

The Current Status of Sentinel Lymph Node Mapping in Non-Small Cell Lung Cancer

Yoshihiro Minamiya, MD and Jun-ichi Ogawa, MD

Sentinel lymph node (SLN) mapping has become a common procedure in the treatment of breast cancer and malignant melanoma. Its primary benefit is that it enables surgeons to avoid nontherapeutic lymph node dissection and the complications that follow. There are also several studies of the use of SLN mapping in the treatment of non-small cell lung cancer (NSCLC) reported in the English literature, and all present evidence for the existence of SLNs in NSCLC. Nevertheless, SLN mapping is not widely used in the treatment of NSCLC for several reasons: first, special precautions are required to minimize exposure when radioisotopes are used as tracers; second, it is difficult to detect the blue dyes used as tracers within anthracotic thoracic lymph nodes; and third, major complications comparable to the arm edema seen in breast cancer or the lymphedema and nerve injury seen in melanoma are not seen with mediastinal lymph node dissection (MLND). To address these issues, new techniques are being developed by groups at several institutes, including our own. We believe that SLN mapping will enable surgeons to more precisely stage NSCLC, after which more sensitive techniques can be employed on a limited amount of tissue to detect occult micrometastatic disease with less cost and effort. SLN mapping can also be applied to video-assisted thoracic surgery (VATS) for NSCLC, enabling surgeons to avoid nontherapeutic and technically difficult MLND often necessary with traditional open surgery. For all of these reasons, we think that SLN mapping will be useful in the treatment of NSCLC, and that further development aimed at making SLN mapping a practical surgical procedure is warranted. (Ann Thorac Cardiovasc Surg 2005; 11: 67–72)

Key words: sentinel lymph node mapping, non-small cell lung cancer, mediastinal lymph node dissection, radioisotope

Introduction

Mediastinal lymph node dissection (MLND) is an effective therapeutic procedure when carried out in patients with nodal metastatic non-small cell lung cancer (NSCLC); indeed the status of lymph node metastasis is an important prognostic indicator.^{1,2)} On the other hand, MLND is not therapeutic and may even be harmful for

From Division of Thoracic Surgery, Department of Surgery, Akita University School of Medicine, Akita, Japan

Received July 9, 2004; accepted for publication February 1, 2005. Address reprint requests to Yoshihiro Minamiya, MD, PhD: Division of Thoracic Surgery, Department of Surgery, Akita University School of Medicine, Hondo, Akita 010-8543, Japan.

patients without lymph node metastasis. The sentinel lymph node (SLN) concept is that the lymphatic flux from a primary tumor first flows into the SLN before flowing into more distal lymph nodes. If this concept is correct, then when metastasis is not found in a SLN, it most likely will not be present in the more distal nodes. Although the benefit of SLN mapping and biopsy remains controversial, it has gained acceptance in recent years as a way to avoid the complications of lymph node dissection, and has become a common procedure in breast cancer and melanoma.^{3,4)} In those cases, two kinds of tracers, dyes and radioisotopes, have been applied to detect the SLN. The tracers are generally injected around the tumor and then monitored through direct visualization or gamma

Table 1. SLN mapping in NSCLC

Authors	Year	Tracer	Injection	SLN identification	Reference
Little et al.	1999	Isosulufan blue dye	Intraoperative	42%	15
Liptay et al.	2000	Tc-99m sulfur colloid	Intraoperative	82%	7
Nomori et al.	2002	Tc-99m tin colloid	CT-guided preoperative	87%	10
Schmidt et al.	2002	Isosulufan blue + Tc-99 sulfur colloid	Intraoperative	–	17
Sugi et al.	2003	Indocyanine green	Intraoperative	6.3%	16
		Isosulufan blue dye Tc-99 tin colloid	Intraoperative	50.0%	
			CT-guided preoperative	64.3%	
Melfi et al.	2003	Tc-99 albumin nanocolloid	Pre- and intraoperative	96.1%	21
Lardinois et al.	2003	Tc-99	Transbronchoscopic	95%	22
			Preoperative		
Nakagawa et al.	2003	Magnitite	Intraoperative	82%	33

counter measurements of individual lymph node stations to determine the first site of efferent lymphatic drainage from the tumor.

Several studies on the use of SLN mapping in the treatment of NSCLC have been reported in the English literature, and all present evidence of the existence of SLNs in NSCLC. Nevertheless, for several reasons the SLN concept is not yet approved for NSCLC, and SLN mapping is not widely used as a practical procedure in the treatment of NSCLC. The first reason is that special precautions are required to minimize exposure to radioisotopes. Second, it is difficult to detect blue dyes in the anthracotic thoracic lymph nodes. Third, major complications comparable to the arm edema seen in breast cancer or the lymphedema and nerve injury seen in melanoma are not seen with MLND. In this context, we will review the current status of SLN mapping in NSCLC.

Purpose of SLN Mapping in NSCLC

The primary benefit of SLN mapping and biopsy is that it enables surgeons to avoid nontherapeutic lymph node dissection and the complications that follow. Indeed, SLN mapping and biopsy were developed as techniques for staging the lymphatic basin without the potential morbidity of lymphedema and nerve injury in cases of melanoma,³ or lymphedema of the arm in cases of breast cancer.⁴ Lung resection for NSCLC with MLND leads to greater production of postoperative exudate than lung resection without MLND, but the morbidity caused by MLND is not excessive,⁵ and the procedure is therapeutic.¹ Liptay et al. argued that the primary function of SLN mapping and biopsy is to direct pathologic examination to specific SLNs, after which more sensitive techniques could be employed on a limited amount of tissue to detect occult micrometastatic disease.^{6,7} In fact, recent stud-

ies suggest that the presence of nodal micrometastatic disease in lung cancer may lead to the same poor prognosis as metastases evident by conventional techniques.^{8,9} Using SLN mapping, we can make a more precise N-status diagnosis with less cost and effort. Another advantage emphasized by Nomori et al. is that it enables surgeons to avoid nontherapeutic lymph node dissection, especially in segmentectomy for early stage NSCLC.¹⁰ We can also apply SLN mapping and biopsy to video-assisted thoracic surgery (VATS) for NSCLC. Although lymph node dissection with VATS lobectomy is technically feasible, with remnants of only 2-3% of lymph node and other tissues,¹¹ it remains technically difficult to dissect mediastinal lymph nodes completely, especially the level 4 and 7 nodes in left lung cancer. If we could apply SLN mapping and biopsy to VATS lobectomy for NSCLC, we could avoid nontherapeutic and technically difficult MLND.

Tracers and Devices

The technique of SLN mapping basically involves injecting a tracer around a tumor and then detecting it when it reaches the first drainage lymph node downstream of the tumor. In other words, the method simply entails the use of tracers and the respective detection devices. Two major types of tracers, dyes and radioisotopes, are used clinically in SLN mapping, especially for breast cancer and melanoma patients. Unfortunately, neither of these techniques is problem free, and to address these problems other tracers and devices are currently under investigation. Table 1 summarizes the reports on the SLN mapping in NSCLC.

1. Dyes and Eyes

The feasibility of using dyes for intraoperative SLN mapping was first demonstrated in the treatment of melanoma

by Morton et al. in 1992,¹² The dyes were injected around the tumor during surgery, after which the lymph node that stained first was defined as the SLN. Currently, isosulfan blue and patent blue are widely used for SLN mapping in both breast cancer and melanoma, sometimes in combination with a radioisotope. The strong advantages of this technique are that it is comparatively easy and that no special devices are required. On the other hand, anaphylactic reactions to these dyes have occurred, though rarely.^{13,14}

In 1999, Little et al. first reported SLN mapping in NSCLC using isosulfan blue.¹⁵ Unfortunately, because it was difficult to detect the blue dye in the thoracic lymph nodes in the thoracic cavity, the rate of SLN detection (46%) was too low to be clinically useful. Likewise, Sugi et al. reported a lower rate of SLN detection using isosulfan blue than radioisotope.^{16,17} Thus, dyes are not well suited for SLN mapping in NSCLC at present.

2. Radioisotopes and Gamma Probe

In 1993, a radioisotope and gamma (Fig. 1) probe was applied to SLN mapping for the first time in patients with melanoma and breast cancer.^{18,19} The feasibility of this technique with solid tumors was confirmed in 1998,²⁰ and since then use of this technique in the treatment of breast cancer and melanoma has spread worldwide. In 2000, Liptay et al. initially applied a radioisotope to SLN mapping in NSCLC. They intraoperatively injected technetium 99m-sulfur colloid directly into lung tumors and then achieved an 82% rate of SLN detection using a gamma probe.^{6,7} They discovered, however, that they were unable to obtain useful gamma counts from the upper mediastinal lymph node during surgery, due to an interfering signal from the radioisotope that had migrated into the trachea from the lung. They therefore measured gamma counts after MLND. The use of radioisotopes is strictly prohibited in Japan, except in designated areas; consequently, intraoperational use of a radioisotope tracer is virtually impossible. To overcome this problem, Nomori et al. preoperatively injected technetium 99m-tin colloid into peritumoral regions using a CT-guided technique, and then detected SLNs intraoperatively using a gamma probe.¹⁰ Subsequently, other groups also employed the CT-guided preoperative injection technique, achieving 64-87% rates of SLN detection and confirming the technique's feasibility for clinical use.^{16,21} A further advantage of the preoperative injection technique is that it enables intraoperative measurement of gamma counts in the upper mediastinal lymph node, because coughing by the patient rapidly removes radioisotope from the trachea.



Fig. 1. Gamma Probe.

In addition, preoperative transbronchoscopic injection of the radioisotope may be a useful alternative to CT-guided injection.²² All these reports demonstrated the usefulness of the radioisotope method in SLN mapping of NSCLC. However, a disadvantage of the isotope method was also reported. Ueda et al. mentioned that high radioactivity from the injected radioisotope around the tumor, so-called “shine-through”, disturbs the detection of the radioactivity of the intrapulmonary lymph node,²³ therefore, it is difficult to detect SLN, when SLN exist around the intrapulmonary bronchus.

A number of investigators have reported that when using the radioisotope method, there is minimal exposure of surgeons, pathologists or other medical staff to radiation.²⁴⁻²⁶ The radiation risk to patients is also low when compared to that of numerous other medical procedures.²⁵ Even the radiation levels in the waste are quite low.²⁴ Nevertheless, radioactive materials should always be handled with care in order to avoid secondary contamination. For instance, Waddington et al. reported that surgical swabs can become significantly contaminated, containing up to 22% of the administered activity.²⁵ Awareness of and adherence to radiation safety regulations is strongly recommended in order to further reduce radiation exposure and safely apply this technique.²⁷

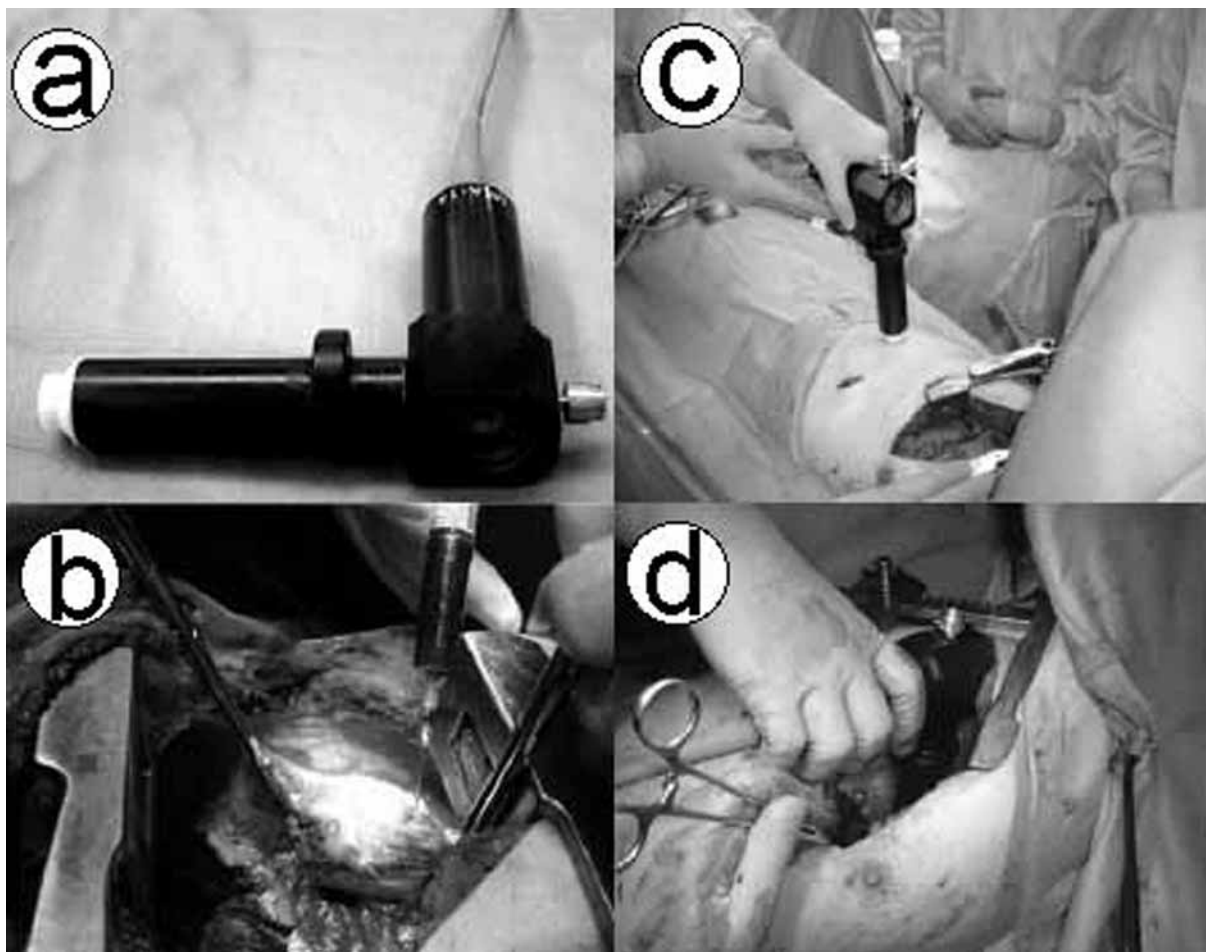


Fig. 2. Detection of magnetite in the SLN, using a new sterilizable magnetometer.

We developed a sterilizable portable magnetometer (a). After injection of 5 ml of ferumoxides around a tumor (b), we intraoperatively measured the magnetic force within lymph nodes (c,d) and identified the SLN.

Colgan et al. recommended that specimens containing the injection site as well as the sample for biopsy should be quarantined for a period of time, which would allow some decay of the radioactivity.^{28,29)} Thus, while radio-guided SLN mapping and biopsy is, on the whole, quite safe, we still need to address problems associated with the complicated management of radioisotopes, especially in Japan.

3. Magnetite and Magnetometer

Magnetite is commonly used as a contrast material when magnetic resonance imaging (MRI) is used to diagnose liver tumors, and several investigators have applied magnetite to detection of SLNs using MRI in animals.³⁰⁻³²⁾ We have focused on the use of magnetite in developing a new technique for detecting SLNs using magnetic force as the indicator. After injection of magnetite (ferumoxides) around a tumor, the magnetic

force within the lymph nodes is detected using a highly sensitive portable magnetometer. With this technique, we have been able to safely detect SLNs in NSCLC without the use of a radioisotope or dye.³³⁾ Thus far, we have only detected the magnetic force of ferumoxides in SLNs after MLND, but our rate of SLN detection is 81.6%, making this approach feasible for clinical use. However, our magnetometer was not suitable for in vivo SLN mapping because of the inadequate sterility and sensitivity of the device. Recently, we developed a new sterilizable magnetometer, and tried to use in vivo measurement in some cases (Fig. 2). The new magnetometer works well. After getting new data, we will report the results in the near future. The advantage of the magnetite method using the new sterilizable magnetometer compared with radioisotope method is that we can avoid “shine-through”, because of lower

sensitivity compared with the radioisotope method.

4. Others

The use of fluorescently labeled agents has been reported for SLN mapping in animals,³⁴⁾ but these agents will need to be investigated further prior to their use in humans.

Conclusion

In conclusion, investigators believe that SLNs surely exist in NSCLC; however, a standard technique for detecting them has not yet been established. This may be due in part to the fact that thoracic surgeons do not yet appreciate the potential surgical advantages provided by SLN mapping in the treatment of NSCLC. To let thoracic surgeon know the usefulness of SLN mapping in NSCLC, further investigation and multi-center trials of SLN mapping in NSCLC will be necessary before SLN mapping is widely used in the treatment of NSCLC.

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