“One-stop shop” tumor tattooing and sentinel lymph node mapping: A new paradigm for lung cancer therapy

Dao M. Nguyen, MD, MSc, FRACS, FACS, and Nestor Villamizar, MD

From the Thoracic Surgery Section, Division of Cardiothoracic Surgery, The DeWitt Daughtry Family Department of Surgery, The Leonard Miller School of Medicine, University of Miami, Miami, Fla.

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Address for reprints: Dao M. Nguyen, MD, MSc, FRACS, FACS, 1611 NW 12th Ave ET 3072, Miami, FL 33136-1005 (E-mail: Dnguyen4@med.miami.edu).

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The frequent use of body computed tomography (CT) scan for unrelated indications and the adoption of low-dose thoracic CT scan for lung cancer screening in high-risk populations have led to a surge of ill-defined pulmonary nodules, many of which require diagnostic and therapeutic resections. Thoracic surgeons play an integral role in selecting the most appropriate approach for tissue acquisition, including transthoracic needle aspirate, transbronchial biopsy with or without the use of navigational bronchoscopy and endobronchial ultrasound, and surgical excisional biopsy. Good surgical candidates with suspicious pulmonary nodules may benefit from surgical biopsy as the initial diagnostic and therapeutic intervention, preferably by minimally invasive thoracoscopic surgery. Once lung cancer is diagnosed, the thoracic surgeon must decide which is the most appropriate curative-intent operation, as well as the extent of intrathoracic lymph node sampling and resection. The most challenging scenarios are “ill-defined” lesions, such as part-solid ground-glass opacity (GGO) or small (<1 cm) solid tumors suspicious of being early-stage primary lung cancer located deeper than 1 cm from the visceral pleura. Attempts at preoperative biopsy of such lesions are not infrequently nondiagnostic. Tumor and patient characteristics may dictate wedge resection, preferably by minimally invasive thoracoscopic approaches, for diagnosis and therapy. These lesions are hard to identify by finger palpitation or by haptic maneuvers at the time of thoracoscopic surgery or even by manual palpation during thoracotomy. Innovative thoracic surgeons have developed many tumor localization strategies to improve the success rate of intraoperative tumor identification and resection. Commonly used tumor localization techniques include thoracoscopic ultrasound, preoperative coil insertion, hook-wire placement, peritumoral injection of methylene blue, radionuclear colloids, and more recently near-infrared (NIR)

Nestor Villamizar, MD, and Dao M. Nguyen, MD, MSc, FRACS, FACS

Central Message

Simultaneous localization of ill-defined lung cancers and mapping of SLN by NIR optical imaging defines a novel paradigm of surgical therapy for early-stage lung cancer.

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indocyanine green (ICG) dye. The use of a chromophore such as ICG that fluoresces in the NIR wavelengths for intrathoracic tumor localization is especially attractive because this compound is approved by the Food and Drug Administration, is not radioactive, and is easily visualized by an integrated system of thoracoscopic light source (color and NIR fluorescence) and specialized cameras capturing both NIR and color images producing a merged real-time image on the monitor. The advantages and disadvantages of each technique are well summarized in a comprehensive review by Keating and Singhal.¹

Pulmonary lobectomy and, in properly selected cases, anatomic sublobar segmentectomy together with thoracic lymph node sampling/dissection continue to be the treatment of choice for clinical stage 1 non-small cell lung cancer (NSCLC). Nonanatomic sublobar wedge resection is considered an acceptable surgical approach in patients with limited pulmonary reserve or in specific clinical settings, such as small peripherally located NSCLC detected by low-dose CT scan screening.² Careful intrathoracic lymph node sampling/dissection is an integral part of pulmonary resection for lung cancer. Identification of unsuspected N1 or N2 metastasis in clinical T1/2N0 NSCLC mandates consideration for adjuvant chemotherapy (N1) or sequential chemotherapy and mediastinal radiation for optimization of cancer-specific survivals.^{3,4} Moreover,

the ability to perform intrathoracic lymph node sampling/dissection and accurate cancer staging sets the thoracic surgeons apart from the radiation oncologists in the treatment of clinical T1/2 NSCLC. Unfortunately, studies using the National Cancer Database demonstrate the low propensity for intrathoracic lymph node sampling in patients receiving wedge resections.^{5,6} This lack of attention to intrathoracic lymph node sampling/resection during sublobar resection for early-stage NSCLC also was observed in a more focused review of specific patient populations, such as reported by Altorki and colleagues.² Lymph node status upstaging after resection of cN0 recently has been reported to range from 5% to 12% for cN0 → pN1 and 5% to 8% for cN0 → pN2.⁷⁻⁹ The concept of identifying sentinel lymph nodes (SLNs), those that have the greatest risk of harboring nodal metastasis, as part of the pathologic staging for breast cancer and melanoma is well accepted. Its clinical use is not well studied in NSCLC. The development of SLN mapping techniques and their clinical applications for NSCLC have been extensively reviewed by Hachey and Colson,¹⁰ and Gilmore and colleagues.¹¹ Coincidentally, ICG has been shown to be a versatile chromophore for SLN mapping for lung cancer staging.^{10,11} Perhaps, wider use of SLN mapping may lead to more conscientious efforts in performing intrathoracic targeted lymph node sampling or lymphadenectomy at the time of sublobar lung resection for early-stage NSCLC. Clinical adoption of intrathoracic SLN mapping may become a reality by developing a reliable, user-friendly, and preferably cost-effective method for SLN identification.

Hachey and colleagues¹² recently reported their first-in-human phase 1 clinical trial of tumor localization and identification of SLNs by using intraoperative navigational bronchoscopy and fluoroscopy to access the targets, to perform biopsy for preresectional diagnosis when appropriate, and to inject ICG into the lung parenchyma adjacent to the lesions before thoracoscopic resection. Tattooing of the lung and identification of SLNs containing the ICG dye were successfully visualized by NIR thoracoscopy. All lung cancers, especially those presented as “ill-defined” GGOs, were identified by NIR imaging and completely resected with adequate normal lung margins. More important, SLNs were identified and targeted lymph node samplings were performed in all cases. Colson and colleagues at Harvard have been the pioneers in this field of optical tumor localization and SLN identification. This work represents a clever integration of cutting-edge technology (navigational bronchoscopy, endobronchial ultrasound, NIR imaging) and innovative translational research (endoscopic tumor tattooing with ICG for both tumor localization and SLN identification) to address an emerging clinical need of accurate localization of “ill-defined” lung tumors that thoracic

surgeons are called on to resect. This study is significant for many reasons. It was performed by surgeons and scientists to address an important clinical issue related to the increasing need for resection of “ill-defined” lung tumors using minimally invasive thoracic surgery platforms. Second, the strategy used in this study represents a “1-stop shop” approach to diagnosis and treatment of “hard to find” peripheral lung nodules. Given that clinically favorable early-stage lung cancer (smaller tumor ≤ 1 cm, subsolid GGOs, peripheral location) can be appropriately managed by nonanatomic wedge resection especially in high-risk patients, this unified intraoperative approach is attractive to patients and referring clinicians in considering surgical therapy instead of other nonsurgical modalities. Third, potential application of this technology is the identification of SLNs that would encourage practitioners to perform lymphadenectomy of accessible N1 nodal stations (anterior and posterior hilar lymph node stations 10 and interlobar lymph nodes station 11) and N2 mediastinal lymph nodes.

One would not be too critical of the design and conduct of this first-in-human clinical trial. Beautiful and informative composite pictures are provided that illustrate the peritumoral ICG tattooing, the fluorescent lymphatic tracks, and the location of the “ill-defined” tumors on CT scan. The main question is how one would preoperatively define a tumor as being “hard to find” by standard practice of finger palpation and by haptic maneuvers at the time of thoracoscopy to apply this tumor localization approach. A 1.8-cm solid tumor, 1 cm deep from the pleural surface (as measured with aerated lung on CT scan) (patient 1) or a 7-mm subsolid GGO in the immediate subpleural location (patient 7) certainly would not be considered as “hard to find.” One would agree that a 1.5-cm solid tumor that is 2.1 cm deep (patient 6) or a very “soft” GGO in the right lower lobe of patient 12 would be ideal for intraoperative localization using the technique described in the article. The other question is how soon (not how late) after peritumoral ICG dye infiltration that one would expect to see lymphatic tracking and localization of the SLNs. One interesting finding is the high incidence of SLN being N2 stations. Intuitively speaking, one would expect the SLN likely would be N1 stations (peribronchial, interlobar, or hilar). Is this an artifact due to the long time elapse between ICG injection and SLN resection (64-180 minutes) and washing out of the ICG dye from the N1 stations? These questions would be addressed best by a larger multi-institutional study, which we believe will attract a lot of interested participants.

Looking into the future, we have no doubt that technologic refinements and larger experience with multi-institutional clinical trials will make this strategy more widely applicable.

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