Developing intrathoracic sentinel lymph node mapping with near-infrared fluorescent imaging in non–small cell lung cancer

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With poor survival and high recurrence rates, early-stage lung cancer currently appears to be understaged or undertreated, or both. Although sentinel lymph node biopsy is standard for patients with breast cancer and melanoma, its success has been unreliable in non–small cell lung cancer. Sentinel lymph node biopsy might aid in the identification of lymph nodes at the greatest risk of metastasis and allow for more detailed analysis to select for patients who might benefit from adjuvant therapy. The early results in our recent clinical trial of patients with early-stage lung cancer have suggested that near-infrared imaging might offer a platform for reliable sentinel lymph node identification in these patients. (J Thorac Cardiovasc Surg 2012;144:S80-4)

Lung cancer continues to be the leading cause of cancer death in the United States. Because of the large number of patients presenting with advanced disease, the 5-year survival for all patient with lung cancer has improved only slightly from 11.5% in 1975 to 16.0% in 2003.[1] Furthermore, for patients with stage I disease thought to have undergone curative resection, the recurrence rates have remained high, at nearly 40%, with overall 5-year survival of 52.2%.[1] When the local lymph nodes are involved, the 5-year survival decreases by nearly one half, making nodal involvement the most important prognostic factor. The high incidence of recurrent disease among patient with stage I lung cancer suggests that these patients are currently understaged or undertreated, or both. To stage the disease more accurately and identify those patients for whom adjuvant therapy might be beneficial, detailed lymph node evaluation is prudent.

Sentinel lymph node (SLN) mapping seeks to identify the first lymph node to harbor metastatic disease from a nearby tumor and has become an integral part of patient selection for adjuvant treatment in solid malignancies such as breast cancer and melanoma. However, no reliable method is available for SLN evaluation in non–small cell lung cancer (NSCLC), mostly because of the physical properties of the lung and thoracic cavity. The ability to identify the lymph nodes at greatest risk of metastatic spread (ie, SLNs) to conduct more detailed histologic and molecular analysis would allow for better patient selection for adjuvant therapy in the hopes of improving survival and decreasing recurrence. To date, the use of radioisotopes or blue dye for lymphatic mapping has not been successfully translated to lung cancer secondary to anthracotic nodes, poor intraoperative visibility, and procedural feasibility. In the present report, we review previous attempts at SLN identification in non–small-cell lung cancer and discuss our research using indocyanine green (ICG) dye and near-infrared (NIR) fluorescence imaging to identify the SLN in early-stage lung cancer.

HISTORY OF SLN MAPPING

Early Greek philosophy supported the hypothesis that cancer was a local manifestation of a systemic disease. However, early in the 19th century, Virchow implicated the lymph nodes in the process of the local spread of solid tumors to a more widespread systemic disease. This hypothesis led to the Halstedian model in breast cancer of en bloc dissection.[2] Numerous reports by Gould and colleagues,[3] Cabanas,[4] and Chiappa and colleagues[5] individually identified lymphatic mapping in parotid, penile, and testicular cases, respectively; however, the term ''sentinel'' was finally coined by Weissbach and Boedefeld[6] while examining the feasibility of limited retroperitoneal lymph node dissection. The concept of SLN biopsy, as we currently know it, was first made popular from studies by Morton and colleagues[7] in 1989. Using blue dye, they performed a feasibility study in a feline model and translated this into clinical trials of patients with melanoma. Their results indicated that biopsy and analysis of SLNs accurately reflected the tumor status of the lymph node basin. Soon after, SLN biopsy was introduced for breast cancer patients.[8] Additional studies have supported SLN biopsy as a method of identifying patients at greatest risk of locoregional recurrence and metastatic spread and, therefore, most likely to benefit from adjuvant therapy.

SLN MAPPING IN NON–SMALL CELL LUNG CANCER

SLN biopsy is currently the standard of care for patients with melanoma and breast cancer; however, these methods have not been successfully translated to non–small lung cancer. Understaging of early lung cancers could be secondary to inadequate node sampling because the hilar or

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Presented at the 3rd International Minimally Invasive Thoracic Surgery Summit, Boston, Massachusetts, October 7-8, 2011.

Received for publication Dec 16, 2011; revisions received April 6, 2012; accepted for publication May 18, 2012; available ahead of print June 22, 2012.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2012.05.072

Abbreviations and Acronyms
ICG = indocyanine green
NIR = near-infrared
NSCLC = non–small cell lung cancer
SLN = sentinel lymph node

mediastinal lymph nodes are not completely sampled at tumor resection in nearly 50% of patients.[9-11] In addition, the lymphatic drainage patterns in the lung are highly variable, making it difficult to predict the draining lymph node basin that should be sampled. An estimated 20% of SLNs have bypassed the nearby nodal basin (N1) and skipped to the mediastinal (N2) stations.[12] By removing only the nodes included with the resection specimen and failing to sample the hilar and mediastinal nodes, surgeons are missing these ''skip'' metastases. However, even if the SLN is removed at surgery, it is currently processed using conventional histological analysis that often fails to detect micrometastatic disease. This prospect is particularly worrisome, given that nearly 16% of patients with histologically node-negative lung cancer and up to 27.5% of patients with subcentimeter adenocarcinoma have evidence of micrometastatic disease or disseminated tumor cells within the sampled nodes when analyzed retrospectively with more time-intensive ''SLN'' histologic analysis techniques. Additional immunohistochemistry staining and polymerase chain reaction evaluation reserved for SLN analysis have been shown to increase the detection of occult micrometastasis in nodal disease. This is important because untreated occult micrometastatic disease has been shown to correlate with a threefold increase in recurrence and a significant decrease in patient survival.[13] If pathologists knew which nodes to scrutinize (ie, the SLN), focused histologic and molecular examination could be performed of these nodes for evidence of micrometastasis. As such, intraoperative lymphatic mapping could help guide surgeons directly to the draining lymph nodes so they can be selected for additional in-depth analysis.

The conventional methods of SLN mapping have been attempted for NSCLC but have remained unreliable. The first attempt at SLN biopsy in lung cancer was performed using blue dye in 1999 by Little and colleagues.[14] A total of 36 patients were studied, and only 47% of patients had a SLN identified. This was attributed to difficulties visualizing the dye in anthracotic nodes and poor technique. The investigators concluded that the rate of SLN identification was unacceptably low but equivalent to those from early melanoma and breast SLN trials. The investigators advocated for the addition of radiolabeled tracers to improve the sensitivity and specificity; however, this combination has also not proved successful.

Liptay and colleagues[15] were the first group to report the use of an intraoperative radioactive tracer in lung cancer studies in 2000 (Table 1). Their technique of intraoperative injection of technetium-99m resulted in successful radioisotope migration in 81% of patients and SLN identification in almost 87%.[15] Also, SLN analysis of previously deemed negative lymph nodes resulted in a diagnosis of occult micrometastatic disease in 24% of these patients. Furthermore, in just more than one third of the patients in whom a positive SLN was identified, the sentinel node was the only node with metastatic disease. In addition, 25 of the 104 SLNs had skipped directly to the mediastinum, highlighting the difficulty with SLN mapping in the lung. This initial phase I study with technetium-99m was encouraging and led to a phase II Cancer and Leukemia Group B multicenter trial focusing on intraoperative injection of technetium-99m in patients with suspected stage I NSCLC. However, the results from that study were discouraging, because patient accrual was less than 50%, and of those enrolled, only 51% of the SLNs were identified. The slow accrual was attributed to the logistic issues of organizing nuclear medicine, surgery, and pathology for intraoperative injection and analysis and the cumbersome regulations for radioactivity handling. Failure of SLN identification was attributed to the learning curve for the injection technique, the ''shine through'' effect in which the high radioactive signal from the tumor injection site produces false-positive results from increased background signal in nearby tissue, and background aerosolization of radioactivity.[16] After that study, it was clear that additional measures were needed to successfully identify the SLN in the thorax.

Various techniques have been attempted to increase the sensitivity and specificity of SLN identification in lung cancer using radioisotopes. From the idea that lymphatic vessels might be disrupted during intraoperative incision and dissection, preoperative computed tomography-guided injection and intraoperative injection using a transbronchial approach were proposed. However, Japanese law states that radioisotopes can only be injected in dedicated rooms. Thus, preoperative injection of radioisotopes was normally performed 18 hours before surgery. SLN identification, however, remained low at only 81% of a total 104 patients in that study. Failure to reliably identify the SLN was again attributed to the ''shine through'' effect of radioactivity from the tumor into nearby tissues, making detection separate from the background difficult, residual radioactivity in the tracheobronchial tree, and possible decreased lymphatic density or impaired lymphatic flow in patients with a low forced expiratory volume in 1 second/forced vital capacity ratio.[17] The technical complications associated with preoperative injection included bleeding, pneumothorax, and potential tumor seeding along the injection track. Again, locating the SLN in lung cancer in every patient remained an elusive goal.