, with a relatively large particle size, accumulates in the SN of early gastric cancer. In our experiences, the radioisotope-labeled tin colloid migrates into the SN within 2 h and remains there for more than 20 h through phagocytosis by macrophages. The day before surgery, 2.0 ml (150 MBq) radioisotope-labeled tin colloid solution was injected in four quadrants into the submucosal layer of the primary site using an endoscopic puncture needle. Endoscopic injections allowed us to accurately inject the tracer. Preoperative lymphoscintigraphy is useful in detecting sentinel lymphatic basin in unexpected sites. Nakahara *et al.* demonstrated that 71 (67%) of 106 sentinel lymphatic basins were visualized during lymphoscintigraphy (10).

In the first step of laparoscopic intraoperative SN detection, the gastrocolic ligament should be divided to visualize laparoscopically all possible direction of lymphatic flow from the primary site in the stomach (11). Next blue dye (1% isosulfan blue) is injected using intraoperative endoscopy, similar to preoperative injection of the radioactive tracer – it should be injected into the submucosal layer of the primary site using an endoscopic puncture needle in four quadrants. Blue lymphatic vessels and blue-stained nodes can be identified under laparoscopy within 15 min after the injection of blue dye (Figure 1). Blue dye is useful for visualizing the lymphatic vessels in spite of several issues such as the fast movement of the dye and blind sites in dense fat. Simultaneously a hand-held gamma probe is used to locate the radioactive

Figure 1 Laparoscopic sentinel lymphatic basin dissection. Sentinel lymphatic basin dissection is a sort of focused lymph node dissection containing hot and blue nodes. The figure shows the dissection of sentinel lymphatic basin, containing the blue nodes (SN) on the lesser curvature side. Black arrows, sentinel nodes on the greater curvature side; blue arrows, afferent lymphatic vessel. SN, sentinel node.

SN. Intraoperative gamma probing is feasible in laparoscopic gastrectomy using a special gamma detector introducible from trocar ports. Although intraoperative sampling of SN is not always easy because of the shine-through effect, the radio-guided methods allowed us to confirm the complete harvest of SN by gamma probing. In contrast, the dye-procedure enabled us to observe the lymphatic flows in real time. We recommend a combination of blue dye and radio-guided methods for systematic SN mapping of gastric cancer at this moment.

For intraoperative SN sampling, the pick-up method is well established in detecting melanoma and breast cancer. However, it is recommended that the clinical application of intraoperative SN sampling for gastric cancer include sentinel lymphatic basin dissection, a sort of focused lymph node dissection containing hot and blue nodes (Figure 1) (12). On the back table, the resected sentinel lymphatic basin was carefully investigated for hot nodes (SN) sampling with a handheld gamma probe. Identified SN are then sent for intraoperative histological examination. After gastrectomy, the absence of other radioactive SN among the residual lymph nodes in the upper abdominal cavity is confirmed using the gamma probe from the trocar or small abdominal wound.

Some reports have emphasized that clinical utility of indocyanine green infrared imaging as a new tracer using infrared ray electronic endoscopy for laparoscopic SN biopsy (13,14). More recently, indocyanine green fluorescence imaging system has been developed as a promising novel technique for laparoscopic SN mapping (15).

Table 2 SN mapping for gastric cancer (including open and laparoscopic surgery; Keio University Hospital, Tokyo, Japan, 1999–2006)

cT1N0M0 or T2N0M0 gastric cancer: 382 cases	
Detection rate	96% (367/382)
SN number per case	4.1
Sensitivity	94% (44/47)
Accuracy	99% (364/367)

Results of SN mapping for gastric cancer

The results of SN mapping in open and laparoscopic surgery for gastric cancer in our institution are described in Table 2. SN mapping for early gastric cancer are considered acceptable in terms of detection rate and accuracy to determining lymph node status. Our results suggest that an unexpected anatomical skip metastases, possibly resulting from aberrant lymphatic drainage routes from primary lesions; this is compatible with the SN concept in melanoma or breast cancer. As with SN mapping for other carcinomas, we need to confirm the reliability of the procedure through multicentric prospective clinical trials. A study group in the Japan Society of Sentinel Node Navigation Surgery conducted a multicentric prospective trial of SN mapping by a dual-tracer method with radioactive colloid and blue dye that ended in 2008. The results of the clinical trial are expected to provide perspectives on the future direction of SN navigation surgery for early gastric cancer.

Future direction of laparoscopic SN biopsy for early gastric cancer

The distribution of sentinel lymphatic basins and the pathological status of SN would be useful in deciding on the extent of gastric resection. Appropriate indications for proximal gastrectomy, segmental gastrectomy, pylorus preserving gastrectomy and partial resection for cT1N0M0 gastric cancer could be individually determined based on SN (Figure 2). Currently, surgical treatment of cT1N0M0 gastric cancer can be individualized as shown in the flowchart based on SN navigation (Figure 3) (11,16). Various types of laparoscopic function-preserving surgery are applicable for cases with cancer-negative SN. For example, laparoscopic partial (wedge) resection of the stomach is applicable for cases with a sentinel lymphatic basin on the greater curvature side. Laparoscopic segmental gastrectomy with pylorus-preserving procedure is feasible for cases with a primary lesion more than 4 cm from the pylorus ring and two sentinel lymphatic basins on the lesser and greater curvature sides. Earlier recovery after surgery and preservation of QOL in the late phase can be achieved by laparoscopic limited gastrectomy with SN navigation.

Recent representative results of laparoscopic SN biopsy for gastric cancer are described in Table 3 (11,13,17–19). Although the accuracy in determining lymph node status by laparoscopic SN biopsy may vary between institutions, these results are generally accepted in cases with cT1 early gastric cancer. Moreover, these reports have demonstrated that sentinel lymphatic basins contain truly positive nodes, even when the SN biopsy produces a false negative. Sentinel lymphatic basin dissection can provide us with an acceptable "safety net" for clinical application of SN sampling for gastric cancer. Although a well-designed multicenteric feasibility study of laparoscopic SN mapping and biopsy for early gastric cancer should be conducted as the next step, the novel surgical procedure might be feasible and reliable for CT1N0 early gastric cancer.

A combination of EMR/ESD and laparoscopic SN biopsy for superficial gastric cancer is another attractive option as a novel minimally invasive approach. However, it is likely too soon for laparoscopic SN mapping and consequent intraoperative EMR/ESD for SN negative cases to become an accepted approach in clinical practice.

Recently the philosophy of surgery has been dramatically revolutionized by the appearance of a new technique referred to natural orifice transluminal endoscopic surgery (NOTES), which can benefit patients by avoiding scarring on the body's surface (20,21). NOTES might be figuratively regarded as a second coming of the laparoscopic surgery of the 1990s, and currently there has been drastic acceleration in the exploration of new techniques.

Cahill *et al.* reported on lymphatic mapping and SN biopsy by "transgastric" NOTES in the porcine model (22). The authors easily performed lymphatic mapping and SN biopsy in the colonic mesentery using the transgastric

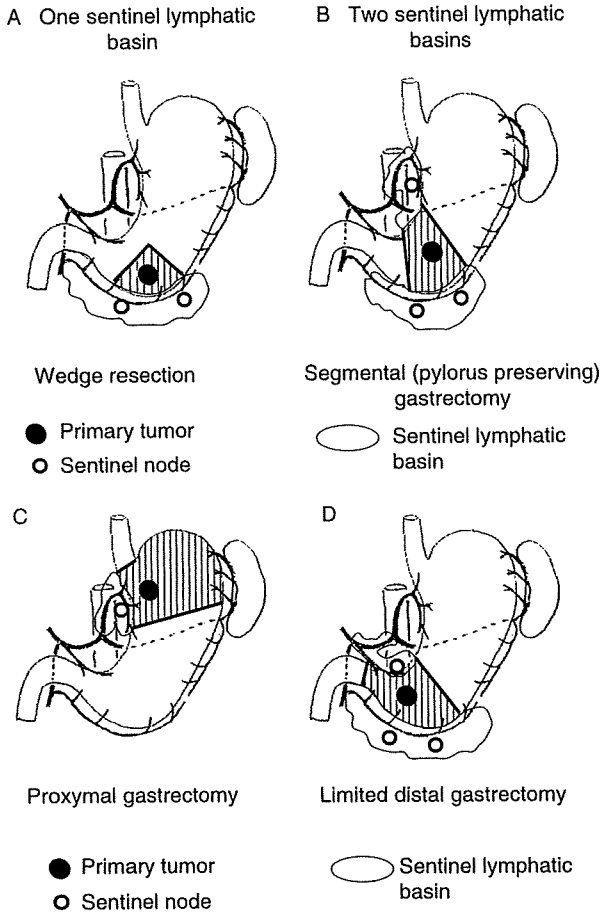

Figure 2 Schema of laparoscopic function-preserving gastrectomy with sentinel lymphatic basin dissection.

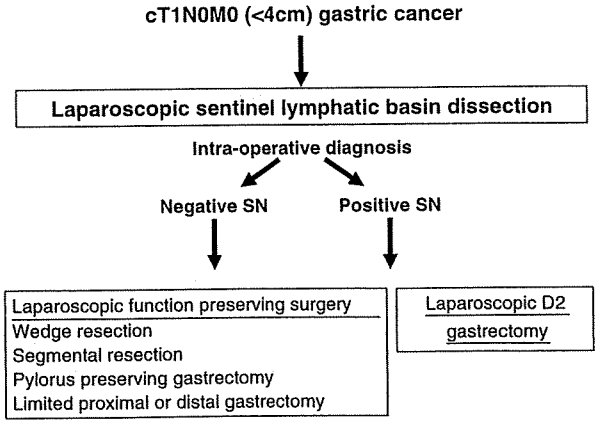

Figure 3 Current approaches for cT1N0M0 gastric cancer based on sentinel node (SN) navigation.

Table 3 Representative reports of laparoscopic sentinel node biopsy for gastric cancer

Author	Year	Method	Tumor depth	#Patients	Detection rate (%)	Sensitivity (%)	Accuracy (%)
Saikawa(11)	2006	RI & Dye (^{99m} technetium tin colloid & 1% isosulfan blue)	cT1	35	33/35 (94)	1/2 (50)	32/33 (97)
Rino(17)	2006	Dye (1% Patent blue)	cT1	38	35/38 (92)	4/4 (100)	35/35 (100)
Ishikawa(13)	2007	Dye (ICG infrared ray)	pT1-T2	16	16/16 (100)	1/2 (50)	15/16 (94)
Lee(18)	2008	RI & Dye (^{99m} technetium HSA & ICG)	cT1	21	20/21 (95)	2/2 (100)	20/20 (100)
Orsenigo(19)	2008	Dye (2% Patent blue)	pT1-T3	34	27/34 (79)	5/12 (42)	20/27 (74)

HSA, human serum albumin; ICG, indocyanine green; RI, radioisotope.

NOTES technique. They concluded that SN biopsy is indeed feasible without abdominal incision. The article by Cahill *et al.* may represent a valuable signpost for the future direction of SN biopsy for early gastrointestinal cancer. The combination of EMR/ESD with SN biopsy by NOTES might be an ideal minimally invasive surgical strategy for cN0 early gastric cancer (23).

Conclusion

For early stage gastric cancer such as cT1N0M0, in which a generally better prognosis is achieved through conventional surgical approaches, an individualized minimally invasive surgery that might retain the patient's QOL should be established as the next surgical challenge. Although there are many issues still to resolve, combined EMR/ESD and laparoscopic minimized gastrectomy with SN navigation surgery both have the potential to achieve this goal.

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SURGERY TODAY

Original Articles

The Possibility of Performing a Limited Resection and a Lymphadenectomy for Proximal Gastric Carcinoma Based on Sentinel Node Navigation

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Abstract

Purpose. This study examined the possibility of performing a limited resection and a lymphadenectomy with sentinel node navigation surgery (SNNS) for the treatment of proximal gastric carcinoma.

Methods. Thirty patients with cT1N0 ($n = 23$) and cT2N0 ($n = 7$) proximal gastric carcinoma that was located primarily in the U area (the upper third of the stomach) were enrolled. indocyanine green (ICG: 0.5 ml) was injected endoscopically into the submucosa of the four quadrants encompassing the cancer. Twenty minutes after injection, infrared ray electronic endoscopy (IREE) was used to identify the lymph nodes that were stained with ICG (sentinel nodes, SNs) around the serosa and surrounding fat tissue.

Results. One hundred percent of the SNs were identified with our SNNS method. The most common location of SNs was No. 3 (T1: 78%, T2: 100%). The main route of lymphatic drainage was from No. 1 or No. 3 to No. 7 (T1: 95%, T2: 100%). In T1 cancer, Indocyanine green was not distributed to the right gastric area, and no patients had SNs in No. 5 or No. 8a. Four cT2 cancer patients had lymph node metastases, all of which were SNs. There were no cases of postoperative metastasis or recurrence.

Conclusions. For the cT1 proximal gastric carcinoma patients, limited dissection of the ICG tracer-positive lymphatic areas alone by SNNS using IREE may be acceptable. The main lymphatic drainage route of proximal gastric carcinoma is the left gastric artery area (Nos. 1, 3, and No. 7) and dissection of this area is important.

Key words Limited gastrectomy · Sentinel node navigation surgery · Proximal gastric carcinoma

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Introduction

Although the overall incidence of gastric cancer has been declining in both Western and Eastern countries, the incidence of adenocarcinoma of the proximal third of the stomach has been increasing at an alarming rate.[1] Owing to an aging population and an increasing proportion of early gastric cancers,[2] Japanese surgeons may be faced with treating a greater number of early cancers in the upper third of the stomach in the future.[3]

An analysis of the outcomes of such patients treated by the standard Japanese D2 total gastrectomy in the 1980s demonstrated that nodal metastasis in the distal perigastric nodes was rare.[3,4] Recently, more attention has been paid to improving the postoperative function and quality of life after early gastric cancer surgery without impairing the long-term outcome.[5] The treatment guidelines of the Japanese Gastric Cancer Association (JGCA) recommend endoscopic mucosal resection (EMR) or a modified gastrectomy (Modified A: D1 + No. 7, Modified B: D1 + No. 7, 8a, 9) for Stage IA (T1N0).[6]

For several years, we have performed sentinel node navigation surgery (SNNS) using infrared ray electronic endoscopy (IREE) combined with indocyanine green (ICG) injection for cT1N0 or cT2N0 gastric cancer.[7] Furthermore, we have previously reported the validity of a modified gastrectomy combined with this method for T1N0 gastric cancer.[8] The present study examined the surgical outcome of a gastrectomy combined with SNNS using IREE combined with ICG for proximal gastric cancer.

Patients and Methods

The protocol was approved by the Ethics Committee for Biomedical Research of the Jikei Institutional Review Board, and all patients provided written informed consent. The patients who were admitted to Jikei University Hospital with gastric cancer with no obvious metastases were prospectively enrolled.

Between July 2000 and December 2006, 135 patients with proximal gastric cancer that was located primarily in the U area (the upper third of the stomach) underwent resection with lymph node dissection. Of these, 30 patients with cT1N0 and cT2N0 gave their informed consent for SNNS and thereafter were enrolled in this study.

Sentinel node navigation surgery was performed according to the method of Nimura et al.[7] Firstly, 0.5 ml ICG (5 mg/ml; Diagnogreen; Dai-Ichi Pharma, Tokyo, Japan) was injected via an endoscope into each of the four submucosal sites surrounding the gastric cancer using an endoscopic puncture needle during open or laparoscopic surgery. Twenty minutes after the injection, the lymph nodes that were stained with ICG (sentinel nodes, SNs) were observed intraperitoneally around the serosa, and the surrounding fat tissue from the serosal side. Infrared ray electronic endoscopy (Olympus Optical, Tokyo, Japan) was used to illuminate the regional lymph nodes from the serosal side. Positive staining was confirmed by at least four surgeons or endoscopists during surgery (Fig. 1).

In principle, a lymph node dissection and a gastrectomy were performed according to the criteria established in the gastric cancer treatment guidelines of the JGCA, followed by a definitive pathological examination that included hematoxylin–eosin staining, and immunohistochemical staining with an anticytokeratin antibody (CAM 5.2; Becton Dickinson, San Jose, CA, USA). When metastases to SNs (hard or swollen SNs) were suspected, quick sections were examined pathologically. If informed consent was obtained from the cT1N0 patients, then a limited gastrectomy (wedge resection, segmental gastrectomy, or pylorus-preserving gastrectomy) with a dissection of the lymphatic area positive for ICG (lymphatic basin dissection, LBD[9]) was performed. In such cases, the SNs were examined using the frozen section diagnosis procedure. A pylorus-preserving gastrectomy or a segmental gastrectomy was performed for the patients with a lesser curvature lesion if the tumor margin was located greater than 2 cm from

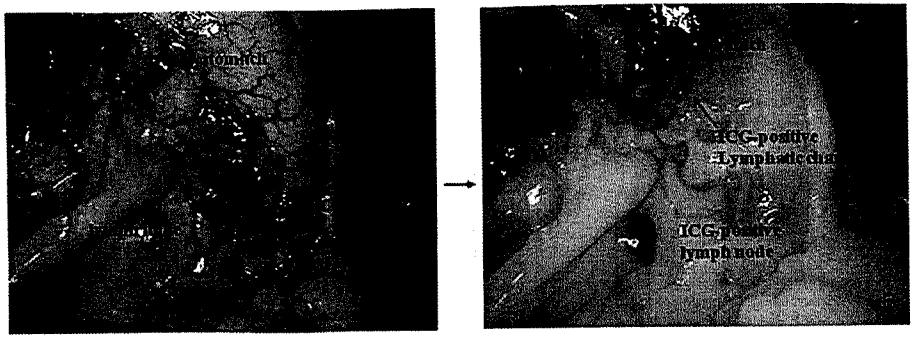

Fig. 1A,B. Intraperitoneal observation of the stomach during laparoscopic surgery, 20 min after the injection of indocyanine green (*ICG*). With infrared ray electronic endoscopy (IREE), lymph nodes (sentinel nodes) and lymphatic vessels positive for ICG were clearly detected. **A** Ordinary light, **B** IREE

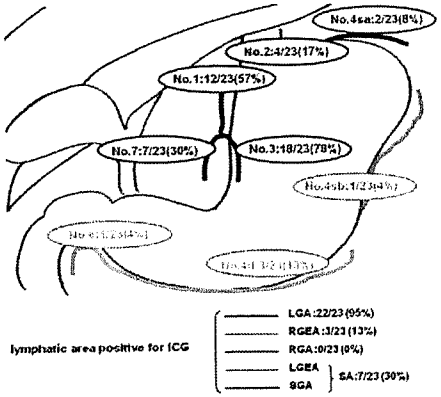

Fig. 2. Location of identified sentinel nodes (SNs) and lymphatic areas positive for ICG in T1 cancer cases. *LGA*, left gastric artery area; *RGEA*, right gastroepiploic artery area; *RGA*, right gastric artery area; *LGEA*, left gastroepiploic artery; *SGA*, short gastric artery; *SA*, splenic artery area

Table 1. Patients' characteristics

Age (years)	62.9 ± 9.14 (43–84)*
Sex (M:F)	23:7
Tumor size (mm)	42.6 ± 32.1 (7–160)*
Depth of invasion	
m	13
sm	10
mp	3
ss	2
se	2
Lymph node metastasis	
n0	26
n1	3
n2	1
Anatomical subsite	
Lesser curvature	15
Greater curvature	4
Anterior wall	3
Posterior wall	8

*Mean ± SD (range)

Table 2. Identification of sentinel node (SN) and lymph node (LN) metastasis

	T1 (n = 23)	T2 (n = 7)
SN identification	23 (100%)	7 (100%)
LN metastasis	0	4
Sensitivity	—	100%

the gastroesophageal junction in order to preserve the cardia. The gastric lymphatic area was divided into the left gastric artery (LGA) area, the right gastric artery area (RGA), the right gastroepiploic artery area, and the splenic area according to the criteria of Roviere[10] and Coller et al.[11]

Results

The patients' characteristics are listed in Table 1. The pathological findings included the depth of invasion and lymph node metastasis. Of the 30 proximal gastric cancer patients examined by SNNS, 23 patients were pT1 and 6 patients were pT2. All of the 4 patients with lymph node metastasis had T2 cancer. Our SNNS methods permitted an accurate identification of SNs and metastatic lymph nodes (Table 2). The number of SNs per patient was 4.8. Although the maximum tumor size was 160 mm, the SNs could be identified. The operative data are listed in Table 3. A wedge resection combined with a dissection of the lymphatic area positive for ICG was performed for 4 patients. The SNs of these 4 patients was examined by a frozen section, and they were confirmed to be free of any metastasis.

Table 3. Operative procedures

Type of gastrectomy	
Open	27
Laparoscopically assisted	3
Extent of resection	
Proximal gastrectomy	8
Total gastrectomy	16
Pylorus-preserving gastrectomy (segmental gastrectomy)	2
Wedge resection	4
Extent of dissection	
D1	4
D1 + α	15
D1 + β	2
D2	5
LBD	4

LBD, lymphatic basin dissection

The locations of the identified SNs and the lymphatic areas positive for ICG are shown in Figs. 2 and 3. In T1 cancer patients, the most common lymphatic area of the upper third cancer was the LGA area (22 patients, 95%), and No. 3 was the most common location of the SNs (18 patients, 78%), while No. 1 was the second most common location (12 patients, 57%). The main route of lymphatic drainage was from No. 1 or No. 3 to No. 7. Nevertheless, in some patients, the lymphatic area positive for ICG was in the right gastroepiploic artery or the left gastroepiploic artery area despite the presence of a lesser curvature lesion. Indocyanine green was not distributed to the right gastric area, and no patients had SNs in No. 5 or No. 8a.

As in the T1 cancer cases, in T2 cancer cases the most common lymphatic area was the LGA, and No. 3 was the most common SN location. In comparison to the T1 cancer cases, there was an increase in the number of cases with the lymphatic area in the greater curvature. Furthermore, the SNs were Nos. 8a and 11p.

The mapping of the four patients with lymph node metastases is shown in Fig. 4. All patients had cT2 cancer. The postoperative pathological examination showed that the depth of the tumor in Case 1 was SE. Cases 1, 2, and 4 underwent a standard total gastrectomy with a D2 dissection. However, Case 3 received a proximal gastrectomy with D1 + α, which was insufficient according to the criteria of the JGCA guidelines, because this patient did not want a total gastrectomy, but gave informed consent for a limited gastrectomy and a dissection for ICG-positive lymphatic areas. In all four patients, all metastatic lymph nodes were positive for ICG. After a median follow-up of 61 months, none of the patients had either postoperative metastases or recurrence.

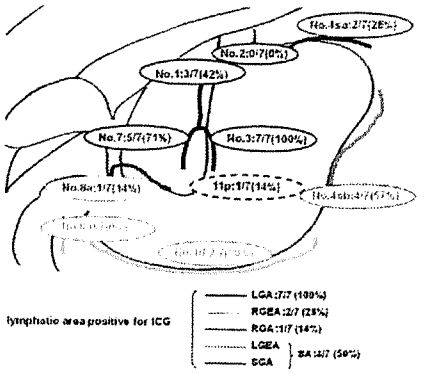

Fig. 3. Location of identified SNs and lymphatic areas positive for ICG in T2 cancer cases. *LGA*, left gastric artery area; *RGEA*, right gastroepiploic artery area; *RGA*, right gastric artery area; *LGEA*, left gastroepiploic artery; *SGA*, short gastric artery; *SA*, splenic artery area

Discussion

With respect to a lymph node dissection for proximal gastric carcinoma, Kobayashi et al. mapped the arterial areas of lymphatic drainage by studying the cases of single lymph node metastasis, in which the left gastric arterial area was reported to be the main stream, extending to the whole stomach except for the greater curvature of the upper one-third of the stomach or pylorus.[12] Furthermore, these investigators classified lymph nodes No. 5 and No. 8a in the right gastric arterial area, and reported that this arterial area was small and included only the lesser curvature of the antrum. Ohta et al. analyzed the appropriate indications for a proximal gastrectomy for cancer in the upper third of the stomach.[13] They concluded that localized, superficial lesions less than 30 mm in size, or other macroscopic types including differentiated and undifferentiated lesions with neither lymph node metastasis nor a serosal involvement, have no lymph node metastasis in No. 4d, No. 5, and No. 6. Nevertheless, these studies were based on the results of a postoperative histopathologic examination.

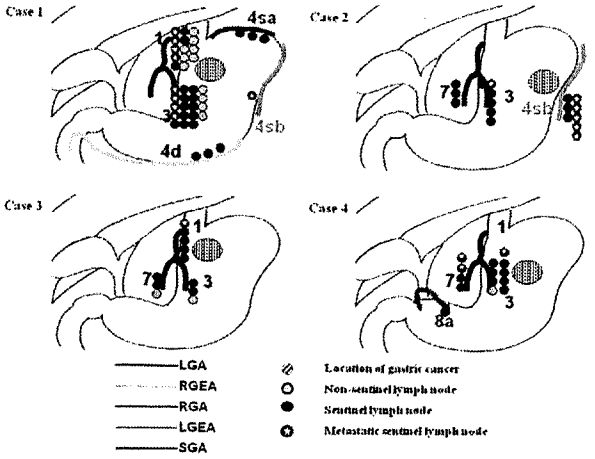

Fig. 4. Patients who had metastatic lymph nodes. *Case 1* had a 65-mm, SE mucinous carcinoma in the anterior wall, which had three lymphatic areas (LGA, SA, RGEA) and SNs in Nos. 1, 3, 4sa, 4sb, and 4d. The metastatic lymph nodes were located in Nos. 1, 3, and 4sb, which were all SNs. *Case 2* had a 25-mm, MP well-differentiated adenocarcinoma in the greater curvature, which had two lymphatic areas (LGA) and SNs in Nos. 3, 4sb, and 7. The metastatic lymph nodes were located in Nos. 3 and 4sb, which were all SNs. *Case 3* had a 62-mm, MP poorly differentiated adenocarcinoma in the lesser curvature, which had one lymphatic area (LGA) and SNs in No. 1. A metastatic lymph node was included in No. 1, which was an SN. *Case 4* had a 75-mm, SS moderately differentiated adenocarcinoma in the posterior wall, which had two lymphatic areas (LGA, RGA) and SNs in Nos. 3, 7, and 8a. The metastatic lymph nodes were included in Nos. 3 and 7, which were all SNs. *LGA*, left gastric artery area; *RGEA*, right gastroepiploic artery area; *RGA*, right gastric artery area; *LGEA*, left gastroepiploic artery; *SGA*, short gastric artery

In the present intraoperative study with SNNS, the most common location of SNs was No. 3, and the main lymphatic drainage was LGA (from No. 1 or No. 3 to No. 7). These results are in agreement with previous reports that described the importance of the dissection of LGA for proximal gastric carcinoma.[12,13]

None of the T1 cancer patients had SNs in No. 5 or No. 8a, and none of the No. 5 or No. 8a lymph nodes that were dissected contained metastatic lymph nodes. Furthermore, the maximum size of the T1 tumors was 68 mm. Therefore, it seems unnecessary to dissect these lymph nodes in early cancers that occur primarily in the upper third if the tumor does not extend to the lesser curvature of the antrum. A proximal gastrectomy, segmental gastrectomy, or wedge resection is possible if the surgical margin can be secured. In fact, in the present study, no postoperative metastases or recurrences were observed after either a wedge resection, pylorus-preserving gastrectomy (segmental gastrectomy), or proximal gastrectomy.

However, in T2 cancer cases the ICG-positive lymphatic area included the RGA area. This suggests that, in principle, a total gastrectomy with dissection of the RGA area is necessary for T2 cancer. Furthermore, all patients with lymph node metastasis had T2 cancer. Importantly, all metastatic lymph nodes were included in the ICG-positive lymphatic area and the SNs.

Recently the number of reports of SNNS for gastric cancer has increased, and such techniques have been improving.[9,14–19] Ichikura et al. reported lymphatic mapping using ^{99m}Tc-labeled tin colloid and ICG in the patients with clinical T1N0 cancer.[14] In their study, a postoperative pathologic examination revealed lymph node metastases in 3 of the 61 patients for whom the SNs were diagnosed intraoperatively as negative on the frozen section. All of their metastatic lymph nodes were included in the lymphatic areas where RI or ICG was distributed.

Ajisaka et al. analyzed micrometastases in SNNS using reverse transcription–polymerase chain reaction (RT–PCR) and immunostaining.[20] Three of the 35 patients had metastases in non-SNs, whereas all of the metastatic non-SNs were identified in the same lymphatic basin as the metastatic SNs. They concluded that the dissection of the lymphatic area containing SNs is a minimal requirement for curative resection of early-stage gastric cancer, even for patients without histologically detectable metastases in the SNs.

In most institutions, a standard total gastrectomy with D2 dissection is performed for lymph node metastasis in the SNs. Based on our results and those of previous studies, none of the patients in our study have lymph node metastasis in SNs, and a limited dissection to only the lymphatic areas where the tracers are distributed appears acceptable for cT1. For example, in the future we may be able to preserve the spleen if the tracers are not distributed to the splenic artery area. Furthermore, a limited gastrectomy such as a proximal gastrectomy, wedge resection, or pylorus-preserving gastrectomy may be indicated according to the size and the location of the cancer if the surgical margin can be defined.

In conclusion, for the patients with cT1 proximal gastric carcinoma, although a further accumulation and analysis are necessary, a limited dissection of the ICG tracer-positive lymphatic areas alone by SNNS using IREE may be acceptable. The main lymphatic drainage route of proximal gastric carcinoma is the left gastric artery area (Nos. 1, 3 to No. 7), and the dissection of this area is important when performing limited surgery.

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Tailoring Treatment for Early Gastric Cancer after Endoscopic Resection Using Sentinel Node Navigation with Infrared Ray Electronic Endoscopy Combined with Indocyanine Green Injection

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Key Words
Early gastric cancer, tailoring treatment · Endoscopic resection · Indocyanine green · Infrared ray electronic endoscopy · Sentinel node navigation surgery

Abstract
Background: This study evaluated the efficacy of sentinel node navigation surgery using infrared ray electronic endoscopy (IREE) combined with indocyanine green in patients after endoscopic treatments of early gastric cancer. ***Methods:*** 14 patients with early gastric cancer after endoscopic treatments were included. Each patient underwent sentinel node navigation surgery using IREE. Sentinel node detection rate, accuracy of sentinel node metastases and clinical efficacy including the presence or absence of recurrence were evaluated. ***Results:*** The intraoperative sentinel node detection rate was 100% (14/14), and accuracy for sentinel node metastases was 93% (13/14). Based on the results of sentinel node mapping, 2 patients received standard gastrectomy with D2 lymphadenectomy, and the remaining 12 patients underwent limited surgery with lymphatic basin dissection. After median follow-up of 32 months, no patients had tumor recurrence. ***Conclusion:*** The validity of limited surgery based on sentinel node navigation for early gastric cancer remains unclear because the results of a well-designed multicenter clinical trial of sentinel node mapping for gastric cancer have not yet been reported. However, this study suggests that sentinel node navigation surgery using IREE combined with indocyanine green is useful for early gastric cancer after endoscopic resection.

In Japan, early-stage gastric cancer now accounts for more than half of all cases. Among others, patients with mucosa-limited gastric cancer <2 cm in diameter are good candidates for endoscopic mucosal resection [1]. Advances in endoscopic therapeutic technique and development of new instruments have led to expansion of the indications for endoscopic treatments of early gastric cancer. Endoscopic submucosal dissection is a new technique developed to obtain en-bloc resection in cases of early cancer >2 cm in diameter [2, 3].

Unfortunately, a substantial percentage of patients who receive endoscopic treatment for early gastric cancer require additional treatments because of incomplete resection and/or improper indications for endoscopic re-

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