

Sentinel Node Mapping in Lung Cancer

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Lymph node metastases are the most significant prognostic factor in localized non-small-cell lung cancer (NSCLC). Nodal micrometastases may not be detected with current standard histologic methods. We review our experience with intraoperative injection of radioisotope, the current state of the technique, and the experience of other groups with alternate methods and tracers.

Key Words: Lung cancer—Lymph node metastases—Sentinel node mapping.

Lung cancer remains the most common cause of cancer-related mortality in both sexes worldwide. More than 180,000 new cases will be diagnosed this year. Only 25% to 30% of these patients are considered candidates for potential curative resection. If pathologic lymph node involvement is recognized, the chances of long-term survival are less than 50%. Improved staging techniques should allow homogenous study group selection and balanced assessment of treatment effects.

Sentinel node mapping techniques have been applied to the resection and treatment of nearly all solid tumors. A lymphatic tracer (either blue dye or a radioisotope) is injected and followed by visualization or gamma counter measurements of individual lymph node stations to determine the first site of efferent lymphatic drainage from a tumor. This sentinel node station should be the first site of lymphatic involvement if metastases have occurred.

Use of this technique has become the 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 Nodal involvement decreases the 5-year survival by nearly 40%. Nonetheless, up to 40% of completely resected histologically node-negative patients relapse and die from recurrence within 2 years. This is due, at least in part, to inaccurately staged nodal disease. Recent studies suggest that the presence of nodal micrometastatic disease in lung cancer may have the same poor prognosis as metastases evident by conventional techniques.^{4,5} A powerful application of the sentinel node technique in lung cancer is the identification of specific nodes for ultrastaging by pathologic and molecular examination.

TECHNIQUE

We have performed intraoperative sentinel node mapping in more than 150 patients by injecting technetium-99m suspension directly into lung masses at the time of thoracotomy. Our original technique has been described in a previous publication detailing our experience with our first 52 patients.⁶ An important modification to the technique is a decrease in the amount of radioactivity injected into the tumors, from an original total dose of 2 mCi to our current dose of 0.25 mCi. This has significantly decreased background radiation from the tumor, which can hinder identification of a unique sentinel node station in vivo. The tumor mass itself is injected in four outer quadrants with technetium sulfur colloid filtered once through a 20-micron filter. The filtering of the particles ensures rapid passage of radioisotope through

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the lymphatics to allow for sentinel node identification without prolonging the planned resection.

A standard lymph node dissection is performed to complete an anatomic resection of the tumor. Readings are taken with the hand-held gamma probe counter (Navigator System, United States Surgical Corporation, Norwalk, Connecticut) after calibration. The minimum required interval between injection of the tumor with radiocolloid and detection of radioactivity in the lymph nodes is 10 to 15 minutes, as determined by our initial series.⁶ During this migration period, care is taken to avoid dissection of the bronchial structures and peribronchial tissues, where the majority of lymphatics are located. Bronchial dissection and division are performed last in the majority of cases if the operative dissection permits.

The tumor specimen and nodes are initially surveyed in the thorax. Radiolabeled nodes are also examined off the operative field and separately from the tumor specimen. The migration of the radiocolloid solution is considered successful if a specific node registers counts per second greater than three times the background values.

PATHOLOGIC EVALUATION

After identification of the sentinel node station, these nodes are examined with use of both serial sections and immunohistochemistry for cytokeratins. Additional resected nodes are bivalved and stained with hematoxylin and eosin (H&E). Sentinel and nonsentinel lymph nodes are subsequently examined by cytokeratin antibody immunohistochemistry (IHC).

RESULTS

Intraoperative sentinel lymph node mapping was performed on 165 consecutive patients presenting as candidates for anatomic resection of a suspected primary lung cancer. Of these, 148 consecutive patients had completely resected non-small-cell lung cancers and were

included in this study. Successful migration of the radioisotope through lymphatics was seen in 120 of 148 patients (81%). An SN was identified in 104 of 120 patients (87%) with successful migration of radioisotope, or 70% (104) of all 148 attempted mapping procedures. Our initial experience included all patients undergoing resection for suspected lung cancers, regardless of the presence of hilar or mediastinal adenopathy or large necrotic tumors.

In 28 of the 148 patients (19%), we failed to demonstrate migration of the radioisotope through the lymphatics. Hilar and/or mediastinal adenopathy was present in eight patients, whereas nine patients had tumors greater than 5 cm. Two patients underwent preoperative chemoradiation, and in 11 patients no explanation was found for the technical failure.

Micrometastases

In our series the sentinel node was positive for metastatic disease in 33 of 104 patients (32%); the sentinel node was the only metastatic node in 12 of 33 patients (36%). We detected micrometastatic disease in the sentinel node with immunohistochemistry or serial sectioning in 8 of 33 patients (24%). Thus, in our first experience with the sentinel node procedure, lung cancers were upstaged in 8 of 148 cases (5.5%).

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 is between 20% and 30% in most series.⁷ In our study, 25 of 104 sentinel nodes (24%) were mediastinal.

Selection Criteria for Future Studies

Table 1 lists the currently reported series of sentinel node mapping in lung cancer,^{6,9,11-17} including method

TABLE 1. Sentinel node mapping in lung cancer series

| Authors | Year | n | Injection time | Tracer | Success rate (%) |
|--------------------------------|------|-----|-----------------------------|--------------------------|------------------|
| Little et al. ¹¹ | 1999 | 36 | Intraoperative | Isosulfan blue dye | 47 |
| Nomori et al. ⁹ | 2002 | 46 | Preoperative | Tc-99 tin colloid | 87 |
| Schmidt et al. ¹² | 2002 | 31 | Intraoperative | Tc-99/isosulfan blue dye | 81 |
| Sugi et al. ¹⁶ | 2003 | 65 | Preoperative | Tin colloid | 60 |
| Nakagawa et al. ¹⁷ | 2003 | 38 | Intraoperative | Magnetite | 82 |
| Sugi et al. ¹³ | 2003 | 16 | Intraoperative | Indocyanine green | 6 |
| | | 18 | Intraoperative | Isosulfan blue dye | 50 |
| | | 14 | Preoperative | Tc-99 tin colloid | 64 |
| Lardinois et al. ¹⁴ | 2003 | 20 | Preoperative, bronchoscopic | Tc-99 | 95 |
| Liptay et al. ^{6,15} | 2002 | 148 | Intraoperative | Tc-99 sulfur colloid | 70 |

and tracers used. We have now performed the intraoperative mapping procedure in over 160 patients. We have noted less success of the technique in patients with large necrotic tumors and in those with hilar and mediastinal adenopathy. The reasons for this are intuitive. In larger necrotic tumors, altered lymphatic and vascular supply as well as adenopathy can cause efferent lymphatic obstruction. Clearly the technique holds the most promise for 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 obstructive lung disease (COPD) were less likely to have identifiable sentinel nodes. One possible explanation would be an attenuation of lymphatics secondary to loss of alveoli and functional lung tissue in emphysema. Further study will elucidate whether these patterns continue.

With the growing number of early-stage tumors identified by computed tomography and positron emission tomography, sentinel node mapping and the identification of micrometastatic disease have become more appealing. In a sobering study, Ohta and colleagues¹⁰ used immunohistochemistry to search for micrometastases in 3081 nodes from 181 patients with stage I peripheral lung cancers. The authors found no micrometastases in squamous cell tumors less than 2 cm in diameter. However, nodal micrometastases were found in 20% (19) of 95 patients with adenocarcinomas of 1.1 cm to 2.0 cm in diameter and in 4 of 11 patients with adenocarcinomas measuring 1 cm or less.

The exhaustive analysis of all lymph nodes resected is impractical to do on a daily basis. Sentinel node mapping offers the ability to limit the more extensive pathologic or molecular study to the node(s) most likely to be involved with tumor if metastases are present.

New data suggest that the nearly 40,000 patients with locoregionally advanced (stage III) disease have a wide range of prognoses.⁸ Recent studies have attempted to distinguish between skip N2 metastasis and traditional N1 and N2 metastasis by arguing that the skip pattern has a prognosis similar to stage II disease (N1) rather than stage III (N2).⁷ The sentinel node technique may allow better understanding of common drainage patterns from different tumor locations. This may lead to improved prognostic separation of patients on the basis of 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.

Although the sentinel node technique may not ever be used to distinguish patients who require a full mediastinal node dissection from those in whom a sampling or no dissection is adequate, the information gained from map-

ping the nodal drainage of each tumor will continue to blur the lines between N1 and N2 disease, calling for reconsideration of the staging of single-site skip-pattern metastases.

With the increasing availability of real time RT-PCR 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. 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 determine postoperative treatment.

Before the sentinel node technique becomes widely applied in the treatment of patients with potentially resectable lung cancers, confirmation of the feasibility of the technique in a multiinstitutional setting is required. The Cancer and Leukemia Group B has a phase II trial in development to address the utility of sentinel node mapping in lung cancer surgery.

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