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REAPPRAISE THE ADVANCED TECHNIQUE FOR TUMOR LOCALIZATION AND SENTINEL LYMPH NODE ASSESSMENT IN CLINICAL EARLY-STAGE

NON-SMALL CELL LUNG CANCER

To the Editor:

We read with interest the report “A Novel Technique for Tumor Localization and Targeted Lymphatic Mapping in Early-Stage Lung Cancer” by Hachey and colleagues,¹ which published online on March 6, 2017, in the *Journal*. While congratulating them for their great effort in investigating the safety and feasibility of navigational bronchoscopy (NB)-guided near-infrared (NIR) tumor localization and sentinel lymph nodes (SLNs) for accurate staging in patients with non-small cell lung cancer, we want to share some significant concerns.

Our first concern pertains to the necessity of applying NB-guided NIR to every undetermined pulmonary lesion. In this study, several lesions were 1 cm or greater with depth from the pleural surface of 1 cm or less. For these cases, we would argue that Hachey and colleagues¹ did not need such a complicated technique to find a lesion just beneath the pleura. Direct visualization, digital palpation, or a sliding method with an instrument might be enough for the localization of the target nodule. In our practice, most lesions 8 mm or greater with depth from the pleural surface 2 cm or less can be located by digital palpation without any other redundant methods. In addition, the average time to visualization after injection was 65 ± 31 minutes. For patients with compromised physical status, the shorter the operating or anesthetic time, the less postoperative complications there will be. The technique of NB-guided NIR was truly helpful, but it might have been overused.

Our second concern pertains to the effectiveness of SLNs in predicting the whole status of lymph nodes (LNs). Studying the effectiveness of SLNs was truly helpful for

surgeons to make a decision on how many LNs should be dissected especially for early-stage disease or patients with compromised physical status because the incidence of macroscopic skip metastasis has been reported to range from 20% to 38% in patients with lung cancer.² In this study, several patients underwent only 1- or 2-station LN dissection after examining the SLN. We think this is not enough to evaluate the concordance of the SLN with the overall nodes. In addition, the incidence of micrometastasis was reported to be approximately 19%,² and it usually could not be detected by standard hematoxylin-eosin staining. The potential existence of micrometastasis in the SLN might attenuate the effectiveness of the SLN. Therefore, we suggest that only if the authors perform standard systemic LN dissection can they evaluate effectively the concordance of the SLN with the overall nodes. Also, taking consideration of micrometastasis in SLNs might be helpful to enhance the effectiveness of SLN in predicting the whole nodal status.

In short, we agree with them that NB-guided NIR lesion localization and SLN identification may permit the accurate localization and nodal staging of early-stage lung cancers. We also believe that NB-guided NIR lesion localization is useful, but this does not mean it should be used in every case. We are looking forward to their further study on the histopathologic status of SLN versus overall nodes and concordance with the final pathologic stage in a larger cohort.

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A “GREEN” LIGHT FOR STAGING IN EARLY LUNG CANCER

Reply to the Editor:

We thank Drs Liu and Liu for their interest and insightful comments regarding our article “A Novel Technique for Tumor Localization and Targeted Lymphatic Mapping in Early Stage Lung Cancer.”

C.S.D. and Y.L.C. acknowledge Novadaq for the donation of indocyanine green dye for the initial 10 patients as proof-of-concept for navigational bronchoscopy labeling. There has been no preview, restrictions, or direct monetary sponsorship for this trial.

We shall respond to both of the concerns that were raised: First, that navigational bronchoscopy (NB) is being proposed as a localization technique for all nodules and second, that the sentinel lymph node (SLN) may not represent the true nodal status. Similar to our initial SLN trial, which successfully demonstrated that near-infrared (NIR) imaging could be used for SLN mapping after the transpleural injection of indocyanine green (ICG) during lung cancer surgery,¹ the initial aim of the current trial was to demonstrate the safety and feasibility of the peritumoral injection of ICG for both NIR tumor localization and SLN mapping when the injection was delivered via NB.² This experimental design required that lesions be localized and the SLN identified in a single setting with the use of NIR imaging. We sought to establish initial success in NIR SLN mapping via NB-guided NIR marking in patients with palpable lesions (>1 cm) as a proof of concept before seeking to translate this application to nonpalpable early stage tumors.

For patient safety and data accuracy, the initial patients represented by this cohort were purposely enrolled with lesions amenable to digital palpation to ensure that all lesions could be identified digitally and correlated with the site of subsequent NB-guided NIR marking. Given the novel nature of using ICG to create an NIR “tattoo” of a lung lesion via NB, it was critical for patient safety that we assure all nodules of interest in the initial cohort were palpable so that resection could still be performed in the event NIR localization failed.

Once we established that NB-guided NIR localization was successful, patient selection moved to include nonpalpable lesions as small as 0.7 cm and included ill-defined ground-glass opacities—a patient population more likely to benefit from this technology. We do not claim that all tumors require NB-guided NIR localization, and we agree this is not necessary in patients with sizeable tumors that can be palpated intraoperatively. However, intraoperative peritumoral injection of ICG, either via NB for small nonpalpable lesions or via a transpleural technique for larger palpable tumors, does provide the opportunity for SLN mapping.

Furthermore, the added operative time for ICG injection is less than a minute if NB already is being performed for other reasons (ie, biopsy), and the average time for navigation and injection was only 20 minutes. The reported time of 65 minutes for injection to visualization also includes the subsequent placement of a double-lumen endotracheal tube, positioning of the patient in the lateral decubitus position after NB, prep and drape, and video-assisted thoracoscopic surgery incision time before the insertion of the NIR videoscope.

Although not yet established as a standard of care, as SLN mapping becomes more widely accepted, an NB-guided technique for peritumoral ICG injection may represent an excellent opportunity to improve staging of early-stage tumors because many patients who present with small tumors do not undergo sufficient nodal staging. Although we agree that the ultimate assessment of SLN status correlation to overall nodal status would be a comparison with a complete radical lymph node dissection, Darling and colleagues³ did not find a difference in overall or disease-free survival in a prospective randomized trial comparing nodal sampling with extensive nodal dissection. This is likely to be particularly true in ground-glass opacities and small T1a tumors in which preoperative mediastinoscopy or endobronchial ultrasound are not performed routinely, given the low histological yield. Including the status of the negative nodal stations accessed in the current NB cohort via preoperative endobronchial ultrasound and mediastinoscopy (which were not included in Table 2), the patients in this study did have exploration and sampling of ipsilateral N1 and/or N2 nodal stations, which are most at risk for metastatic disease. Given that these examined ipsilateral nodal stations were pathologically negative and all patients ultimately demonstrated T1a tumors, the likelihood of an isolated contralateral nodal metastasis would be very unlikely.

However, we do appreciate the concern, continue to strive for complete nodal sampling and resection whenever clinically possible, and we continue to closely follow patients who have undergone NIR SLN mapping to assess long-term outcomes. It is of note that to date, no patient with a pathologically negative SLN has developed nodal recurrence or distant disease, suggesting that the SLN is in fact predictive of the true overall status, even though a complete radical lymph node dissection was not performed in all patients. This work recently was presented at the American Association for Thoracic Surgery annual conference and has been submitted for publication.⁴ Although analysis for micrometastatic nodal disease has not yet been performed in this initial pilot trial, this was assessed by Gilmore and colleagues¹ after transpleural

NIR SLN mapping and the SLN status remained unchanged. We will continue to validate this approach through a larger, multicenter trial, and we anticipate that transpleural ICG injection will be used for larger palpable lesions and tailored via navigational bronchoscopy for smaller nonpalpable lesions.

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