

## Preliminary Study for Sentinel Lymph Node Identification with Tc-99m Tin Colloid in Patients with Esophageal or Gastric Cancer

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The purpose of this study is to determine whether a lymph node identified with high radioisotope (RI) activity is a sentinel node. We studied 26 patients with either esophageal or gastric cancer whose preoperative imaging studies showed no lymph node metastasis. Before surgery, Tc-99m tin colloid was injected via endoscopy into the submucosa. In lymph nodes dissected at surgery, RI activity was measured by a scintillation counter, and metastatic status was examined by hematoxylin-eosin staining. The number of dissected nodes was  $45 \pm 15$  (mean  $\pm$  SD) per patient, and the number of nodes with high RI activity was  $4 \pm 1$ . Nodal metastasis occurred in 11 of 26 patients. In 9 of these 11 patients, metastatic foci were found in one or more nodes with high RI activity. In one of the 2 remaining patients, endoscopic clipping was applied just above the injection sites, and in the other patient, the tumor invasion was beyond the muscle layer. For further analysis, the case with clipping was excluded, and only those in which the tumor invasion was confined within the muscle layer were evaluated. Six of 18 patients in this analysis showed nodal metastasis. Each of the 6 patients had at least one node that showed high RI activity and that was positive for metastasis. We conclude that when tumor invasion remains within the muscle layer, lymph nodes with high RI activity can be regarded as sentinel nodes.

**Key words :** Sentinel lymph node, Lymph node metastasis, Isotope, Esophageal cancer, Gastric cancer

### INTRODUCTION

In patients with malignant melanoma [9] and breast cancer [10, 13], sentinel lymph node (SLN) biopsy provides information for determining the need for lymph node dissection. SLNs can be identified with radioisotope (RI) [4]. Prior to the surgery, RI is injected into the area surrounding the tumor, and during the surgery, a hand-held gamma probe is used to detect lymph nodes with high RI activity. Lymph nodes with high RI activity are identified as SLNs. In malignant melanoma and breast cancer, lymphatic drainage from the primary tumor can be traced with RI.

In Japan, extended lymph node dissection has been the standard treatment for gas-

trointestinal cancers. Many surgeons, however, believed that extended lymph node dissections are unnecessary in patients without lymph node metastases. To date, no indicators have been established to determine the status of regional lymph nodes. The technique used for melanoma and breast cancer may be applicable to gastrointestinal cancers. This preliminary study examined in patients with esophageal or gastric cancers whether or not lymph nodes with high RI activity can be identified as SLNs following RI injection into the area surrounding the tumor.

### SUBJECTS AND METHODS

The study was approved by the Tokai University Ethics Committee. Between April and October, 2000, 26 patients with either

**Table 1** Patient Characteristics

Patient No.	Age/Sex	Location	Depth of Tumor Invasion	No. of Dissected Nodes	No. of Metastatic Nodes	No. of Nodes with High RI Activity
1	77/F	Stomach	pT1	42	0	3
2	53/M	Stomach	pT1	32	0	3
3	65/M	Esophagus	pT1b	42	0	2
4	67/M	Esophagus	pT1b	38	2	3
5	67/M	Esophagus	pT1b	35	6	3
6	73/M	Esophagus	pT2	52	2	5
7	51/M	Esophagus	pT1b	74	0	5
8	70/M	Esophagus	pT3	46	4	3
9	77/M	Stomach	pT2	28	0	4
10	76/M	Esophagus	pT1b	42	1	6
11	49/M	Stomach	pT1	62	2	7
12	70/M	Stomach	pT2	39	11	3
13*	55/M	Esophagus	pT1b, pT2	57	0	8
14	54/M	Stomach	pT1	39	0	4
15	47/F	Stomach	pT2	54	0	3
16	73/M	Esophagus	pT1b	87	0	3
17	58/M	Stomach	pT1	32	0	4
18	53/M	Stomach	pT1	38	0	4
19	48/M	Stomach	pT2	50	2	5
20	72/M	Esophagus	pT2	59	3	5
21	58/M	Esophagus	pT3	19	0	2
22	64/M	Stomach	pT2	27	0	5
23	58/F	Esophagus	pT2	30	4	4
24	72/M	Esophagus	pT3	46	3	7
25	62/F	Stomach	pT1	51	0	5
26	56/M	Stomach	pT1	41	0	4

\*: Isotope injection was done at two lesions.

esophageal cancer or gastric cancer gave their informed consent and participated in this study. The patients had no apparent signs of lymph node metastases on preoperative imaging studies. Patients underwent standard surgeries with extended lymph node dissections. Patient data are listed in Table 1.

On the day before surgery, 0.5 cc (46 MBq) of Tc-99m tin colloids were injected endoscopically into four sites of the submucosa surrounding the tumor. All dissected nodes were placed in test tubes, and RI activ-

ities were measured by a scintillation counter (Auto Well Gamma System, Aloka ARC-300, Tokyo, Japan). Based on the radioactive count rates, each lymph node was categorized as either high RI activity or low RI activity lymph node. In each patient, high and low RI activities were defined, respectively, as count rates that were exceedingly higher than the rates for other lymph nodes, and those that were within one-tenth of the patient's maximum count rate. A few days after the surgery, histopathological reports were obtained, and the status of metastasis

**Table 2** Correlation between RI activity and metastasis

Lymph Node with High RI Activity	Lymph Node with Low RI Activity	Esophagus n=13	Stomach n=13	Total
(+)	(+)	4	3	7
(+)	(-)	2	0	2
(-)	(+)	2	0	2
(-)	(-)	5	10	15

(+): metastatic nodes present, (-): metastatic nodes absent

**Table 3** Correlation between RI activity and metastasis

Lymph Node with High RI Activity	Lymph Node with Low RI Activity	Esophagus n=8	Stomach n=10	Total
(+)	(+)	3	1	4
(+)	(-)	2	0	2
(-)	(+)	0	0	0
(-)	(-)	3	9	12

(+): metastatic nodes present, (-): metastatic nodes absent

was determined for each lymph node. The RI activity and the result of histopathology for metastatic status were compared for each lymph node. Histopathological examination was performed by routine hematoxylin and eosin (H & E) preparations.

### RESULTS

The number of lymph nodes dissected at surgery ranged from 19 to 87 (mean  $\pm$  SD;  $45 \pm 15$ ) per patient. The number of lymph nodes with high RI activity was 2 to 8 ( $4.0 \pm 1.5$ ) in esophageal cancer patients and 3 to 7 ( $4.1 \pm 1.1$ ) in gastric cancer patients. Histopathological examinations revealed lymph node metastases in 11 of 26 patients. In these 11 patients, the number of metastatic lymph nodes was 1 to 11 ( $3.6 \pm 2.7$ ) (Table 1). In 9 of these 11 patients, metastatic foci were recognized in at least one lymph node with high RI activity. This indicated that the lymph nodes with high RI activity provided accurate information as to whether the patient had regional lymph node metastases. In the remaining 2 patients, all lymph nodes with high RI activity were negative for metastases (Table 2). One of the 2 discordant cases was a patient with esophageal cancer in whom, after the isotope injection, three endoscopic clippings were applied just above the injection sites. The other discordant case

was a patient with esophageal cancer whose tumor invasion was beyond the muscle layer. Because the use of the clipping may have disturbed the physiologic lymphatic flow of the isotope, this case was excluded from the further analysis. The subsequent analysis was performed on the 18 cases in which the tumor invasion was confined within the muscle layer. In 6 of these 18 patients, lymph node metastases were observed. In these 6 patients, at least one lymph node with high RI activity was positive for metastasis (Table 3).

### DISCUSSION

SLNs are the first lymph nodes to receive lymphatic drainage from a primary tumor. Tc-99m sulfur colloid has been commonly used as a radiopharmaceutical for the intraoperative detection of SLN [2, 3, 8, 9, 10]. This radiocolloid is approved by the Food and Drug Administration as a lymphoscintigraphic agent in the United States [1]. In Europe, Tc-99m nanocolloidal albumin is used [1, 11], and in Australia, Tc-99m antimony sulfide colloid is used [5, 11]. In Japan, these radiocolloids are unavailable commercially, but Tc-99m tin colloid is available and has been used as a liver scintigraphic agent. This radiocolloid is inexpensive and readily available. Although the par-

ticle size of tin colloid is larger than that of sulfur colloid [12], a few institutions have began to use Tc-99m tin colloid, and favorable results have been obtained in patients with breast cancer [12] or gastrointestinal cancer [6]. Our present results showed that lymphatic flow from the primary site can be traced reliably with Tc-99m tin colloid. In this and a previous studies in gastrointestinal cancer patients [6], lymph nodes with high RI activity were logically defined as SLNs if the invasion was limited to the proper muscle layer. Our speculation is that when tumor invasion reaches the muscle layer, the lymphatic network in the submucosal layer is distorted, and this eventually leads to the disturbance of physiological lymphatic flows. Additional studies with a larger patients groups are warranted to confirm our present findings.

In this study, we used RI methods instead of dye technique for the detection of SLN because it is difficult to differentiate dye-positive nodes from anthracotic nodes in patients with esophageal cancer.

Problems remain regarding the intraoperative application of the SLN biopsy technique to patients with esophageal or gastric cancers. Count rates obtained by scintillation counter must correlate positively with the data obtained by intraoperative gamma probe. Furthermore, because the isotope remains at the injection sites during intraoperative search with a gamma probe, high RI activity at the injection sites can mask the activity of lymph nodes near the injection sites, so-called shine-through effect. Intraoperative probes are used successfully in melanomas and breast cancers. The distance between primary sites and SLNs is usually greater in melanomas and breast cancers than in esophageal and gastric cancers.

Particularly in esophageal cancers, the injected isotope may exude through the esophageal wall to the outside of the adventitia. In a few cases, we found that connective tissues adhering to the adventitia at the injection site showed high RI activity. To prevent isotope exudation, caution should be taken to inject isotopes into the submucosa and not into deeper muscle layers.

A limitation of this study is that the histopathological examinations were done with routine H & E preparations. Conventional histopathological examination

by H & E staining is inadequate to detect all metastases [7]. More intensive methods, such as immunohistochemistry and reverse transcriptase polymerase chain reaction, may be needed. Our criteria for the differentiation between high and low RI activity may not be generally accepted. Further studies including a large number of patients are necessary to establish more critically the cut-off values between high and low RI activity. We conclude that lymph nodes with high Tc-99m tin colloid can be defined as SLNs when tumor invasion is within the muscle layer.

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