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Near-Infrared Sentinel Lymph Node Identification in Non–Small Cell Lung Cancer

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What Is the Innovation?

Non–small cell lung cancer (NSCLC) prognosis is linked to lymphatic spread of disease, but localizing metastatic disease within locoregional lymphatics to accurately stage and guide therapy represents a clinical challenge. This challenge is evident in the nearly 30% recurrence rate and suboptimal overall survival among patients thought to have early-stage disease.¹ Complex thoracic lymphatic pathways and variable surgeon practices result in inadequate nodal analysis in nearly 50% of patients with lung cancer undergoing surgery.² Furthermore, the current practice of hematoxylin and eosin staining of sampled nodes misses metastatic disease in up to 22% of patients.³ Sentinel lymph node (SLN) mapping allows surgeons to target the first tumor-draining lymph node for sampling and for in-depth pathologic analysis. Previous applications of SLN mapping in NSCLC have been met with variable success. However, recent advances in image-guided surgery, specifically near-infrared (NIR) imaging, have led to renewed interest in the diagnostic and therapeutic benefits of SLN mapping. Two phase 1, single-institution clinical trials examined real-time NIR SLN mapping after peritumoral injection of the NIR fluorescent dye indocyanine green in patients with NSCLC. These trials resulted in a greater than 80% detection of NIR-positive SLN(s) without adverse events and identified metastatic disease exclusively within the SLN in several patients.^{4,5} The fluorescence itself is physiologically independent of disease status and is intended to function as an anatomical indicator of the most clinically relevant node (ie, the first tumor-draining lymph node). To reach tumors of varying sizes and locations, several approaches have been developed for peritumoral indocyanine green injection, including transthoracic injection for palpable tumors and navigational bronchoscopy-guided (Figure) or intraoperative computed tomography-guided injections for small, ill-defined early-stage tumors.

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Conflict of Interest Disclosures: Novadaq Technologies Inc loaned us the near-infrared imaging system and initially donated the indocyanine green dye that was used in our pilot Navigational Bronchoscopy-Guided Sentinel Lymph Node trial. There has been no data preview or monetary sponsorship for this collaboration.

What Are the Key Advantages Over Existing Approaches?

Approaches to nodal sampling in lung cancer are controversial, with advocates for extensive radical dissection and clearance of all nodal basins vs sampling of accessible nodal basins with minimal morbidity. The debate continues despite the prospective randomized clinical trial by Darling et al,⁶ which demonstrated no significant difference in overall or disease-free survival among patients undergoing extensive dissection vs nodal sampling. This finding suggests that the key to accurate staging is not performing the most extensive dissection but rather the ability to correctly identify the tumor-draining lymph node most likely to harbor occult metastases. By identifying the most clinically relevant node, SLN mapping may improve staging and potentially yield better outcomes. Near-infrared imaging is advantageous over previous SLN mapping methods in NSCLC because of excellent tissue penetration, ability for real-time imaging, minimal toxic effects, and lack of radiation exposure to the patient and staff.

How Will This Affect Clinical Care?

Conventional lymphadenectomy is the standard of care in NSCLC; however, with further validation, SLN mapping may significantly improve staging for patients undergoing sublobar resection because 35.3% of patients undergoing sublobar resection in the multicenter, prospective ACOSOG (Alliance for Clinical Trials in Oncology) Z4032 trial underwent no nodal assessment.⁷ Sentinel lymph node mapping is particularly advantageous in the era of lung cancer screening during which small and semisolid nodules are subject to limited resection for diagnosis and therapy but still require accurate nodal staging. In addition, a limited nodal dissection facilitated by SLN mapping permits subsequent nodal staging if a second primary tumor occurs.

Is There Evidence That Supports the Benefits of the Innovation?

In an analysis of 2 initial single-institution pilot trials to assess feasibility, Hachey et al⁴ demonstrated that 100% of patients with an NIR-identified SLN had concordant pathologic findings between the SLN and the overall nodal status (ie, the SLN was 100% sensitive and 100% specific with respect to identifying metastatic nodal disease). This study also demonstrated that in-depth analysis of the SLN can facilitate identification of occult metastatic disease, leading to upstaging and early initiation of chemoradiotherapy. Previous studies using SLN mapping in NSCLC focused on techniques and SLN yield; however, a recent report⁵ on long-term outcomes of NIR-identified SLN(s) demonstrated a statistically significant improvement in disease-free survival in patients with a pathologically negative SLN over patients who underwent standard lymph node sampling. Although further study with larger numbers of patients is required to validate this report, these results highlight the potential benefits of SLN mapping in patients with NSCLC.

What Are the Barriers to Implementing This Innovation More Broadly?

Sentinel lymph node mapping has become standard practice in melanoma and breast cancer, but adoption in lung cancer surgery has been slow. The multicenter Cancer and Leukemia

Group BSLN mapping trial by Liptay et al⁸ was closed because of poor patient accrual and logistical impediments, such as coordination among surgeons, pathologists, and radiation technologists. Limited availability of specialized equipment makes wider adoption challenging. Added operative time (approximately 20 minutes) is a potential deterrent; however, if long-term studies demonstrate equivalent (or improved) survival outcomes, surgeons may be more inclined to incorporate SLN mapping into their practice. In addition, there is potential to decrease operative times with a targeted lymph node resection. As SLN mapping gains broader acceptance, there is a need for more specific SLN markers. Although indocyanine green is currently the best method of SLN detection in the lung and is already approved by the US Food and Drug Administration for use in humans in other applications, it lacks molecular and disease specificity and is vulnerable to imprecision in the context of quick lymphatic transit or suboptimal signal-to-background ratio. Molecular targeted agents are increasingly entering clinical practice and offer promise to improve precision and accuracy.

In What Time Frame Will This Innovation Likely Be Applied Routinely?

With further validation of this technique and demonstration of reproducibility through multicenter trials, SLN mapping in lung cancer will likely enter broader clinical practice. Our institution is currently driving the development of a 2-year, multicenter trial for further vetting of NIR-based SLN mapping in the lung. We aim to demonstrate safety and large-scale reproducibility of this technique and the ability to more accurately predict long-term survival. Advances in imaging techniques and optical contrast agents will continue to improve the success of SLN detection, transforming SLN mapping into an accepted method to improve nodal staging of lung cancer.

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Figure.
Navigational Bronchoscopy–Guided Sentinel Lymph Node Mapping in Non–Small Cell Lung Cancer