Commentary on sentinel lymph node identification with technetium-99m tin colloid in non–small cell lung cancer

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Sentinel node mapping techniques have been applied to the resection and treatment of nearly all solid tumors. The principle involves the injection of a lymphophylic tracer (either blue dye or a radioisotope) followed by visual or gamma counter measurements of individual lymph node stations to assess the first site of lymphatic drainage from a tumor. This sentinel nodal station should be the first site of lymphatic involvement if metastases have occurred.

The technique has become standard of care in both breast cancer and melanoma. The primary utility in these tumors is avoidance of nontherapeutic axillary or groin lymph node dissections and their incumbent morbidities. The morbidity of a complete mediastinal node dissection for lung cancer is not excessive and the procedure may be therapeutic.1,2

An equally important potential role may be directing pathologic examination to specific sentinel nodes and applying more sensitive techniques on a limited amount of tissue to detect occult micrometastatic disease.

Lymph node status is the single most important prognostic factor for localized potentially resectable non–small cell lung cancer.3 Recent studies suggest that the presence of nodal micrometastatic disease in lung cancer may garner the same poor prognosis as metastases evident by conventional techniques.4,5 Nonetheless, more than 40% of “histologically node negative” patients who have a complete resection have a relapse and die of their original cancers, usually within 2 years. This is at least in part due to inaccurately staged nodal disease.

Sentinel node mapping in lung cancer is in the developmental phase. Numerous questions regarding technique, patient selection, and ultimate utility still remain unanswered. Initial studies by our group and others6-8 have demonstrated the feasibility of intraoperative injection of both blue dye and radioisotope for sentinel node mapping.

The report by Nomori and colleagues9 in this issue of the Journal examines the sentinel node procedure by preoperative tumor injection with technetium Tc 99m tin colloid. The larger technetium tin colloid molecule required at least 6 hours to migrate to a sentinel node station as demonstrated by lymphoscintigraphy. This is compared to 10 to 15 minutes with the 20-μm filtered smaller technetium 99m sulfur colloid particle used in our intraoperative studies. The larger particle appears better suited for the preoperative injection performed the day before surgery.

The current study details results in 46 patients after injection 1 day preoperatively with technetium tin colloid. Nomori and associates obtained accurate sentinel node readings in 40 of the 46 patients undergoing anatomic resection with mediastinal node dissection for NSCLC. No inaccurate sentinel nodes were found in the 14 patients with N1 or N2 disease.

Technical Factors and Selection Criteria

We have now performed the intraoperative mapping procedure in more than 150 patients. We have noted less success of the technique in patients with large necrotic tumors as well as those with hilar and mediastinal adenopathy. The reasons for this are intuitive. Larger necrotic tumors may have altered lymphatic and vascular supply and established adenopathy may cause efferent lymphatic obstruction. Clearly, the technique holds the most promise in patients with small clinically early...
stage tumors. Those patients with adenopathy and bulky tumors will more than likely have multiple involved nodal stations.

Nomori and colleagues9 also noted that patients with chronic obstructive pulmonary disease were less likely to have identifiable sentinel nodes with their technique. One possible explanation would be an attenuation of lymphatics along with the loss of alveoli and functional lung tissue seen with emphysema. Further study will elucidate whether these patterns continue.

Intraoperative Versus Preoperative Technique

In Japan the use of radioisotopes is strictly limited to designated areas. The intraoperative injection technique is impractical in this environment. The benefits of preoperative tumor injection the night before include better logistical coordination with nuclear medicine and radiation safety issues and the ability to perform preoperative imaging to plan surgery. These are balanced by the patient requiring a separate procedure with the small but real risks of pneumothorax, bleeding, and tumor seeding of the needle tract. Which technique will ultimately be used is unclear, as currently available data show both to have reasonable sentinel node detection rates.

"Skip Metastases"

 Mediastinal lymph node involvement without concurrent spread to the intraparenchymal and hilar nodal basins has been termed “skip metastasis.” The incidence of this phenomenon in patients with positive N2 mediastinal nodes has been reported to be between 20% to 30% in most series.10 Recent studies have attempted to distinguish between patients with skip N2 metastases and those with traditional N1 and N2 positive findings by arguing that patients with the skip pattern have a prognosis similar to that of patients with stage II (N1) rather than stage III (N2) disease.11 New data suggest that the nearly 40,000 patients with stage III locoregionally advanced disease have a wide variation of prognoses within the same stage.11 The sentinel node technique may allow better understanding of common drainage patterns of different tumor locations. This may lead to improved prognostic separation of patients based on the number and degree (gross/micrometastatic) of nodes involved. The impact on overall prognosis, therapeutic decision-making, and new staging systems remains to be determined.

Nomori and colleagues9 reported 14 of 40 sentinel nodes as mediastinal. Their ability to identify these in vivo was highly accurate (88%). Although the sentinel node technique may not ever be used to stratify those requiring a full mediastinal node dissection from a sampling or no dissection, the information gained from detailing the actual nodal drainage of each tumor will continue to blur the lines between N1 and N2 disease, calling for a reconsideration of the staging of single site skip pattern metastases.

Micrometastases/Ultrastaging

Nomori’s group9 found no micrometastases in the 26 sentinel nodes classified as negative by standard histologic evaluation. The authors report performing additional 3-step sections and immunohistochemistry with cytokeratin antibodies. This is in contrast to our recent report7 detailing results in our first 100 patients in which 7 patients were upstaged with the identification of micrometastastic disease in the sentinel nodes. We performed serial sections at 30-μm intervals (average 10 per slide) as well as cytokeratin antibody staining.

With the increasing availability of real time reverse transcriptase–polymerase chain reaction analysis and other even more sensitive techniques to identify single cell nodal metastases, the future role of sentinel node identification in directing these examinations to the most likely site for metastases remains promising. Likewise molecular staging techniques may become more prognostically important as more specific markers and patterns are identified.12 The partnering of more precise sentinel node identification with more sensitive and informative ultrastaging molecular techniques will likely revolutionize the way we stage lung cancer and decide on appropriate postoperative treatment plans.

Currently, conflicting data exist to support the administration of chemotherapy for localized completely resected lung cancer, although clinical trials continue to investigate this intervention. If improvements in systemic therapy are forthcoming, more accurate or “ultrastaging” techniques may assist in selecting patients at highest risk for recurrence and perhaps most likely to benefit from additional therapies.

The current study by Nomori and colleagues9 is a welcome addition to the growing experience of the sentinel node mapping technique. Their results confirm the promise of this staging tool to assist in giving patients the most precise information about their disease and aid in the identification of those most likely to benefit from future adjuvant therapies. These findings await broader application in resectable lung cancer to refine the sentinel node mapping technique and patient selection criteria.

Reference


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