

FIGURE 1. A 48-year-old man with a Warthin tumor. (A) Right lateral image of the right parotid gland with a round lead marker on the mass. A round defect localizing the tumor is shown. (B) The same view after lemon juice stimulation. Persistent uptake was noted in the lower portion of the right parotid gland.

defects, persistent uptake after lemon juice stimulation (when compared with the normal salivary gland), and no abnormalities. The coexistence of a persistent defect with persistent uptake after lemon juice stimulation suggests WT with cystic degeneration. Subjects with these findings were categorized into the persistent uptake group.

Treatment

Treatment policies for parotid tumors were determined in accordance with radiologic assessments, for all patients. Treatment strategies were divided into surgery and clinical follow-up. For clinical follow-up, patients were initially assessed a few months after the treatment decision and every 6 to 12 months thereafter.

Statistical Analysis

First, scintigraphic and surgical results were compared with evaluate the diagnostic accuracy of WT. Second, for all 127 patients who had undergone surgery or had been followed up, the relationship between the treatment decision and scintigraphic results was evaluated. Third, the characteristics of the patients for whom observation was selected were evaluated. Furthermore, the characteristics of the patients who had undergone surgery were compared with those of patients who were scintigraphically suspected to have a WT. A value of $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Pathologic and Scintigraphic Results

Surgical treatment was chosen for 100 patients (80%). There were 60 pleomorphic adenomas (60%), 19 WTs (19%), 9 other benign masses (9%), and 12 malignant tumors (12%).

Among the 100 surgically excised tumors, salivary gland scintigraphy with lemon juice stimulation had shown persistent defects in 68, persistent uptake in 25, and no abnormality in 7 (Table 1). The sizes of the resected tumors in these groups were 28 ± 9 mm (range, 10–52 mm), 27 ± 15 mm (12–90 mm), and 12 ± 2 (10–15 mm), respectively. In the no abnormality group, the masses were significantly smaller than those of the persistent defect ($P < 0.0001$) and persistent uptake ($P < 0.0001$) groups. The sensitivity, spec-

TABLE 1. Scintigraphic Findings in 100 Surgically Confirmed Tumors

Histology	Pleomorphic Adenoma	Warthin's Tumor	Other Benign Diseases	Malignant Tumors
Scintigraphic results*				
Persistent defect	54	0	7	7
Persistent uptake	3	18	1	3
No abnormality	3	1	1	2

*Lemon juice stimulation.

ificity and accuracy for differentiating WTs from nonWTs were 95%, 91%, and 92%, respectively.

Seven false-positive results included pleomorphic adenoma (n = 3), mucoepidermoid carcinoma (n = 2), adenoid cystic carcinoma (n = 1), and oncocytoma (n = 1). Contrary to our expectation, 5 of these 7 tumors were relatively large (25–90 mm). False-negative results were obtained in only 1 patient, a 61-year-old woman with a small WT (11 mm).

Relationship Between Treatment Decision and Scintigraphic Results

Table 2 shows the relationship between treatment decision and scintigraphic results. The χ^2 test revealed a significant relationship between treatment decision and scintigraphic results ($\chi^2 = 16.5$, $P = 0.00026$). The main reason for selecting observation, rather than surgery, is shown in Table 3. It is noteworthy that 66% of the patients who were followed up (18/27) were suspected of having a WT on the

TABLE 2. Relationship Between Treatment Decision and Scintigraphic Results

Treatment	Surgery	Clinical Observation
Scintigraphic results*		
Persistent defect	68 (89%)	8 (11%)
Persistent uptake	25 (58%)	18 (42%)
No abnormality	7 (88%)	1 (12%)

*Lemon juice stimulation.

TABLE 3. Main Reasons for Clinical Observation in 27 Patients

Reason	No. Patients with Scintigraphically Suspected Warthin's Tumor
Comorbidity (n = 13)	13/13 (100%)
Angina or other heart diseases (n = 5)	
Cerebral infarction or recent TIA (n = 4)	
Malignancy other than parotid gland (n = 3)	
Severe respiratory dysfunction (n = 2)	
Chronic pyelonephritis (n = 1)	
Severe diabetes (n = 1)	
Refusal of surgery (n = 11)	4/11 (36%)
Age* (n = 3)	1/3 (33%)

TIA, transient ischemic attack.
*Their ages were 78, 79, and 92-year-old.

basis of scintigraphic results. Also, 42% of those with persistent uptake (18/43) were examined regularly without surgical treatment. Tumor growth was confirmed in only one of the 27 patients during a follow-up period of 28 ± 12 months (range, 12–48 months). This patient refused surgery even after tumor growth was recognized.

Patients Undergoing Surgery for WT and Scintigraphically Suspected WT

The characteristics of patients who were operated on or scintigraphically suspected to have WT, but did not receive surgical treatment, are shown in Table 4. Gender, age, and smoking habits were obtained from clinical records, as these factors may be related to this tumor. Tumor size in the followed-up patients was determined on the basis of CT or MRI. Other than age, there were no significant differences in characteristics between the 2 groups. Those under observation were significantly older than the surgical patients ($P < 0.05$).

TABLE 4. Characteristics of Operative Patients and Those Suspected to Have WT

Characteristics	Patients Operated on for WT (n = 19)	Patients with Scintigraphically Suspected WT (n = 18)
Gender		
Male	16*	13
Female	3*	5
Age		
Average ± SD	61 ± 7 [†]	66 ± 10 [‡]
Smoking habit		
Yes	15 [‡]	10 [§]
No	2 [‡]	2 [§]
Unknown	3	6

WT, Warthin's tumor.
* $P < 0.01$.
[†] $P < 0.05$.

Smokers significantly outnumbered nonsmokers among both surgically treated WT patients ($P < 0.01$) and those suspected to have WT ($P < 0.05$). Among those who underwent surgery for WT, male patients significantly outnumbered female patients ($P < 0.01$).

DISCUSSION

Basically, it is not difficult for experienced head and neck surgeons to perform surgery on parotid gland tumors. The operation can be accomplished in a short time and hemorrhage from the surgical site is minimal. Furthermore, the incidence of postoperative facial nerve dysfunction and Frey's syndrome are low in patients with solitary parotid tumors. For these reasons, the first choice of treatment of a parotid tumor is surgery, irrespective of tumor pathology. On the other hand, there are some parotid tumor patients, particularly those with significant comorbidities or older individuals, for whom the optimal treatment is not necessarily surgery. In addition, one encounters in clinical practice certain patients who are reluctant to undergo any operation. Because the malignant potential of WT is extremely low, its diagnosis in such patients can be among the reasons for choosing careful observation rather than immediately resorting to surgery. Indeed, treatment strategies vary among countries. According to head and neck surgeons in Japan, patients for whom the avoidance of surgery is preferred can be followed up by serial physical examinations once a diagnosis of WT has been made. Similar policies have been described in other reports.^{4,5}

Salivary gland scintigraphy with Tc-99m pertechnetate is useful for the diagnosis of WT, especially in combination with lemon juice stimulation. The mechanism of Tc-99m pertechnetate uptake by a WT has been described in other studies.^{2,6–8} Indeed, the diagnostic accuracy of the scintigraphy employed herein was 92%, which is consistent with previously reported results.^{3,9} Murata et al found the sensitivity, specificity, and accuracy of scintigraphy with lemon juice stimulation to be 78%, 91%, and 87%, respectively,⁵ while Miyake et al reported all 3 to be 94%.⁹ Salivary gland scintigraphy is a simple, noninvasive test, and the results obtained in the current study, as well as those cited above, confirm its very high diagnostic accuracy and reproducibility.

WT is known to be the second most common benign tumor of the parotid gland, as affirmed in our study. Its incidence varies among countries, ranging from 5% to 30%.^{10–13} As there was no pathologic evidence for WT in the patients suspected to have this tumor based on scintigraphy, the prevalence in the current study is surmised to be between 15% (19/129) and 29% (37/129). Gender and smoking habits are major factors influencing WT incidence,^{11,14,15} and our current results are consistent with these observations (Table 4). The male-to-female ratios were found to be 5.3:1 for pathologically confirmed WT, and 3.6:1 for those patients with confirmed or suspected WT. According to some large studies, the ratios were reported to range from 10:1 to 2:1.^{16–18} Our patient population showed no clear differences from those of other studies.

One possible difference between our results and those of other studies involves tumor size. The false-negative rate for the detection of parotid tumors can change, depending on the proportion of patients with a small tumor, because tumor size may be correlated with the WT detection rate.⁹ Our study population did not include patients with multiple parotid gland tumors, which means that incidentally identified tumors, other than the largest and probably those responsible for the patient's symptoms and the treatment decision, are excluded. In this study, the smallest tumor was 10 mm, whereas previous radiologic studies have evaluated smaller parotid tumors.^{19,20}

One limitation of this study is that we could not collect sufficient fine needle aspiration (FNA) data to provide meaningful results. Only 15 patients underwent FNA and it was successful in only eight. Although FNA is a relatively safe method of determining tumor pathology, its diagnostic role has not been well established.²¹⁻²³ Leverstein et al, describing the surgical results of 88 patients with parotid gland WT,¹⁷ noted that the FNA results correctly represented WT in 47 of 71 patients.

In our study, salivary gland scintigraphy does yield false-positive WT cases. Therefore, this procedure should not be used alone in making treatment decisions. Rather, it is advisable to use scintigraphy in combination with other radiologic findings, FNA results and clinical data whenever possible.

CONCLUSION

In our current patient population, a significant relationship was noted between treatment decisions and scintigraphic results. Forty-two percent of the patients with persistent uptake on salivary gland scintigraphy were followed up without surgery, which may be explained by the high diagnostic accuracy of this modality for the diagnosis of WT. Salivary gland scintigraphy is a useful noninvasive method for deciding on further management strategies for patients with a solitary parotid tumor that may otherwise result in unnecessary surgical procedures.

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**Preoperative Lymphoscintigraphy for Detection of
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Preoperative Lymphoscintigraphy for Detection of Sentinel Lymph Node in Patients with Gastric Cancer—Initial Experience

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Background: Preoperative lymphoscintigraphy may be informative when assessing nodal status in patients with early gastric cancer, especially for surgeons who are scheduled to introduce or have just introduced SLN biopsy.

Methods: A total of 80 patients with clinical T1N0M0 gastric cancer were injected with technetium-99 m tin-colloid and then underwent preoperative lymphoscintigraphy. The detection rate of SLN per lymphatic basin was determined on the basis of the results of confirmatory lymph node dissection.

Results: By means of lymphoscintigraphy, 71 of 106 basins were found (67%; 95% confidence interval [CI], 57.2–75.9%). Patients were stratified into the following subgroups: successful (S; all basins visualized), partially successful (PS; some basins visualized), and unsuccessful (U; none visualized). The body mass index (BMI) was significantly higher in the U (24.0 ± 2.5) than in the S (22.3 ± 2.4) group ($P = 0.037$). All patients in the U group had a single basin. Multivariate analysis showed that BMI was associated with unsuccessful lymphoscintigraphy (OR, 1.43; 95% CI, 1.06–1.92; $P = 0.019$), whereas all factors were similar between the S and PS groups.

Conclusion: BMI affects SLN detection during lymphoscintigraphy. Unsuccessful lymphoscintigraphy suggests that SLNs are located in a single basin. When lymphoscintigraphy is positive, no preoperative factors can predict whether all lymphatic basins can be visualized.

Key Words: Lymphoscintigraphy—Gastric cancer—Tin-colloid—Body mass index.

The detection rate of early-stage cancers with no clinical lymph node metastasis has increased with

improved diagnostic techniques and, hence, sentinel lymph node (SLN) biopsy for lymph node staging in various types of cancers has been investigated. SLNs were intraoperatively detected for the first time in 1992 using blue dye in patients with malignant melanoma.¹ The value of SLN biopsy in melanoma and breast cancer has been established, and treatment strategies are influenced by the outcome. One current focus is whether SLN biopsy also has clinical impact on other malignancies. Since lymph node metastasis occurs in as few as 9% of early gastric cancers,² SLN

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biopsy might lead to the selection of gastric cancer patients who are likely to benefit from less invasive treatment. Extensive investigations into the efficacy of SLN biopsy in gastric cancer have recently produced encouraging results, especially from Asian groups.³⁻⁶

Another focus is the role of preoperative lymphoscintigraphy in gastric cancer patients. Lymphoscintigraphy often permits preoperative SLN detection as a guide to intraoperative survey in melanoma and breast cancer, although this lymphoscintigraphic SLN detection has failed in some patient subgroups.⁷⁻⁹ Few investigators, however, have reported clinical results using this technique for the detection of SLNs in gastric cancer.¹⁰

For surgeons who have not had enough experience intraoperatively detecting SLNs in patients with early gastric cancer, prior knowledge of their locations using lymphoscintigraphy may be useful for intraoperative survey. We aimed to confirm what information this technique provides prior to SLN biopsy in patients with early gastric cancer.

MATERIALS AND METHODS

Patients

Between May 2005 and February 2007, 80 patients with clinical T1N0M0 gastric cancer were endoscopically injected with radioisotope (RI) for SLN biopsies and underwent preoperative lymphoscintigraphy the day before surgery. All patients were scheduled to undergo curative gastrectomy with D2, modified D2 lymphadenectomy (removal of all N1 nodes and nodes along the left gastric artery and common hepatic artery), or laparoscopic distal gastrectomy. Our institutional review board and radiation safety committee approved the study protocol, and we obtained written informed consent from all patients enrolled in this study. Patient characteristics are shown in Table 1.

Preparation and Endoscopic Injection of Technetium-99m Labeled Tin-colloid (TcTC)

A mixture of 1.5 ml technetium-99m and 1.5 ml stannous solution (Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan) was incubated at 4°C for 30 min to prepare TcTC particles of a homogeneous size (approximately 600–800 nm). We have previously reported that TcTC of a relatively large particle size stays in SLNs long enough to permit similar

TABLE 1. Patients' characteristics

Age (years)	
Mean	61.4 ± 11.0
Median	62
Range	36–87
Sex	
Male	51 (64%)
Female	29 (36%)
BMI	
Mean	22.6 ± 2.5
Median	22.5
Range	16.3–28.0
Tumor depth	
Mucosal	41 (51%)
Deeper than mucosa ^a	39 (49%)
Nodal status	
pN0	76 (95%)
pN1	4 (5%)
No. of SLN basins	
1	56 (70%)
≥2	24 (30%)
Tumor size (cm)	
Mean	2.71 ± 1.15
Median	2.8
Range	0.5–5.0
Tumor location	
Upper	12 (15%)
Middle	39 (49%)
Lower	29 (36%)
Tumor pathology	
Favorable	41 (51%)
Unfavorable	39 (49%)
Lymphatic invasion	
Yes	14 (18%)
No	66 (82%)
Vascular invasion	
Yes	6 (8%)
No	74 (92%)
Combination of RI and blue dye method	
Yes	55 (69%)
No	25 (31%)

BMI, body mass index; SLN, sentinel lymph node; RI, radioisotope.

^a Including T2 cancers in six patients.

detection of SLNs with 2-day protocols as with 1-day protocols.¹¹ A total of 2.0 ml TcTC (4 mCi) was endoscopically injected into four quadrants of the submucosal layer around the primary lesion using a sclerotherapy tube for esophageal varices (Sumitomo Bakelite Co., Ltd., Shinagawa, Japan). An experienced surgeon administered the RI injection to prevent endogastric spillage of TcTC.

Scintigraphy and SPECT/CT Image Fusion

After fasting for at least 4 h to suppress gastric peristalsis, patients were scintigraphically scanned using a dual-headed rotating gamma camera (Toshiba GCA-9300A/DI; Toshiba Corporation, Tokyo). The scanning protocol included anteroposterior static and single-photon emission computed tomography

(SPECT) imaging for the first 10 patients. Since we found that static imaging was unnecessary, only SPECT imaging proceeded in the remaining 70 patients. During SPECT data acquisition, an external marker with 0.05 ml technetium-99m solution (5 μ Ci) was placed on the umbilicus. SPECT data were collected for 30 min with a 4.3-mm matrix (128 \times 128). Images were reconstructed using ordered-subset expectation maximization (OSEM).

If SPECT images revealed SLN-like activity, they were fused with CT images to localize radioactive nodes. The CT data were obtained during routine clinical practice. Both SPECT and CT data were transferred to a personal computer in DICOM format. Two data sets of CT and SPECT were manually fused with reference to the injection sites and the landmark using fusion software (fusion viewer; Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan).

Intraoperative SLN Detection and Pathological Examination

We located radioactive lymph nodes during surgery using a hand-held gamma probe (Navigator; Tyco Healthcare Japan Inc., Tokyo, Japan). These nodes were separated from other radioactive materials, including the resected stomach and, thereafter, RI uptake in individual nodes was calculated using the gamma probe with an energy window of 105–160 keV over 20 s. We then diagnosed SLN as a node with 10-fold more radioactive counts than the background activity.¹¹ These nodes were assigned specific numbers indicating localization of the lymph node according to the guidelines of the Japanese Society of Gastric cancer.¹²

Excised SLN specimens were formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin (H&E) at the department of pathology. Immunohistochemical cytokeratin staining was performed when the specimens were H&E negative.

Lymphoscintigraphic and Surgical Results

Lymphoscintigraphic results were based on a database preoperatively established by an experienced radiologist. The results included the presence and localization of radioactive nodes on SPECT images. Since SPECT had a poor spatial resolution and was not accurately fused with CT, we could not construct an analysis for lymphoscintigraphy based on lymph nodes. Therefore, sites of radioactive nodes were classified based on dividing the lymphatic basin into five directions along the main

gastric arteries:¹³ left gastric (LGA), right gastric (RGA), right gastroepiploic (RGEA), left gastroepiploic (LGEA), and posterior gastric (PGA) arteries. Radioactive nodes on lymphoscintigraphy were compared with surgically proven SLNs on a per-basin basis.

According to lymphoscintigraphic results, patients studied were separated into groups labeled as successful (S; all basins visualized), partially successful (PS; some basins visualized), and unsuccessful (U; no basin visualized). This study focused on the diagnostic ability of lymphoscintigraphy as a preoperative surrogate for intraoperative gamma probing; we, therefore, did not evaluate the blue dye results.

Statistical Analysis

Differences among the three groups (S versus PS versus U groups) were assessed using analysis of variance for continuous variables, followed by the Tukey–Kramer test for pair-wise comparisons. Group means were compared using Kruskal–Wallis H statistics. A two-group comparison was performed using Fisher exact test for nodal status, number of SLN basins, and vascular invasion, because a three-group comparison cannot be adequately statistically analyzed. Differences were considered significant at $P < 0.05$.

To identify variables associated with the failure of lymphoscintigraphy, we also performed multivariate logistic regression analysis to determine the adjusted odds ratio for age, gender, body mass index (BMI), tumor size, location, and pathology. These variables can be defined before lymphoscintigraphy. We used the Hosmer–Lemeshow test to evaluate the validity of the regression analysis. All statistical analyses were performed using the SPSS software (version 14.0J; SPSS Inc., Chicago, IL).

RESULTS

Of the 81 patients, only 4 (5.0%; 95% confidence interval [95% CI], 1.4–12.3 %) had lymph node metastasis (Table 1), which was found in 5 (4.7%; 95% CI, 1.5–10.7%) of 106 basins. Of the five metastases, four were microscopic (LGA and RGEA basins, $n = 2$ and 2 , respectively); for the fifth, there was coexistence of microscopic and macroscopic metastases in the LGEA basin. Despite the small number of patients with lymph node metastasis, the sentinel node concept in early gastric cancer was acceptable in our study.

TABLE 2. Detection rate of sentinel lymph node (SLN) during lymphoscintigraphy

Lymphatic basin	Detected during lymphoscintigraphy	Missed during lymphoscintigraphy	All
Left GA	34 (71%)	14 (29%)	48
Right GA	5 (38%)	8 (62%)	13
Right GEA	30 (79%)	8 (21%)	38
Left GEA	2 (33%)	4 (67%)	6
Posterior GA	0 (0%)	1 (100%)	1
Total	71 (67%)	35 (33%)	106

GA, gastric artery; GEA, gastroepiploic artery.

Lymphoscintigraphic Results of SLN Detection

Of the 80 patients, 46, 17, and 17 were categorized into the S, PS, and U groups, respectively. Table 2 shows the lymphoscintigraphic results of SLN detection on a per-basin basis. Of the 106 basins proven by means of the RI method, 71 (67.0%) were visualized during lymphoscintigraphy (95% CI, 57.2–75.9%).

Factors for SLN Visualization During Lymphoscintigraphy

Table 3 summarizes the lymphoscintigraphic results by clinical variables. BMI was significantly higher in the U, than in the S group ($P = 0.037$, using Tukey–Kramer test). This index tended to be higher in the U, than in the PS group ($P = 0.084$). All variables were similar in the S and PS groups.

All patients in the U group had only one lymphatic basin (Table 3), whereas patients in the S and PS groups tended to have more than one ($P = 0.001$).

Predictive Factors Associated with Unsuccessful Lymphoscintigraphy

Table 4 shows the results of multivariate regression analysis. The BMI was associated with unsuccessful rather than successful plus partially successful ($P = 0.019$) or successful ($P = 0.022$) lymphoscintigraphic findings. However, this factor was marginally significant when compared with the S versus PS plus U groups ($P = 0.078$). No other factors were associated with the lymphoscintigraphic findings. No significant differences were observed for any factor, including BMI, between the S and PS groups. The Hosmer–Lomeshow test showed that these comparisons were suitable for multivariate regression analysis ($P > 0.05$). Figure 1 illustrates a representative example of successful lymphoscintigraphy.

DISCUSSION

To our knowledge, only one group has systematically investigated the accuracy of lymphoscintigraphy for evaluating nodal status in gastric cancer; Ozmen et al.¹⁰ evaluated 50 patients with gastric cancer, comprising 10 with T1, 33 with T2, and 7 with T3 cancers. They found all metastatic lymph nodes by means of lymphoscintigraphy in 34 patients (68%) with lymph node metastases. However, their study population differed from ours (Table 1). They evaluated tracer accumulation into metastatic nodes only with lymphoscintigraphy and did not examine radioactivity in resected lymph nodes. Moreover, other reports have already demonstrated that SLN mapping is not useful for patients with advanced tumors, probably because of destroyed or altered lymphatic drainage.^{6, 14} The present study was part of a clinical trial to validate the SLN concept in early gastric cancer and was applied only to clinical T1 cancers, which could account for the lower incidence of metastasis.² We believe that for patients with a high risk of lymph node metastasis there are no indications for sentinel node navigation surgery in terms of reduction of the extent of lymphadenectomy. We found that the detection rate with lymphoscintigraphy was only 67%, and that the major reason for unsuccessful lymphoscintigraphy was relatively high BMI. Factors are known that affect the success rate of SLN mapping, particularly in breast cancer. Possible factors are BMI, age, and breast size.^{7–9} In a report by Derossis et al.⁹, obesity significantly lowered not only the success rate of intraoperative SLN mapping but also the frequency of positive lymphoscintigraphy. Lerman et al.¹⁵ reported that the failure to detect SLNs during lymphoscintigraphy is attributable to a large amount of photon scattering from the injection site (so-called shine-through phenomenon), and that SPECT improves the detection rate of SLN compared with conventional lymphoscintigraphy. Similarly, SPECT might be useful during lymphoscintigraphy to overcome such adverse effects in head and neck cancers.¹⁶ Our study demonstrated that regardless of SPECT, BMI was a risk factor for unsuccessful lymphoscintigraphy in gastric cancer. A major difference between gastric cancer and those cancers is that the former is located deep in the abdomen; thus, the sensitivity of detecting radioactive nodes from outside the body is significantly reduced. In terms of cost-effectiveness, preoperative lymphoscintigraphy is not positively recommended, especially in patients with high BMI or in western patients. In our study, the median BMI in the U

TABLE 3. Clinical variables in the three subgroups according to lymphoscintigraphic results

	Successful (n = 46)	Partially successful (n = 17)	Unsuccessful (n = 17)	P-value
Age (years)				
Mean	61.1 ± 10.5	61.4 ± 13.7	62.0 ± 10.0	0.965
Median	62	67	62	
Sex				
Male	30 (65%)	11 (65%)	10 (59%)	0.755
Female	16 (35%)	6 (35%)	7 (41%)	
BMI				
Mean	22.3 ± 2.4*	22.2 ± 2.6	24.0 ± 2.5*	0.037
Median	22.0	23.0	23.8	
Tumor depth				
Mucosal	25 (54%)	7 (41%)	9 (53%)	0.712
Deeper than mucosa	21 (46%)	10 (59%)	8 (47%)	
Nodal status				
pN0	43 (93%)	16 (94%)	17 (100%)	0.430**
pN1	3 (7%)	1 (6%)	0 (0%)	
No. of SLN basins				
1	39 (85%)	na	17 (100%)	0.001***
≥2	7 (15%)	17	0 (0%)	
Tumor size (cm)				
Mean	2.68 ± 1.23	2.92 ± 1.07	2.55 ± 1.02	0.635
Median	2.2	3.0	2.5	
Tumor location				
Upper	7 (15%)	2 (12%)	3 (18%)	0.804
Middle	21 (46%)	9 (53%)	9 (53%)	
Lower	18 (39%)	6 (35%)	5 (29%)	
Tumor pathology				
Favorable	24 (52%)	6 (35%)	11 (65%)	0.230
Unfavorable	22 (48%)	11 (65%)	6 (35%)	
Lymphatic invasion				
Yes	8 (17%)	4 (24%)	2 (12%)	0.669
No	38 (83%)	13 (76%)	15 (88%)	
Vascular invasion				
Yes	4 (9%)	0 (0%)	2 (12%)	0.491**
No	42 (91%)	17 (100%)	15 (88%)	

BMI, body mass index; SLN, sentinel lymph node; na, not applicable. Definition of the subgroups is described in the text.

* P = 0.037 (Tukey-Kramer).

** Comparison of successful versus partially successful and unsuccessful groups.

*** Comparison between successful plus partially successful versus unsuccessful groups.

TABLE 4. Predictive factors of unsuccessful lymphoscintigraphy

	Successful group versus unsuccessful group			Successful plus partially successful groups versus unsuccessful group		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (every 1 year)	0.99	0.93-1.05	0.689	0.98	0.93-1.04	0.555
Sex (male/female)	0.58	0.16-2.15	0.415	0.47	0.13-1.68	0.243
BMI (every 1 kg/m ²)	1.43	1.05-1.93	0.022	1.43	1.06-1.92	0.019
Tumor size (every 1 cm)	1.08	0.60-1.96	0.793	0.98	0.57-1.70	0.943
Location (upper/middle, lower)	2.01	0.32-12.6	0.456	2.53	0.42-15.1	0.310
Location (upper, middle/lower)	1.24	0.32-4.79	0.758	1.21	0.32-4.50	0.781
Pathology (favorable/unfavorable)	0.95	0.22-4.00	0.942	1.23	0.30-5.06	0.780

OR, odds ratio; BMI, body mass index. Definition of the subgroups is described in the text.

group was 23.8 compared with 22.0 in the S group. Certainly, in western patients, a BMI of 23.8 would not constitute an overweight patient (BMI > 25). However, if surgical groups are in a learning phase of SLN biopsy, our results may be useful for them to take a surgical approach with a reference of lymphoscintigraphic results.

In clinical settings, some radioactive nodes visualized in lymphoscintigraphy may be missed with intraoperative gamma probe. We did not encounter such a case, probably because surgeons knew about lymphoscintigraphic results at the time of surgery in all cases.

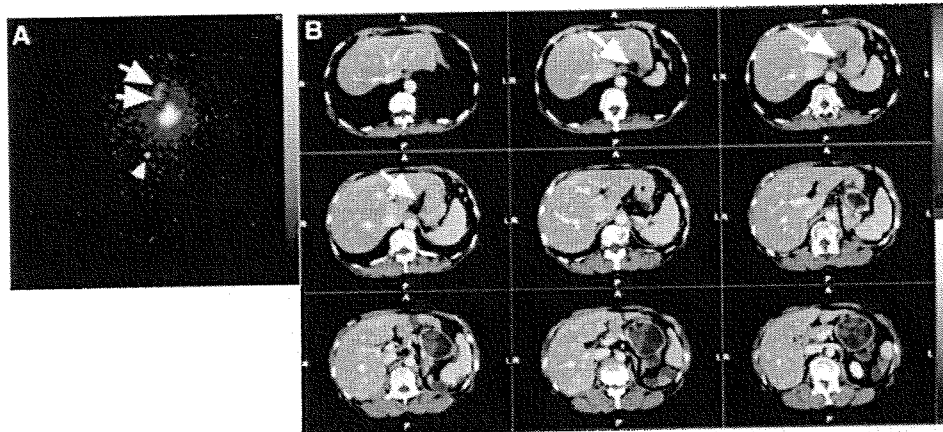


FIG. 1. Lymphoscintigraphy of a 63-year-old female patient with 2-cm submucosal gastric cancer. Body mass index of this patient was 21.5. (A) Anteroposterior pre-reconstructed image shows SLN-like radioactive areas (arrows) in upper aspect of injection site. External marker is visible in lower aspect of injection site (arrowhead). (B) SPECT images show SLN-like radioactive areas (arrows) located along the left gastric artery (LGA). Surgery revealed SLNs without metastasis only in LGA basin. (CT images in gray-scale and SPECT images in color).

Notably, all of the patients in the U group had only one lymphatic basin (Table 3). A single lymphatic basin is likely to be located near the injection site. This could explain why radioactive nodes in the basin were undetectable during lymphoscintigraphy, particularly in obese patients. If lymphoscintigraphy is negative, then a single lymphatic basin is probably found near the injection site during the surgical procedure.

We separated patients with SLNs on lymphoscintigraphy into successful (S) and partially successful (PS) groups because whether positive lymphoscintigraphy represents visualization of all SLNs is a valuable preoperative assessment. However, we could not identify predictive factors that could discriminate these two groups. For example, BMI was similar (Table 3), and thus we could not determine a cut-off value of BMI for selecting patients in which lymphoscintigraphy is likely to be successful. When lymphoscintigraphy is positive, no preoperative factors could predict whether all lymphatic basins are visualized.

Interestingly, lymphoscintigraphy achieved good detection rates of SLNs in the LGA and RGEA basins (well-detected basins) relative to those in the other basins (poorly-detected basins) (Table 2). It seems difficult to explain why there were such differences of detection rates according to the location of basins, although relatively rich supply of lymphatics might be present in the well-detected basins on the basis of the following additional results in our study: there were 16 patients in which SLNs were identified in both well-detected and poorly-detected

basins. In 12 of the 16 patients (75%), accumulation of TcTC in the SLNs was higher in the former than in the latter basins. Moreover, the fact that SLN metastases were mainly found in the well-detected basins (4 of the 5 basins) may support our speculation.

The potential weakness of this study is that we could not compare radioactive counts in the lymph nodes with lymphoscintigraphic results. Due to hospital scheduling conflicts, the timing of lymphoscintigraphy could not be fixed. Regarding intraoperative calculation of radioactive counts in the SLNs, the time of calculation was not clearly documented, so the amount of radioactivity in the SLNs could not be corrected for decay at the time of lymphoscintigraphy for intersubject comparisons.

In conclusion, BMI significantly affects the SLN detection during lymphoscintigraphy even with SPECT and, thus, accounts for the low detection rate (67%) of radioactive lymphatic basins. Negative lymphoscintigraphy indicates that a single lymphatic basin is probably located near the injection site. When lymphoscintigraphy is positive, no preoperative factors can predict whether or not all lymphatic basins are visualized.

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Sentinel Node Navigation Surgery の進歩

7. トレーサーについて

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キーワード 色素, ラジオアイソトープ, 粒子径, 副作用

I. 内容要旨

センチネルリンパ節の同定は、色素法とラジオアイソトープ (RI) 法が主流である。双方とも様々なトレーサーがあり、病変の種類・局在などによってトレーサーを変えて用いることも可能であるが、その際には各トレーサーの特徴を理解しておく必要がある。色素については、以前はイソサルファンブルーやサルファンブルーなどが主に用いられていたが、副作用を考慮して現在はインドシアニングリーン (ICG) やインジゴカルミンの使用が増えつつある。乳癌や悪性黒色腫、胃癌などでは、色素を腫瘍周囲に投与して5-20分後に染色されたセンチネルリンパ節 (blue node) を同定可能だが、blue node の同定に長時間費やすと非センチネルリンパ節まで blue node と判定されてしまう可能性がある。

RI 法については、本邦ではテクネチウム-99m 標識スズコロイドあるいは同標識フチン酸を用いている施設が大半である。術中にはガンマプローブを用いて放射活性の有するリンパ節を検索するが、手術前日に投与を行っておくと shine-through 現象による影響が軽減される。また、RI 法では術前にガンマカメラを用いてリンパ節シンチグラフィを撮像することが可能であり、シンチグラフィは術中センチネルリンパ節検索におけるガイド的な役割がある。色素法と RI 法を併用することにより高いセンチネルリンパ節同定率が得られる。

II. はじめに

人間のリンパ流は主に①毛細リンパ管より上流に存在する弁構造、②周囲に存在する筋や他組織の運動によるリンパ管収縮、および③リンパ管壁内に存在する平滑筋運動によって生じているとされている。結合組織の間質液から毛細リンパ管内に流入するにあたり内皮細胞接合部の開大が重要な役割を果たしているが、エンドサイトーシスやピノサイトーシスを介したメカニズムも存在する。内皮細胞接合部は弁構造となっており、結合組織の間質圧が高まることによってはじめてリンパ液がリンパ管内へと流入する。また、毛細リンパ管においては細胞質フィラメントやHメロミオシン、集合リンパ管レベルでは平滑筋運動によってリズミックなリンパ管収縮を生じ、リンパ液が中枢へと移行するとされている¹⁾。

トレーサーを用いたセンチネルリンパ節の同定は、このようなリンパ流の生理学的特長を利用している。直径が1-2nmの粒子は、リンパ管へと移行せず直接静脈系へと流れてしまう。また、5-25nmの粒子は内皮細胞接合部の開大を介してリンパ管へと効率よく移行する。25-75nmの粒子はエンドサイトーシスやピノサイトーシスの影響が大きい。それ以上の粒子は生理的な状態においては結合組織の格子を通過することは困難であるため、腫瘍周囲に投与した場合には周囲に大量のトレーサーが残存することになる。大きな粒子を用いた場合、比較的大量 (例 0.5cc) に投与することによって組織間質圧上昇に伴う内皮細胞接合部の開大を促すことでリンパ管内へと移行する。このような

TRACERS USED FOR THE DETECTION OF SENTINEL LYMPH NODES

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7. トレーサーについて

表1 主に使用される色素の種類

色素	分子量	使用濃度	使用用途
イソサルファンブルー	566.7	1%	リンパ管染色
サルファンブルー	566.7	1%	リンパ管染色
メチレンブルー	319.9	0.08%	神経染色
インドシアニングリーン	775	0.5%	肝・循環機能検査薬
インジゴカルミン	466.4	0.4%	腎機能検査薬

非生理的な条件下では腫瘍からのリンパ流以外のリンパ流へとトレーサーが移行してしまうおそれがあるが、実際の臨床経験では少なくとも腫瘍からのリンパ流は障害されていないようである。

小粒子を用いるとセンチネルリンパ節のみならず非センチネルリンパ節へとトレーサーが移行してしまう傾向にある。リンパ流を動的に捉えたい場合や、投与部位直近のリンパ節への集積を視覚的に同定したい場合はこの小粒子が有効である。一方、センチネルリンパ節へのRI集積を安定させ、ガンマプローブにて確実に同定することを目的とした場合は比較的大きな粒子が有利である。その場合の粒子径は200-1,000nmが臨床的に使いやすい²⁾。

III. 色素法の安全性

表1に示すように、センチネルリンパ節を同定するために用いる色素にはさまざまなものがあるが、本邦ではこれまでにイソサルファンブルー（商品名：リンファゾリン, Auto Suture Company, CT, USA）や、その異性体であるサルファンブルー（商品名：パテントブルー, Wako Pure Chemical Industry, 大阪）を中心に用いられていた。これらの色素は生体内でアルブミンと結合する傾向を有し、リンパ管やリンパ節が染色される。副作用として青緑色尿（投与12-24時間後）、投与部位の入墨様染色（1-2週間程度）があり、まれにアナフィラキシーショックもあるとされている。

600例を超えるリンファゾリン投与例での報告では、1.1%に蘇生術を要するアナフィラキシーショックがあった³⁾。2,000例を超える大規模な検討では1.6%にリンファゾリンに対するアレルギー反応が見られ、色素投与から症状が顕在化するまで平均44分であった⁴⁾。サルファ剤に対するアレルギーの既往はリンファゾリンに対すアレルギー出現とは関連がないと言われている。

また、術中・術後のモニタリングにおいてパルスオキシメーター計測値が数%低下することが知られている⁵⁾。メチレンブルーはこのような副作用の頻度は低いが、真皮への投与を行うと投与部位の潰瘍や重篤な脂肪壊死などが見られることがあり臨床現場での使用は難しい。

一方、最近ではこれらの副作用を留意してインドシアニングリーン（ICG）やインジゴカルミンを用いた色素法が注目されている。リンファゾリンは高価であり、かつ、保険収載が見込まれないこともあり今後の使用頻度は極端に少なくなると予想される。2008年の乳癌学会にて報告された臨床的腋窩リンパ節転移陰性の原発性乳癌に対するセンチネルリンパ節生検の安全性に関する多施設共同臨床確認試験の中間報告では、副作用の調査対象1,709例中、色素注入による重篤な副作用は発生しなかった。

IV. 色素注入からセンチネルリンパ節同定までの至適時間

色素がリンパ管を早く流れるため、注入からセンチネルリンパ節同定までの時間は同定率に影響する可能性がある。乳癌や悪性黒色腫、胃癌では、腫瘍周囲に投与して5-20分後に色素で染色されたセンチネルリンパ節（blue node）を同定することが一般的であるが、blue nodeの同定に長時間費やすと非センチネルリンパ節までblue nodeと判定されてしまう可能性がある。乳癌の場合、色素注入後乳房マッサージを行うと同定率が向上する⁶⁾。脂肪増生が著明な症例や高齢者ではリンパ流が不良なため、色素投与に生理食塩水投与を追加して組織間質圧上昇に伴う内皮細胞接合部の開大を促すこともある。また、色素法とRI法を併用している施設においては、色素法はリンパ流（basin）を見ることを主目的とし、basin内のセンチネルリンパ節同定にはガンマプローブを用いる傾向にある。

V. ラジオアイソトープ (RI) の種類・粒子径

センチネルリンパ節生検に用いる RI には様々な種類が存在するが、本邦で用いられているのはそのうちテクネチウム-99m 標識スズコロイド、同標識フチン酸、および同標識ヒト血清アルブミンである。主に前2者が用いられている。ヒト血清アルブミンは粒子径が非常に小さく (2-3nm)、リンパ管に容易に移行するため投与直後からのリンパ流を観察できるメリットがある反面、センチネルリンパ節内の網内系細胞の捕捉を免れて多数の非センチネルリンパ節にも流れる傾向にある。したがって真のセンチネルリンパ節に留まる RI 量は他2者のトレーサーと比較して明らかに少ない⁹⁾。

テクネチウム-99m 標識スズコロイドの粒子径は 400-5,000nm とされているが、テクネチウム-99m 標識過テクネチウム酸ナトリウムと塩化第一スズ溶液との配合率ならびに配合時から投与までの時間により粒子径は大きく変化する。これを利用して 200nm 未満の小粒子化スズコロイドから、各腫瘍に適した粒子径の調整も可能である⁹⁾¹⁰⁾。また、調整後から投与までの時間を一定にすれば患者間でのリンパ流の比較も可能と思われる。一方、テクネチウム-99m 標識フチン酸は生体内のカルシウムイオンとキレートすることによりコロイドを形成するが、カルシウムイオン濃度により粒子径は 200-1,000nm と大きく変化する。したがって、フチン酸に関しては患者間で粒子径が異なり、リンパ流の比較は難しいと思われる。

VI. RI 注入からセンチネルリンパ節同定までの至適時間

前述したように、テクネチウム-99m 標識スズコロイド、同標識フチン酸はともに比較的大きい粒子である。これらを手術前日に投与しても、手術時にセンチネルリンパ節にしっかりと集積残存が確認できる。手術前日投与は、(1)術者や病院スタッフの被曝が軽減される、(2) shine-through 現象が少なくなりセンチネルリンパ節が同定しやすくなる、(3)手術スケジュールや手術プロトコルに全く影響を受けない、という利点がある。しかしながら、患者への被曝は手術当日に比べ 10 倍以上増加する点について理解しておく必要がある。

一方、海外では用いているトレーサーが異なり、米

国では本邦よりも小さい粒子を用いているため手術数時間前に RI を投与する傾向がある。欧州では本邦と同様の粒子径であるテクネチウム-99m 標識 colloidal albumin がよく用いられるため、手術前日投与が多い。

VII. リンパ節シンチグラフィ

RI 法では術前にガンマカメラを用いてリンパ節シンチグラフィを撮像することが可能であり、シンチグラフィは術中センチネルリンパ節検索におけるガイド的な役割がある。各腫瘍のリンパ流に関する研究が進むと、ある程度リンパ流にパターンがあることがわかってきたため、ガンマプローブによる術中検索で十分との意見も多い。しかし、feasibility study を行っている施設ではセンチネルリンパ節の局在をあらかじめ理解して生検に望める点で有用と思われる。また、食道癌ではリンパ流が頸部から腹部にまで広い範囲で存在するため、広い視野を有するリンパ節シンチグラフィは有用である。

将来的には、センチネルリンパ節生検のみならず、放射線治療の照射野決定などにリンパ節シンチグラフィが役立つ可能性がある。

VIII. 色素法と RI 法の併用

Albertini らが最初に色素法と RI 法の併用に関する前向き研究の報告を行った¹¹⁾。その後数々の研究によって併用法の有用性が証明され、現在では併用法が色素法あるいは RI 法単独よりも優れていると認識されている¹²⁾。

IX. おわりに

本邦にて使用される色素ならびに RI の特徴や注意点について、リンパ流の病態生理学的な面を含めて解説した。最近では蛍光法や新しいトレーサーの開発も行われており、センチネルリンパ節生検の精度をより高める今後の研究に期待される。

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TRACERS USED FOR THE DETECTION OF SENTINEL LYMPH NODES

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The dye or isotope technique is generally used for sentinel lymph node mapping. There are many types of tracers available for the two techniques, and it is important to understand their characteristics such as particle size for appropriate use in specific diseases or conditions. There is an increasing tendency to use indocyanine green or indigo carmine dye instead of isosulfan or sulfan blue dye to avoid potentially life-threatening allergic reactions. Sentinel lymph nodes can easily be detected with the dye method 5-20 min after peritumoral tracer injection. When using dye mapping alone, sentinel lymph node detection should be achieved before the dye reaches nonsentinel nodes. Technetium-99m-labeled tin-colloid or phytate is frequently used in the isotope technique. Isotope injection the day before surgery can reduce the effects of the shine-through phenomenon. Lymphoscintigraphy often permits preoperative sentinel lymph node detection as a guide to intraoperative survey. In current practice, the combination of a radioisotope and blue dye for lymphatic mapping is thought to improve the sentinel lymph node identification rate. New techniques such as fluorescence imaging are being investigated.

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Our Protocol

胃癌のセンチネルリンパ節シンチグラフィ

中原 理紀 NAKAHARA Tadaki

Key Words : gastric cancer, sentinel lymph node, lymphoscintigraphy

《はじめに》

センチネルリンパ節とは原発巣から癌細胞がリンパ管を経由して最初に到達するリンパ節を指し、センチネルリンパ節転移陰性の早期癌患者に対しリンパ節廓清を縮小あるいは省略することが可能か(これをセンチネルコンセプトという)についての研究が盛んに行われている。ラジオアイソトープ(RI)を腫瘍周囲に投与することによって、リンパ管を介してRIが最初に到達するリンパ節を同定することが可能である。また、RIの分布を体外から計測するガンマカメラを利用したイメージングが可能であり、イメージング手技そのものあるいは画像のことをリンパ節シンチグラフィ(LSG)と呼ぶ。LSGは術前にセンチネルリンパ節の解剖学的位置を知ることができるため、術中にプローブを用いて検索する際の“ガイド”的な役割がある。

我々の施設では100例以上のcT1N0M0胃癌患者に対しLSGを行っており、ある一定の成果を挙げている¹⁾。本稿では^{99m}Tc標識スズコロイドを用いたLSGの検査方法を中心に説明する。

《LSGの目的》

LSGの目的は、胃癌手術においてセンチネルリンパ節を円滑に摘出するための有用な情報を術者に提供することである。したがって、LSGで描出できたセンチネルリンパ節がどこに存在するかを的確に外科サイドに伝えることが必要である。言い換えれば、偽陽性は術者を混乱させ手術を無駄に長引かせるだけであるから、LSGで明らかに描出できているもののみを報告することが望ま

しい。

《^{99m}Tc標識スズコロイドの標識および投与準備》

スズコロイド^{99m}Tc注調製用キット(日本メジフィジックス社)には塩化第一スズ溶液約2mlと標識用バイアル、放射線遮蔽用鉛容器が含まれている。まず標識用バイアルに^{99m}Tc pertechnetate溶液を6mCi/1.5ccになるように加える。バイアルを転倒攪拌し^{99m}Tc pertechnetateをバイアル全体に広げた後、スズ溶液1.5ccをゆっくり加えて軽く攪拌する。混合溶液を鉛容器に入れ30分間冷蔵保存することにより粒子径が600-800nmとなり、胃癌のセンチネルリンパ節生検に適した^{99m}Tc標識スズコロイド溶液が出来上がる。

出来上がったコロイド溶液を2.5ccのシリンジに2.2cc採取する。食道静脈瘤硬化療法に用いられる穿刺針(住友ベークライト社)には1.2cc弱の容量があるため、穿刺針に三方活栓をつけてコロイド溶液を満たすとシリンジの残量は1.0ccとなる(図1)。側管には1cc以上の生理食塩水を満たしたシリンジをつけておく。我々の施設では^{99m}Tc標識スズコロイド溶液のシリンジと間違えないように側管には3ccの生理食塩水を満たした5ccのシリンジを用いている。このような準備を行う理由については次項を参照されたい。

《^{99m}Tc標識スズコロイドの投与》

^{99m}Tc標識スズコロイドの粒子径が大きく変化しないように、30分間の冷蔵保存後少なくとも20分以内に投与することが望ましい。放射線安全管理区域内に内視鏡装置を用意し(常駐していたほ

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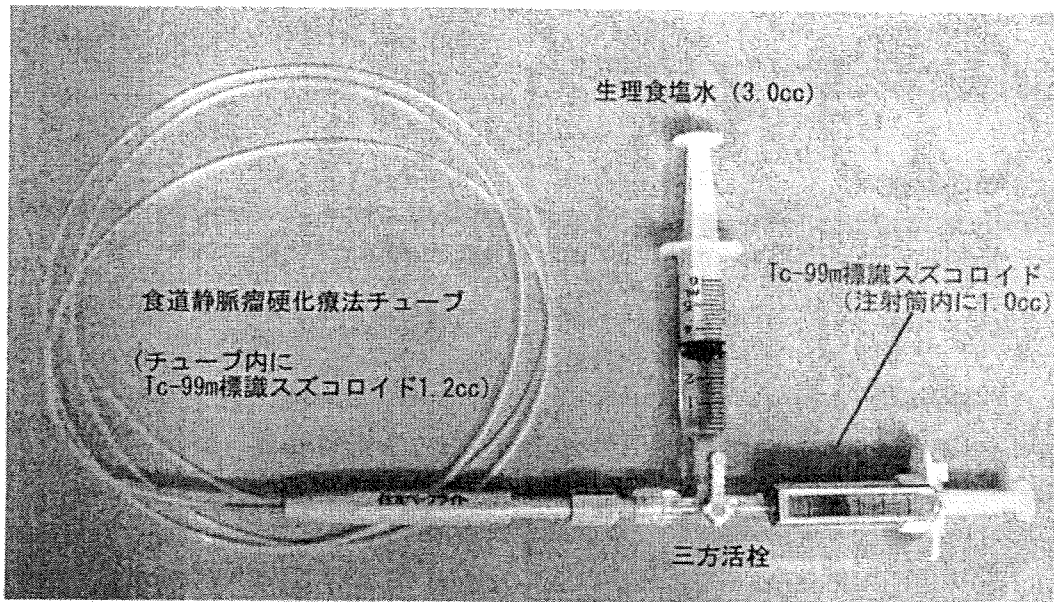


図1
内視鏡下投与に必要な準備(写真協力：酒井香織)
 ^{99m}Tc 標識スズコロイドは2.5cc シリンジに1.0cc, 硬化療法チューブと三方活栓内に1.2cc 封入されている。2.5cc シリンジにはタングステンシールドが装着されている。

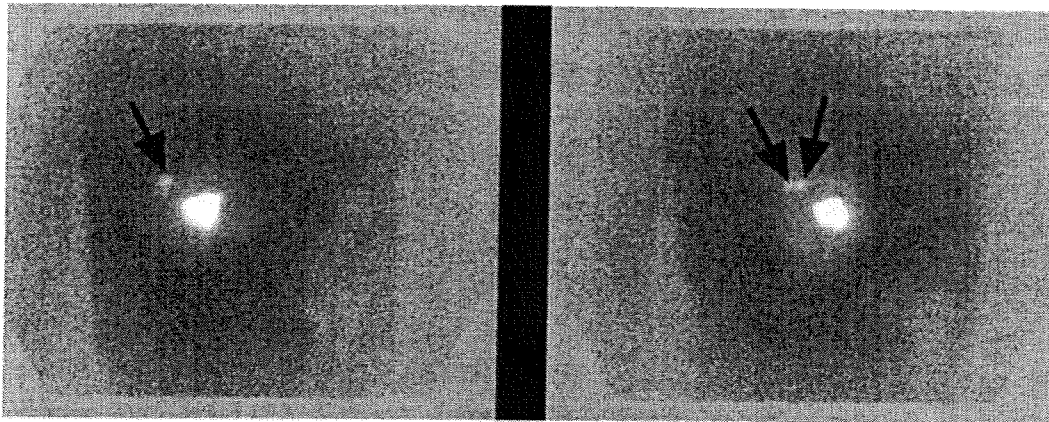


図2
多方向 static 画像によるセンチネルリンパ節の検出
static 画像は体輪郭を描出する処理を行っている²⁾。正面像(写真右)では放射活性を有するリンパ節が1つ描出されているが、右前斜位像(写真左)では2つ描出されている(矢印)。センチネルリンパ節が前後に重なっているためである。

うが楽), 内視鏡下にて胃癌病巣周囲に投与する。我々の施設では内視鏡手技は外科の協力を仰いでいるが, 投与部位や投与の深さを一定にさせるため毎回同じ外科医に行ってもらっている。内視鏡挿入の前処置としてオピスタン1A 静注を行っている。腫瘍周囲粘膜下に0.5cc×4箇所(合計2cc) 投与することで, 腫瘍周囲全体に検査薬剤が行きわたることがわかっている。はじめの1cc は ^{99m}Tc 標識スズコロイド溶液のシリンジから投与し, 残りの1cc は側管の生理食塩水を後押しすることで, 利用した穿刺針内に残存するアイソトープ量を0.2cc に減らすことができる(図1)。投与が終わると穿刺針を抜去するが, 内視鏡から先端が取り除かれる際にアイソトープが飛び散ることがあるので, しっかりとティッシュなどで押さえてから抜去する。アイソトープで汚染された物品は減衰しバックグラウンドと区別ができなくなるまで保管する。

《LSG》

胃の蠕動を抑制するために4時間以上の絶食を行った後にLSGを施行する。センチネルリンパ節の局在を正確に求めるためにはSPECTが必須となるが, 腹部 static 画像でも多方向撮像すればある程度の予測は可能であり(図2), 施設によって適したプロトコールを採用すればよいと思われる。Static 像では10分間の収集を行えば十分な quality の画像が得られる。画像収集時に体輪郭を描出する方法を用いるとわかりやすい²⁾。SPECT を行う場合には最終的にCT画像と重ね合わせるので, CT画像をあらかじめ参照しておく, 体の傾き(左右, 前後)をチェックしておく。SPECT 撮像の際には体の傾きをできるだけ合わせた上で, 患者の臍部に ^{99m}Tc 溶液(5 $\mu\text{Ci}/0.05\text{ml}$) の入った点状マーカーを置く。SPECT 収集時間の設定は各施設の方針に委ねるが, 我々の施設では30分間収集している。

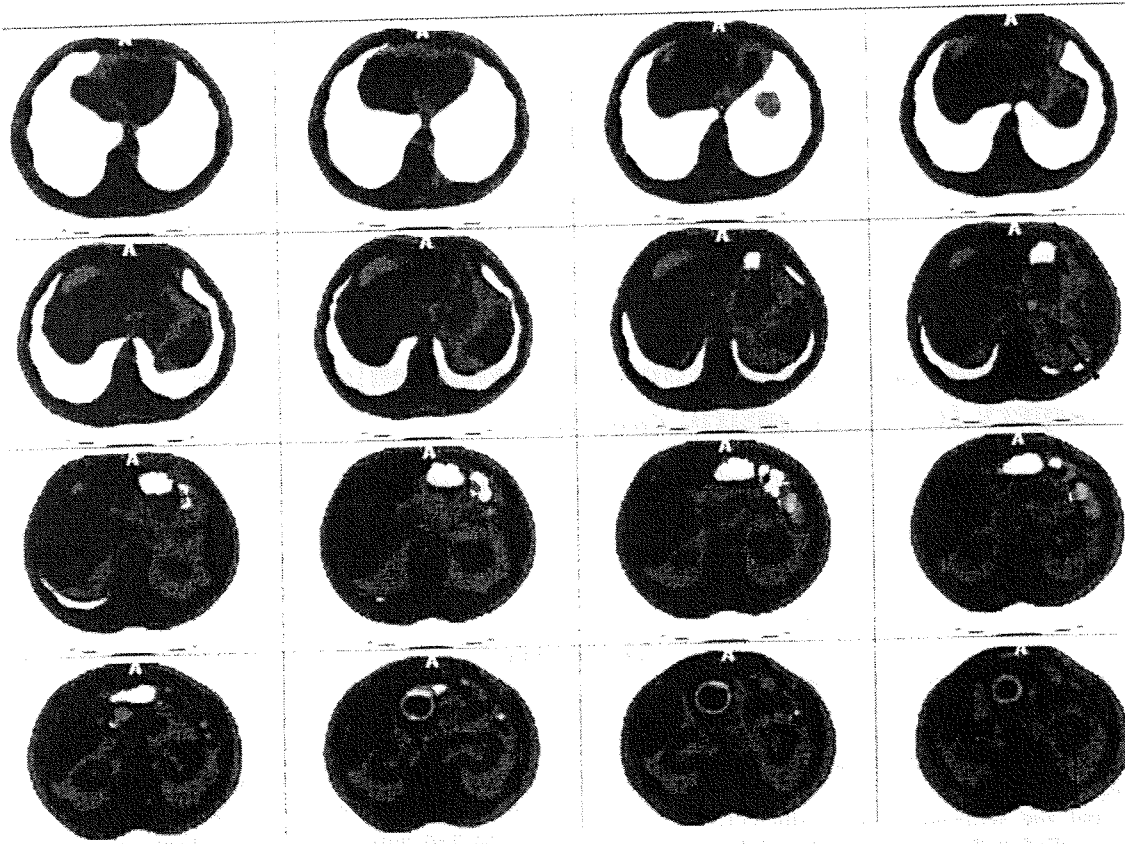


図3
SPECT画像と
CT画像の重ね
合わせ画像
59歳男性、早期
胃癌(0-IIc, 深
達度M, 胃角
後壁やや大弯寄
り)症例。白黒
反転されたCT
画像とSPECT
の重ね合わせ画
像では、左胃動
脈領域に放射活
性の有するリン
パ節が描出され
ている(矢印)。

胃癌手術症例では基本的に原発巣近傍に金属クリップによるマーキングが施されているので、CT画像とSPECT画像ではマーカーと投与部位の双方が描出されている。SPECTとCTの融合画像はどのような重ね合わせソフトウェアを用いてもよいが、我々はfusion viewer(日本メジフィジックス社)を用いている。注意点として、SPECTとCTでは呼吸状態が異なるので(SPECT-CTであれば話は別)、マーカーはあくまで正中線を同定するのに用いて、原発巣を合わせることを重要視する(図3)。

《おわりに》

早期胃癌においてセンチネルコンセプトが成立することを裏付ける、本邦での多施設共同研究結果が近いうちに報告される予定である。それだけでも核医学が十分貢献していることは間違いない。今後LSGなどを用いてより臨床に役立つ情報を提供したいと考えている。

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Original article

Validity of modified gastrectomy combined with sentinel node navigation surgery for early gastric cancer

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Abstract

Background. The present study examined the clinical validity of modified gastrectomy for early gastric cancer, in terms of the results of sentinel node navigation surgery (SNNS), using infrared ray electronic endoscopy (IREE) plus indocyanine green (ICG) staining.

Methods. One-hundred and sixty-one patients with $T1N0$ gastric cancer were enrolled in the study. ICG (0.5 ml, 5 mg/ml) was injected endoscopically into four quadrants of the submucosa surrounding the cancer. Twenty minutes after the injection, sentinel lymph nodes (SNs) stained with ICG were observed intraperitoneally around the serosa and surrounding fat tissue. IREE was used to illuminate regional lymph nodes from the serosal side.

Results. Group 2 lymph nodes were judged as SNs in 52 patients (32%). The most common locations of the SNs were stations No. 7 in each of the upper-, middle-, and lower-thirds of the stomach. In two patients, lymph node metastasis was positive. One of these patients, with cancer in the middle one-third of the stomach, had SNs in stations No. 3, 4sb, 4d, 7, and No. 11p, and had metastatic lymph nodes in No. 3 and No. 7 (all SNs). The other patient, with cancer in the lower one-third of the stomach, had SNs in No. 1, 3, 4d, and 6, and had a metastatic lymph node in No. 4d (SN). Skip metastasis was not observed in this study, and metastatic lymph nodes were judged to have been dissected by the $D1+\alpha$ procedure.

Conclusion. For $T1N0$ gastric cancer, modified gastrectomy ($D1+\alpha$ dissection) combined with SNNS is suitable; however, for those whose Group 2 lymph nodes are judged to be SNs, additional dissection of lymphatic basins detected by SNNS should be performed to confirm the absence of lymph node metastasis.

Key words Modified gastrectomy · Sentinel node navigation surgery · Group 2 lymph nodes

Introduction

In a study by Bonenkamp et al. [1], patients with gastric cancer treated by extended (D2) lymphadenectomy had a significantly higher rate of complications, a higher postoperative mortality rate and a longer hospital stay than those who had limited (D1) dissection, although 5-year survival rates were similar in the two groups. Unnecessary extended lymphadenectomy should therefore be avoided to reduce the incidence of complications.

Recently, much attention has been paid to the improvement of postoperative function and quality of life after gastrectomy for early gastric cancer without impairing long-term outcome. However, several studies have shown features of skip metastasis in gastric, as well as in other cancers [2–4]. Because minimally invasive surgery has been applied to gastric cancer, the occurrence of skip metastasis is an important issue.

According to the treatment guidelines of the Japanese Gastric Cancer Association (JGCA), endoscopic mucosal resection (EMR) or modified gastrectomy (modified A, D1 + No. 7; modified B, D1 + No. 7, 8a, 9) is indicated for stage IA ($T1N0$) disease [5].

During the past several years, in patients with $cT1N0$ or $cT2N0$ early gastric cancer, we have performed sentinel node navigation surgery (SNNS), using infrared ray electronic endoscopy (IREE) combined with indocyanine green (ICG) injection [6]. With this method, we have encountered patients for whom Group 2 lymph nodes were judged as the sentinel lymph nodes (SNs). For such patients, we should be cautious about the extent of lymph node dissection.

In the present study, we examined the clinical validity of modified gastrectomy for early gastric cancer, in terms of the results of SNNS, using IREE combined with ICG staining.

Offprint requests to: H. Ohdaira

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Patients and methods

The study protocol was approved by the Ethics Committee for Biomedical Research of the Jikei Institutional Review Board, and all patients provided informed consent. Patients admitted to Jikei University Hospital with gastric cancer with no obvious metastasis were enrolled prospectively in the study, and cT1N0 or cT2N0 gastric cancer patients who gave informed consent underwent SNNS. In this study, 161 patients with T1N0 (pT1pN0) disease were evaluated. Patients who had lymph node metastasis diagnosed by preoperative abdominal computed tomography or ultrasonography; and those with T2 subserosal or T3 lesions (according to the tumor node metastasis [TNM] classification system), confirmed by endoscopic ultrasonography, were excluded. SNNS was performed according to the methods of Nimura et al. [6]. Briefly, 0.5 ml ICG (5 mg/ml; Diagnogreen; Daiichi Pharmaceutical, Tokyo, Japan)

was injected endoscopically in four quadrants of the submucosa surrounding the gastric cancer, using an endoscopic puncture needle during open or laparoscopic surgery. Twenty minutes after the injection, SNs stained with ICG were observed intraperitoneally around the serosa and surrounding fat tissue. IREE (Olympus Optical, Tokyo, Japan) was used to illuminate regional lymph nodes from the serosal side. Positive staining was confirmed by at least four surgeons and an endoscopist during surgery (Fig. 1). If possible, suspected SNs were examined by frozen section, with hematoxylin-and-eosin staining, to determine the pathological diagnosis. Lymph node dissection and gastrectomy were performed according to the criteria of the gastric cancer treatment guidelines of the JGCA, followed by a definitive pathological examination that included hematoxylin-and-eosin staining, and immunohistochemical staining with anticytokeratin antibody (CAM 5.2; Becton Dickinson, San Jose, CA, USA).

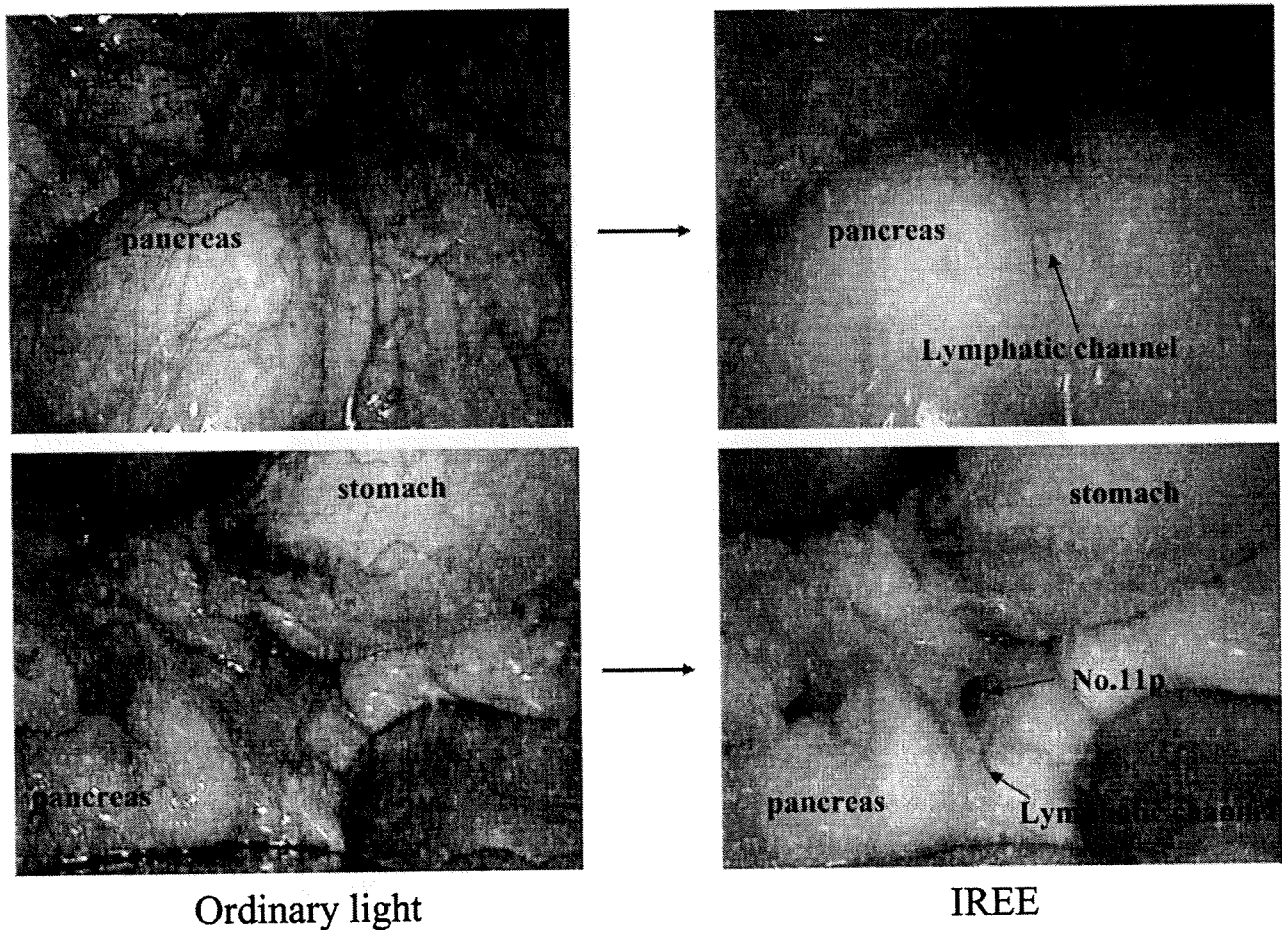


Fig. 1. Lymphatics stemming from the carcinoma. Lymphatic channels from the tumor follow a path crossing the anterior surface of the pancreas, revealing green-stained sentinel nodes (station No. 11p). *IREE*, infrared ray electronic endoscopy