Editorial

Sentinel lymph node mapping in lung cancer: a step forward?

Raul Caso, Gregory D. Jones, David R. Jones

Department of Surgery, Thoracic Surgery Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Correspondence to: David R. Jones, MD, Professor & Chief. Thoracic Surgery Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 7, New York, NY 10065, USA. Email: jonesd2@mskcc.org.

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Early-stage non-small cell lung cancer (NSCLC) currently has a recurrence rate of 20% to 30%, which remains for at least four years after complete resection (1). Patients with occult nodal disease are at high risk of recurrence. Moreover, inaccurate staging in patients with early-stage lung cancer may result in failure to administer appropriate adjuvant treatment. The ACOSOG Z0030 study showed that either mediastinal lymph node dissection (MLND) or mediastinal lymph node sampling (MLNS) is acceptable for patients with early-stage (T1 or T2, N0 or nonhilar N1) NSCLC (2). Systematic identification of sentinel lymph nodes (SLNs) in NSCLC has the potential to detect occult nodal disease and, thus, influence operative planning and/or adjuvant therapy. Conventional SLN identification techniques, such as those involving dye and radiocolloid tracers, have not been reproducible in lung cancer (3). However, intraoperative near-infrared (NIR) image guidance has emerged as a safe method to detect SLNs in lung cancer.

Digesu *et al.* report the first analysis of long-term outcomes with NIR image-guided SLN mapping in patients with early-stage NSCLC (4). Although the authors do not provide a clear definition of early-stage NSCLC, this traditionally corresponds to stage I and II disease (T1–3, N0–1, M0). The authors performed a combined retrospective analysis of patients from two separate clinical trials who underwent NIR SLN mapping plus standard-of-care MLNS (N=23) and compared them to a similar group of patients in whom only MLNS was performed (N=19). The aims were to evaluate the long-term incidence of recurrence and survival among patients with and without NIR SLN mapping. In the NIR SLN mapping group, at least 1 SLN was identified in each patient, and detection of metastatic disease in the SLN samples correlated with overall nodal status found via MLNS. However, it is important to note that the SLNs collected were presumably processed as permanent sections, in contrast to standard intraoperative SLNs, which are processed as frozen sections. In addition, the authors do not address whether the pathologist was blinded to which node was the SLN, which could introduce a selection bias.

Although NIR SLN mapping using indocyanine green (ICG) has been proven to be safe, techniques for ICG injection are variable. Transbronchial tracer injection appears to be preferred for smaller nonpalpable lesions; transpleural injection requires intraoperative palpation of the lesion (5,6). In a previous study, the authors observed a lower yield in identifying SLNs with transbronchial (80%) *versus* transpleural (100%) injection, although issues regarding spillage/overall yield and background signal exist for each method. The current literature regarding this issue is sparse, and there is not a consensus on a standardized injection method regardless of tumor location or size. In the current study, there was no mention of the rationale for choosing either technique.

SLN mapping detected occult metastatic disease in 30% of all SLN specimens; MLNS detected occult metastatic disease in 17.4% of specimens in the SLN cohort and 21% of specimens in the non-SLN cohort. In the SLN cohort, the MLNS may have been more focused in the region of the detected tracer, whereas the non-SLN cohort would not have had this localization advantage. This may have contributed to the increased detection rate of occult metastatic disease in the SLN cohort. Additionally, occult

disease in SLN samples was strongly correlated with lymphovascular invasion (LVI) on final pathologic report. However, 40% of patients with LVI in the non-SLN cohort were initially deemed to be pN0 and, thus, were inaccurately staged. The authors attribute this to missed detection of occult disease during histologic analysis of the MLNS specimen. It is also possible that the disease-containing nodes may not have been collected in the initial MLNS, as there is no mention that occult disease was found on re-examination of these initially pN0 nodes.

The authors did not find a difference in recurrence rates or survival between patients in the two groups who were found to be pN+. However, among pN0 patients, those in the SLN cohort had no recurrences, whereas 26.7% of patients in the non-SLN cohort had recurrence (P=0.04). Similarly, disease-free survival and overall survival were lower among non-SLN pN0 patients than SLN pN0 patients (66.1% *vs.* 100% and 70% *vs.* 100%, respectively), which is likely attributable to missed occult nodal disease.

The authors note several limitations of their study. Although there were no significant differences in the populations of patients in each study cohort (SLN *vs.* non-SLN), this was a retrospective study with a small sample size and short follow-up, and a majority of patients (52%) underwent sublobar resection. The study was not powered to assess survival; therefore, the results cannot be generalized to the overall NSCLC population.

The study suggests that NIR SLN mapping improves the detection of occult metastatic disease and might be a better representation of true nodal status, with the potential to decrease recurrence rates in patients with early-stage NSCLC (7). Both the patient and the surgeon may benefit from the use of this method. Patients with negative SLNs may not require a more-extensive MLNS, although the morbidity associated with MLNS or MLND is extremely low. Alternatively, the finding of positive SLNs may identify patients who would benefit from more-extensive lymph node sampling/lymphadenectomy and/or adjuvant treatment. In this study, the non-SLN patients with LVI who were initially deemed to be pN0 would have been offered adjuvant therapy had occult disease been detected with SLN mapping, thus affecting recurrence rates in this cohort. In terms of surgeon benefit, systematic identification of SLNs can improve accuracy of nodal staging irrespective of the surgical approach or the surgeon performing the nodal sampling, as these have been previously cited as barriers (8-10). Although SLN mapping has the potential to change the current standard of care, larger, multicenter studies are needed to determine how the routine implementation of NIR image-guided SLN mapping might affect intraoperative surgical planning, postoperative treatment regimens, and patient outcomes.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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