Chapter 6

SENTINEL LYMPH NODE MAPPING IN ESOPHAGEAL AND GASTRIC CANCER

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Abstract In recent years, the sentinel lymph node (SLN) concept has been widely investigated in a variety of solid tumors including gastrointestinal (GI) cancer. This chapter reviews the rationale and refined technical aspects for SLN mapping in upper GI cancer for the intraoperative accurate diagnosis of nodal status to perform individualized minimally invasive surgical approaches. We have described the technical details of the procedure as we have performed it in over 350 consecutive patients with esophageal and gastric cancer and introduced pitfalls and issues remaining.

The technical details and clinical applications of SLN mapping differfor patients with esophageal cancer and gastric cancer. Radio-guided method with lymphoscintigraphy using radioisotope-labeled colloid (RI) is essential for SLN mapping for esophageal cancer. Selective lymphadenectomy and SLN-targeted chemoradiotherapy would be feasible and beneficial for the patients with esophageal cancer. For gastric cancer, combined method with dye and RI is recommended for stable and accurate sampling of SLN in the laparoscopic setting. Laparoscopic local resection for superficial gastric cancer with negative SN status would be a reasonable and less-invasive novel procedure based on the SLN concept. We can utilize this procedure not only for an accurate staging but also as a great tool to change the patient care of upper GI cancer by individualized minimally invasive treatments.

INTRODUCTION

The term "orderly progression" can hardly be employed to describe the pattern of spread of upper gastrointestinal (GI) cancer, unlike melanoma and breast cancer. Anatomical skip metastases were found in 50–60% of esophageal cancer and in 20–30% of gastric cancer in a retrospective analysis of the location of solitary metastases.[14,16] Sano et al. reported that the perigastric nodal area close to the primary tumor is the first site of metastasis in only 62% of gastric cancers, based on a retrospective

analysis of cases of solitary metastasis.[18] From these clinical observations, extended radical procedures such as esophagectomy with three-field lymph node dissection and gastrectomy with D2 lymphadenectomy have become recognized as standard procedures in Japan even for clinically node negative cases.[1,15] However, a significant increase of morbidity and mortality after these invasive procedures was reported in randomized trials.[4,6] To eliminate the necessity of uniform application of highly invasive surgery, sentinel lymph node (SLN) mapping may play a role in obtaining individual information to allow modification of the surgical procedure and other multidisciplinal approaches.

Several studies supporting the validity of the SN concept in upper GI cancers have been reported in the past few years.[5,8-10,17] The increasing prominence of endoscopic surgery since the early 1990s has changed surgical thinking in the field of GI surgery. Now the application of SN mapping in the management of GI malignancies is a riveting topic in surgical oncology. Here we review the current status and optimized procedures with some of the remaining issues in SLN mapping of esophageal and gastric cancer.

SENTINEL LYMPH NODE MAPPING FOR GASTRIC CANCER

Current status of SLN mapping for gastric cancer

As in other solid tumors, there are two major procedures to detect SLN in gastric cancer: The radio-guided procedure using radioisotope-labeled colloid and the dye-guided method.

We have performed a validation study for radio-guided SLN mapping for gastric cancer. From 1999 through 2003, 270 consecutive patients with the clinical diagnosis of T1 or T2N0 gastric cancer were prospectively entered under an Institutional Review Committee approved protocol of radio-guided SLN mapping for gastric cancer after informed consent was obtained. An updated result in our institute is summarized in Table 1.

Table 1. Updated data of SLN mapping for gastric cancer
(Keio University Hospital, Tokyo, Japan, Jan. 1999– Dec. 2003)

Indication	cT1or T2 N0
Detection rate	97% (262 / 270)
SLN number	4.1
Sensitivity	92% (34 / 37)
Accuracy	99% (259 / 262)

SLNs in gastric cancer are usually multiple and show multidirectional distributions. The radio-guided method is a reliable and stable technique for detecting multiple SLNs in gastric cancer using a gamma probe. However, there are practical limitations such as the requirement of radiation safety regulations and special equipment in community hospitals to employ the radio-guided method as a routine clinical procedure.

The dye-directed method is also applicable to gastric cancer particularly in open surgery, in which mobilization of the stomach and real-time observation of lymphatic flow are feasible. Although there are several limitations to the dye-directed method such as fast transit and blind sites in dense fat, blue dye is useful for visualizing lymphatic vessels. There are several options in performing actual procedures, such as types of dye, injection routes (submucosal and subserosal), volume of tracer, and observation timing. In general, technical factors affect the results of SLN mapping for gastric cancer by the dye-guided method.

Technical errors using the single mapping agent approach are reduced by adding a different approach for lymphatic mapping. The radio-guided method allows us to confirm the complete harvest of SLNs with multidirectional and widespread distribution by gamma probing while the dye procedure enables us to perform real-time observation of the visualized lymphatic vessels. Therefore, at this moment, we recommend a combination of dye- and radio-guided methods for systematic SLN mapping of gastric cancer. Almost acceptable results for SLN mapping for gastric cancer have been reported from several institutes as single institutional studies using various methodologies as shown in Table 2.[13]

Table 2. SLN mapping for gastric cancer

Investigators	Published	Tracer[a]	Number of cases	Detection rate (%)	Sensitivity (%)
Kitagawa et al.	2000	RI	36	97	100 (5/5)
Hiratsuka et al.	2001	Dye (ICG)	74	99	90 (9/10)
Kitagawa et al.	2002	RI	121	96	92 (22/24)
Ichikura et al.	2002	Dye (ICG)	62	100	85 (11/13)
Miwa et al.	2003	Dye (PB)	211	96	89 (31/35)

[a]RI,colloid labeled with radioisotope;
PB, patent blue;
ICG; indocyanine green

A multicenter prospective validation study for SLN mapping for gastric cancer has been started in Japan in 2004.

Indication of SLN mapping for gastric cancer

Clinical T1 or T2N0 gastric cancer is a suitable target of this procedure. Because the main purpose of introducing this technology into gastric cancer surgery is to extend the indication of minimally invasive surgery for pathologically node negative cases, there is no advantage to include advanced cases for which modified less-invasive surgical approaches are not applicable. The size of the primary lesion is also an important factor to consider regarding this technique. It is difficult to cover a whole lymphatic drainage route from a larger tumor. We enroll patients with single primary lesions having diameters not exceeding 4 cm.

Choice of radioactive tracer

There are several types of radioactive tracers for SN mapping. Technetium-99m tin colloid and technetium-99m phytate are commonly used in Japan. In initial pilot studies, we have chosen technetium –99m tin colloid, which has a relatively large particle size. In our experience, tin colloid migrates into the SLNs within 2 hours and remains there for more than 20 hours through phagocytosis by macrophages. This characteristic of the tracer particle allows us to perform stable detection of SLN regardless of the timing. Technetium-99m phytate has a smaller particle size and there is a risk of migration into the secondary nodes beyond the actual SLN. At this moment, technetium-99m tin colloid is recommended as an optimal tracer for SLN mapping for gastric cancer.[8]

Administration of radioactive tracer

The day before surgery, technetium-99m tin colloid solution in a volume of 2.0 ml (150 MBq) was injected in four quadrants into the submucosal layer of the primary lesion using an endoscopic puncture needle (Figure 1). Technetium-99m Sn colloid solution was labeled by adding 1.5 ml of tin(II) chloride [Sn(II) Cl2] solution (Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan) to 1.5 ml of -99m technetium pertechnetate solution with 111 MBq of radioactivity. Submucosal injection of the tracer is easy to perform by the endoscopic approach and accurate injection of an adequate amount of tracer is crucial for the precise SLN mapping for gastric cancer.

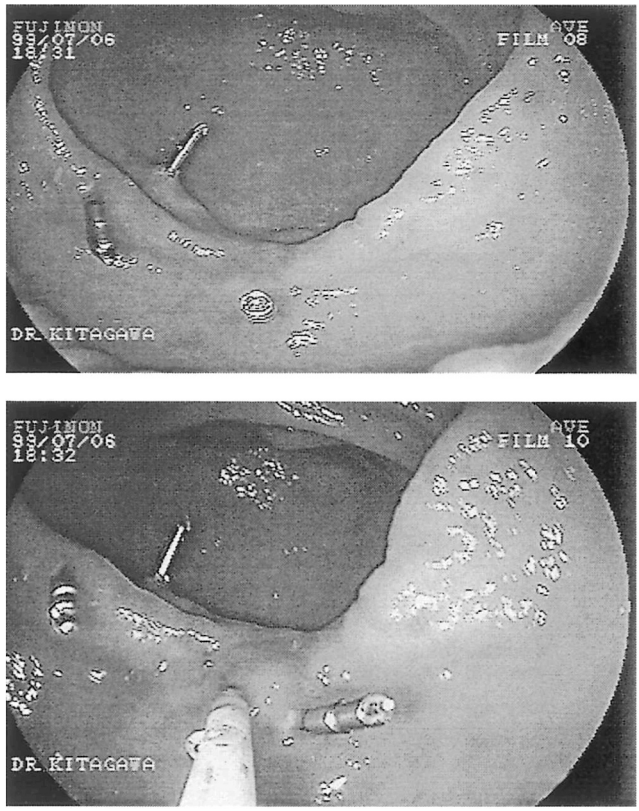


Figure 1. Endoscopic injection of radioactive tracer for gastric cancer. **(A)** Primary lesion of superficial slightly depressed type gastric cancer; **(B)** Endoscopic injection of tracer. Technetium-99m tin colloid solution in a volume of 2.0 ml (150 MBq) was injected in four quadrants into the submucosal layer of the primary lesion using an endoscopic puncture needle.

Intraoperative detection of SLN by a combination of dye and radio-guided methods

Real-time observation of lymphatic vessels and drainage routes from the primary lesion by the dye-guided method is helpful in addition to the radio-guided detection of SLNs using gamma probe. We prefer to perform intraoperative endoscopic injection of blue dye (Lymphazurin; 1% isosulfan blue, Tyco Healthcare) rather than subserosal direct injection for several reasons: (1) Intraoperative subserosal identification of T1 lesions is not so easy. (2) An accurate injection of the blue dye is critically important for SLN mapping. (3) In laparoscopic setting, subserosal injection of the blue dye is not practical. Injection procedure itself is the same as that for the radioactive tracer. Lymphatic vessels are visualized very clearly immediately after the injection (Figure 2).

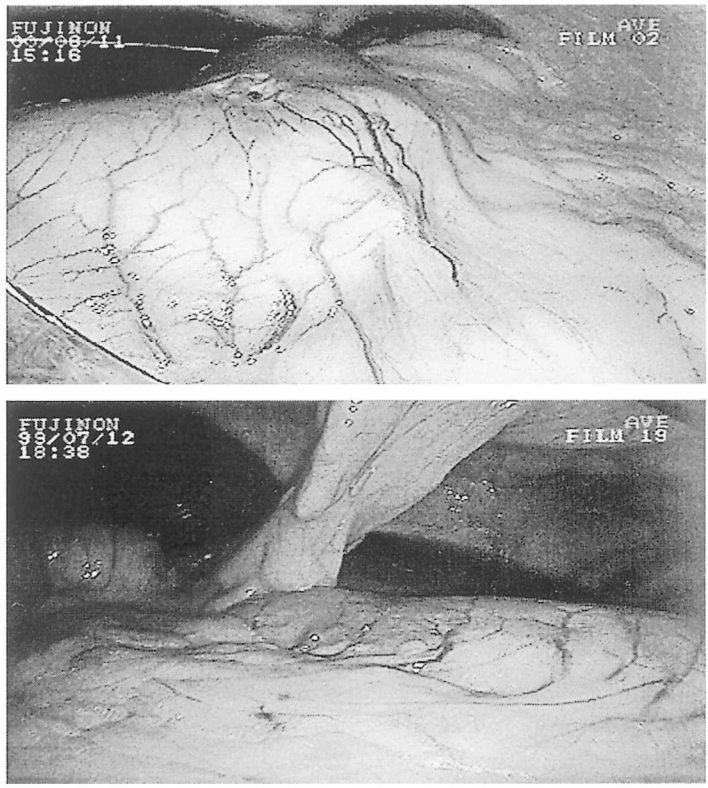


Figure 2. Laparoscopic view of lymphatic vessels from stomach stained by blue dye. Lymphatic vessels are visualized very clearly immediately after the injection of Lymphazurin.

Because of the rapid transit of blue dye, the best observation timing is 5 to 15 minutes after injection. Mobilization of stomach without destruction of lymphatic drainage routes before injection of the blue dye is also critical in detecting multidirectional SLNs properly.
Gamma probe with high collimation is essential for intraoperative final identification of SLNs (Figure 3). It is technically important to avoid shine-through from the primary lesion by handling of the gamma probe for the intraoperative detection of SLN.

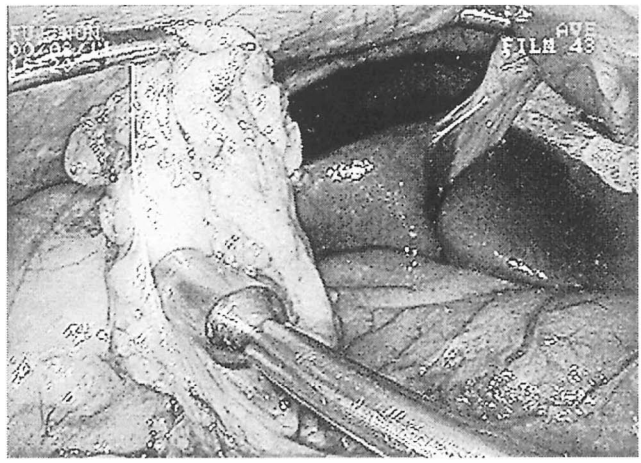


Figure 3. Laparoscopic detection of SLN in gastric cancer using Laparoprobe (Tyco Healthcare)

Intraoperative sampling of SLNs in gastric cancer-picking-up procedure or lymphatic basin dissection

A picking-up procedure of blue and/or hot nodes is feasible as a conventional SLN dissection. Miwa et al.[17] have proposed lymphatic basin dissection as a more reliable sampling procedure of SLNs of gastric cancer. Sentinel lymphatic basins can be identified by dye- and radio-guided methods and these basins should contain true SLNs. An identification of blue and/or hot nodes on the back table after lymphatic basin dissection is easier and more reliable than the picking-up method (Figure 4). Lymphatic basin dissection is considered a sort of selective lymphadenectomy containing SLNs and can be combined with modified resection of the stomach. Miwa et al.[17] recommend this procedure to avoid false-negative results by sampling error.

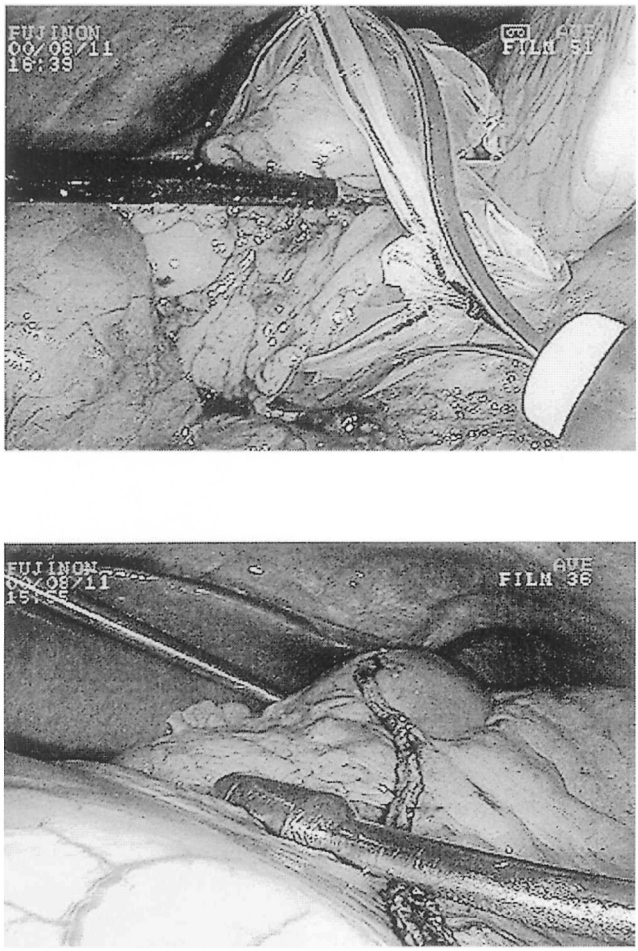


Figure 4. Laparoscopic sentinel basin dissection for gastric cancer. **(A)** Laparoscopic sampling of sentinel basin. Sentinel basin can be detected and retrieved by laparoscopic procedure. **(B)** Confirmation of no residual SLN by gamma probe after sentinel basin dissection.

Clinical impact of SLN mapping for gastric cancer

Gastric cancer is now one of the most suitable targets of an individualized less-invasive surgery based on the SLN concept. Despite the multidirectional and complicated lymphatic flow from gastric mucosa, the anatomical situation of the stomach is relatively suitable for SN mapping in comparison with organs embedded in closed spaces such as the esophagus and rectum. In particular, clinically T1N0 gastric cancer seems to be a good entity for which to try to modify the therapeutic approach. From the data reported in the literature, micrometastases tend to be limited within the sentinel basins in cT1N0 gastric cancer. Sentinel basins are therefore good targets of selective lymphadenectomy for cT1N0 gastric cancer with potential risk of micrometastasis. As indicated in Figure 5, cases with positive SLNs after selective dissection of sentinel basins can be treated by conventional radical surgery. Furthermore, laparoscopic local resection is theoretically feasible for curative treatment of SLN-negative early gastric cancer (Figure 6).[11] In Japan, clinical applications of this novel minimally invasive approach could have a great impact on patient care for gastric cancer because 60–70% of gastric cancer cases treated in major institutes belong to this category.

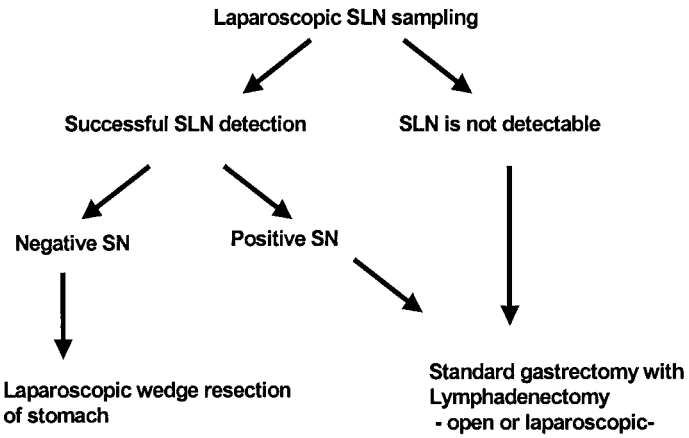


Figure 5. Therapeutic strategies of early gastric cancer with limited size of primary lesion based on SLN mapping.

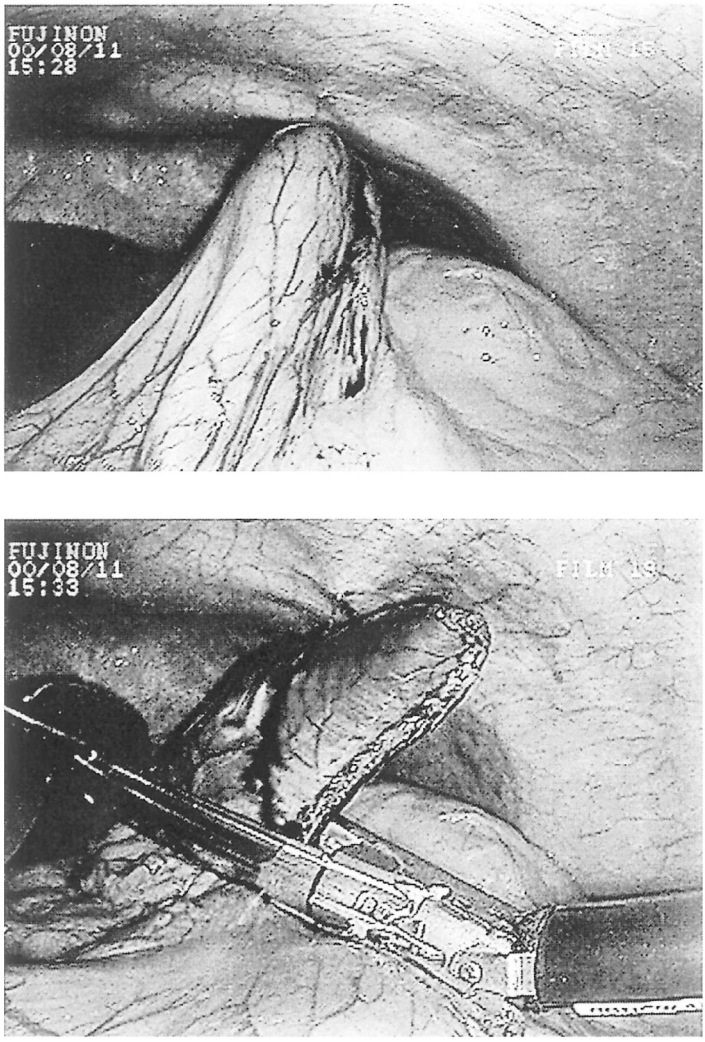


Figure 6. Laparoscopic wedge resection of stomach by lesion lifting method (Ohgami's method). **(A)** The primary lesion is lifted up by metal rod and wire. **(B)** The lesion is resected by endoscopic stapler.

SENTINEL LYMPH NODE MAPPING FOR ESOPHAGEAL CANCER

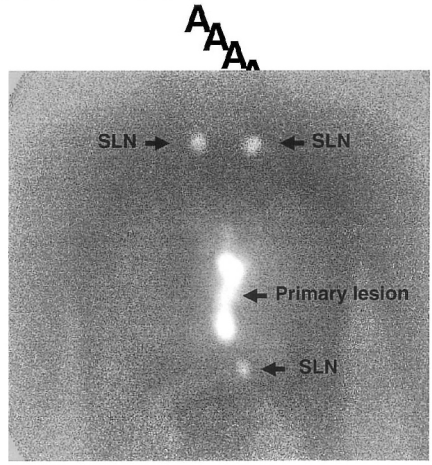
Current status of SLN mapping for esophageal cancer

SLN mapping for esophageal cancer is more complicated than that for gastric cancer. First of all, lymphatic mapping with the dye-guided method is not feasible for esophageal cancer. Regional lymph nodes of the thoracic esophagus are frequently pigmented by anthracosis and it is difficult to identify blue nodes. In organs such as the esophagus and rectum, real-time observation of the lymphatic route using dye is impossible without operative mobilization of the primary site. However, the mobilization itself destroys the active lymphatic flow from the primary lesion. For many of these reasons, the radio-guided method has been used for SLN mapping in esophageal cancer.[10,21] There are few studies demonstrating the feasibility and validity of the SN concept in esophageal cancer.[10,21] In Western countries, the number of earlystage esophageal cancers is very limited and it is difficult to perform clinical studies to investigate the lymphatic mapping in this entity. In esophageal cancer, SNs are multiple and widely spread from cervical to abdominal areas. In more than 80% of the cases, at least one SN is located in the second or third compartment of regional lymph nodes.[10] This characteristic distribution of SNs is attributed to the multidirectional lymphatic drainage routes from the esophagus. It is essential to plan and conduct a multicentric validation study of SLN mapping for esophageal cancer.

Significance of lymphoscintigraphy for SLN mapping for esophageal cancer

Preoperative endoscopic injection of radioactive tracer is basically the same as that described for gastric cancer. However, unlike gastric cancer, preoperative lymphoscintigraphy, taken 3 hours after tracer injection, has been found to be very useful in detecting SLNs in unexpected sites distant from the primary lesion of esophageal cancer (Figure 7). Distribution of SLNs in the esopageal cancer cases is widely spread from cervical to abdominal areas. Preoperative lymphoscintigraphy is essential for the SLN sampling for esophageal cancer.

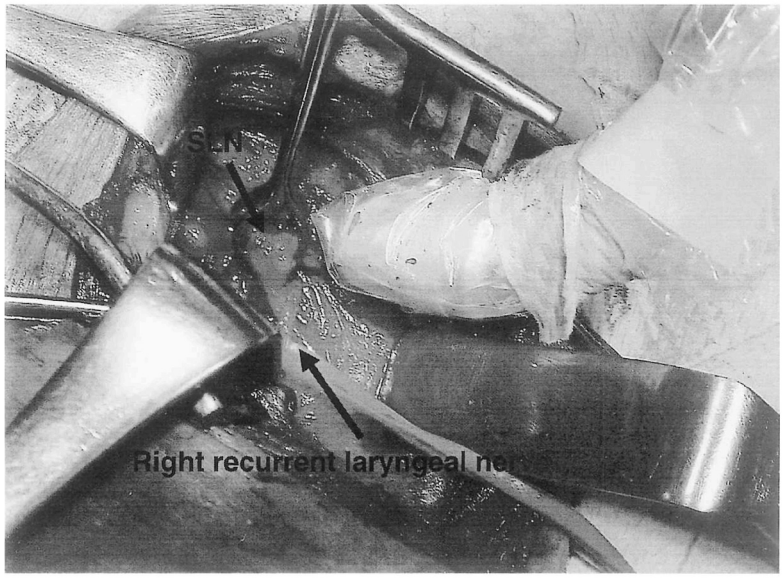
Figure 7. Lymphoscintigraphy for esophageal cancer. Cervical and abdominal SLNs are visualized by lymphoscintigraphy.



Intraoperative SLN sampling for esophageal cancer using gamma probe

SLNs located in the cervical area can be identified by percutaneous gamma probing. These SLNs in the cervical area can be resected by less invasive procedures as shown in Figure 8. Laparoscopic detection and sampling of abdominal SLNs is feasible, as described for gastric cancer. On the other hand, SLN sampling for mediastinal SLNs is relatively complicated and invasive because of the requirement of mobilization of thoracic esophagus. Shine-through from the primary lesion is also an obstacle for gamma probing for mediastinal SLNs.

Figure 8. Sampling of cervical SLN for esophageal cancer.

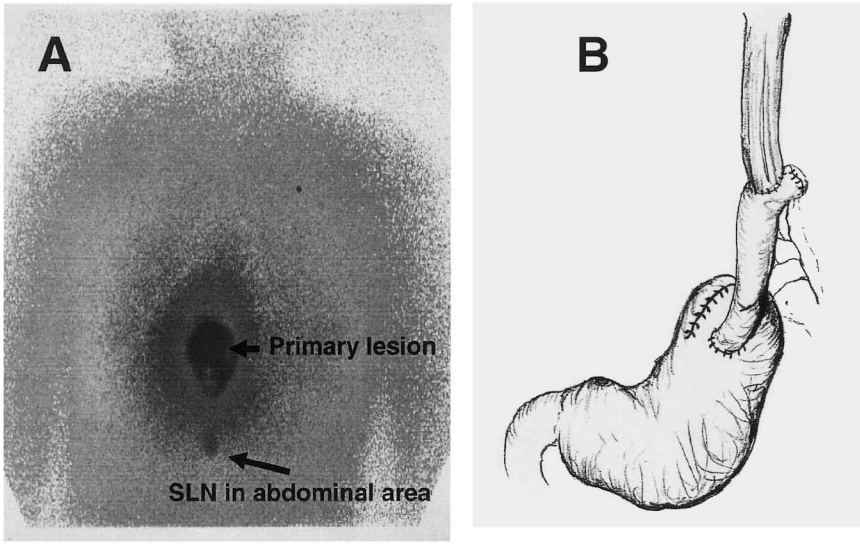


Clinical applications of SLN mapping in esophageal cancer
Selective lymphadenectomy based on SLN status

Transthoracic extended esophagectomy with three-field radical lymph node dissection has been recognized as a standard procedure for thoracic esophageal cancer in Japan because of widely spread and unpredictable metastatic patterns as previously described.[1] Indications of upper-mediastinal lymph node dissection for cervical esophageal cancer and lower-mediastinal lymph node dissection for abdominal esophageal cancer are then controversial. SLN mapping would provide significant information to perform an individualized selective lymphadenectomy based on SLN status.

A complete sampling of multiple and widespread SLNs in esophageal cancer is not a minimally invasive procedure unlike in melanoma and breast cancer. At present, local resection of the primary lesion of esophageal cancer with negative SN is not a practical procedure. However, selective and modified lymphadenectomy targeted on sentinel basins for clinically N0 esophageal cancer should become feasible and clinically useful. In our initial experience, clinically undetectable micrometastases in cT1N0 esophageal cancer tend to be limited within sentinel basins. Although three-field lymph node dissection is recognized as an extensive and curative procedure for thoracic esophageal cancer, its prognostic significance is still controversial. Uniform application of this highly invasive procedure could well increase the morbidity and reduce quality of life after surgery. Individualized selective lymphadenectomy for cN0 esophageal cancer based on SN status therefore seems to be a reasonable surgical approach.[12] The incidence of carcinoma of the esophagogastric junction, including Barrett's carcinoma, is increasing in Western countries, and more recently in Japan, and there are several surgical approaches for this clinical entity.[20] Individualized extent of resection and lymph node dissection for Barrett's carcinoma based on lymphatic mapping will become an important topic in surgical oncology for upper GI tract as shown in Figure 9.[19]

Figure 9. Individualized approach for Barrett's carcinoma based on lymphatic mapping. A case with negative SLN limited in abdominal area (A) can be treated by limited resection and jejunal interposition without extensive mediastinal lymph node resection (B).



Accurate staging to determine the indication of adjuvant chemotherapy

Metastatic status of regional lymph nodes is an important prognostic factor regarding esophageal cancer. Ando et al.[2] reported that postoperative adjuvant chemotherapy with cisplatin and 5-FU has a preventive effect on relapse in patients with esophageal carcinoma when compared to surgery alone, on the basis of randomized trials. A benefit of the adjuvant chemotherapy was observed particularly in the patients with lymph node metastasis in this study. Therefore, accurate and sensitive detection of micrometastasis in lymph nodes in patients with esophageal cancer is clinically very important.

Although a number of reports demonstrate underestimation of micrometastasis in regional lymph nodes by conventional staging procedures employed for solid tumors, the application of intensive examinations such as step sectioning, immunohistochemistry and RT-PCR for all resected lymph nodes is not practical. A focused examination on SNs may help resolve this issue. Bilchik et al.[3] report that ultrasensitive assays by RT-PCR and electrochemiluminescent detection of multiple markers of SLNs from colorectal cancer patients can identify those who may be at high risk for recurrence and, therefore, are more likely to benefit from systemic adjuvant therapy.

Nonsurgical approaches for esophageal cancer targeted on SLN

Recently, chemoradiotherapy (CRT) has attracted attention as a multidisciplinary curative treatment for cT1N0 esophageal cancer. Although an acceptable effect on local control has been reported in this approach, distant node recurrence from the area out of the irradiation field is a serious problem to resolve in long-term observation. In this approach, control of invisible micrometastases is essential. Lymphoscintigrams revealing the distribution of SNs in each individual case are useful in designing the field of irradiation. Currently we are performing curative CRT for cT1N0 esophageal cancer with an individualized irradiation field instead of long T-type uniform irradiation fields.

Variables in Microarray Studies in Lymphoma

A comparison of the different studies of microarray analysis in lymphoma will demonstrate that there are variables in the type of platform used, the number of probe targets present, the control (if any) RNA source utilized, the number of cases studied, and the type of software used to analyze the data. Variables in tissue preservation, percent of tumor cells, and normalization of the data also likely exist, but will not be further detailed here as these data were variably reported. The two major platforms are cDNA microarrays, popularized by Pat Brown, and the oligoprobe microarray developed by Affymetrix. The number of targets in published studies in lymphoma have ranged from 588 to approximately 18,000. The source of control RNA included cell lines, reactive lymph nodes, isolated germinal centers, sorted cells from tonsils, or another subtype of lymphoma. Software analysis methods are characterized into two broad categories of unsupervised and supervised clustering, including ratio ranking, hierarchal clustering, self-organized mapping and others. The number of cases studied per subtype of lymphoma has ranged from 5 to 240.[1, 5, 7-13]

CONCLUSIONS

From recent single-institution reports performed on SLN mapping for gastric and esophageal cancer, the SLN concept seems to be valid even in the upper GI tract. Although further accumulation of the evidence based on multicenter clinical trials using standard protocol is required, SLN mapping would be a great tool to perform individualized surgical and nonsurgical treatment for upper GI cancer.

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