EDITORIAL

Staging of Regional Nodes in Pulmonary Malignancies

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The role of lymphadenectomy in the surgical management of primary lung cancer is controversial. More than half of patients with apparently node-negative non-small cell lung cancer (NSCLC) will die of metastases within 5 years.¹ Some of this mortality may be due to direct hematogenous dissemination, but much may reflect surgical and/or pathologic approaches that fail to identify tumor-containing nodes.

Several randomized clinical trials compared complete mediastinal nodal dissection with systematic nodal sampling. Results were mixed; some showed no benefit (but no harm) with complete dissection, whereas others showed improved survival.^{2–4} A Cochrane review in 2005 reported improved survival with a hazard ratio of 0.78 (95% confidence interval 0.65–0.93, $P = 0.005$), but a subsequent large randomized trial conducted through the American College of Surgeons Cooperative Group found no difference.^{5,6} Current treatment guidelines state that either approach is acceptable, but accurate staging requires assessment of all relevant nodal stations.⁷

Retrospective series have demonstrated that immunohistochemistry (IHC) can detect tumor cells missed by standard pathologic techniques. Chen et al. identified clinically relevant IHC metastases in 38 (63%) of 60 patients whose nodes were tumor-negative by standard pathology.⁸ Gu et al. and Kubuschok et al. also found decreased survival among NSCLC patients with occult metastases detected by IHC.^{9,10} By contrast, Marchevsky's group reported that survival benefits based on IHC staining would be difficult to demonstrate.¹¹ There appears to be room for additional discovery in this area.

Reverse transcriptase-polymerase chain reaction (RT-PCR) can detect tumor signals in nodes that stain negative by

IHC. Although critics of nodal IHC may be tempted to extend their objections to nodal RT-PCR, this molecular assay could prove more useful than IHC. In colon cancer, IHC staining of nodes in pN0 cases was not helpful, but PCR analysis was.¹² Indeed, in NSCLC, Benlloch et al. demonstrated prognostic significance of molecular metastases.¹³ Furthermore, Hashimoto et al. showed that RT-PCR detection of tumor-specific molecular markers was prognostic, while staining by IHC was not independently so.¹⁴

Enhanced pathologic evaluation of lymph nodes by IHC or RT-PCR probably will improve staging in NSCLC but is unlikely to be practical for all nodes removed in a complete nodal dissection.¹⁵ However, lymphatic mapping of the sentinel lymph node (SLN) can yield a nodal specimen whose tumor status reflects the entire basin. If labor-intensive evaluations such as IHC or RT-PCR are limited to this small sample, they become much more feasible. In melanoma and breast cancer, SLN mapping is feasible and reliable when performed by a team with appropriate experience.¹⁶ In NSCLC, this has not been uniformly true.

Little et al. and Liptay et al. reported SLN identification rates of 47% and 82%, respectively, in early experiences with lymphatic mapping for NSCLC.^{17,18} However, in our 2004 series of 67 patients with pulmonary malignancies, SLN identification rate was 100%.¹⁹ More recent reports confirm variable rates of SLN identification. In the CALGB 140203 trial, SLN mapping had an accuracy of 51.3% and an identification rate of only 61.5%.²⁰

Why are the results of SLN mapping in the lung so inconsistent? It is probably a reflection of chest-specific technical difficulties. Nodes are close to the injection site, and their mapping is further complicated by the confined geometry of the thoracic cage and by the carbon pigment that naturally accumulates in lymph nodes draining the lung. Proposed solutions include use of different visual and radioactive tracers (isosulfan blue, Patent V, methylene blue, indocyanine green, sulfur colloid, nanocolloid, tin

colloid, phytate, and ferromagnetic particles), several injection strategies (direct injection at thoracotomy, injection via video-assisted thoracoscopic surgery, computed tomography-guided transthoracic injection and bronchoscopic injection), and alternate surgical mapping procedures (in vivo, ex vivo, or combined).^{18–28} At this point, there does not seem to be an obvious winner, but the level of interest in these technologies speaks to the potential importance of nodal mapping to the field.

In this issue of *Annals of Surgical Oncology*, Yamashita and colleagues report innovations in both surgical and pathologic aspects of the mapping technique.²⁹ They used indocyanine green as a mapping agent because this dye fluoresces in the near-infrared and can be visualized with an intraoperative imaging system, even in carbon-stained nodes. However, the close proximity of the injection site still caused several failed mapping procedures. They addressed this problem with technical modifications in later cases, and their reasonable identification rate of 80.3% should continue to improve.

They also used quantitative RT-PCR to detect cytokeratin-19 mRNA. Because the number of patients with PCR-positive lymph nodes is small and the follow up still relatively short, the clinical significance of these data remain undetermined. There are potential concerns with the particular technical procedure that was used. These include the sacrifice of half of the nodal tissue for analysis and the use of a single keratin marker, which could be affected by the presence of translocated, nonmalignant cells. In recent years techniques have become available to molecularly evaluate fixed, paraffin-embedded tissues.³⁰ This allows for normal pathologic processing of the nodes before molecular analysis. The use of multiple markers or markers specific for malignancy may further improve the clinical relevance of the technique.

Overall, this report underlines the ongoing interest in nodal staging of NSCLC. Innovations in surgical techniques, pathologic evaluation and possibly imaging will help us identify SLNs and determine the significance of nodal micrometastases.

ACKNOWLEDGMENT Supported by grants P01 CA29605 and P01 CA12582 from the National Cancer Institute and by funding from the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (Boston, MA) and the Melanoma Research Alliance (Washington, DC). The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Cancer Institute or the National Institutes of Health.

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