Lymphatic Mapping and Sentinel Lymphadenectomy for Primary and Metastatic Pulmonary Malignant Neoplasms

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**Background:** Mediastinal lymph node sampling understages a significant number of lung cancers, even when nodes are evaluated by immunohistochemical techniques. Intraoperative lymphatic mapping and sentinel lymphadenectomy allows focused pathologic evaluation of a few lymph nodes that accurately stage the entire basin.

**Hypothesis:** Lymphatic mapping and sentinel lymphadenectomy is a practical and accurate method of staging lymph nodes that drain primary and metastatic neoplasms of the lung.

**Design and Setting:** Retrospective review at a tertiary referral center.

**Patients:** Sixty-seven patients undergoing resection of lung tumors.

**Main Outcome Measures:** Sentinel lymph node (SN) identification rate, number of SNs, nodal pathologic features, and survival.

**Results:** Twenty-eight patients had primary lung cancer and 39 had pulmonary metastases from melanoma (33 cases), squamous cell carcinoma (2 cases), colon cancer (2 cases), or other cancers (2 cases). Lymphatic mapping and sentinel lymphadenectomy was successful in all patients. The median number of lymph nodes identified by dye alone was 2 (range, 1-7); the median number identified by dye plus radiocolloid was 4 (range, 1-9). Most SNs (69%) were N1; 31% were N2. Lower lobe lesions drained to upper mediastinal nodes in 3 (13%) of 24 cases. Lymph node metastases were found in 11 patients with lung cancer (39%) and 8 patients with pulmonary metastases (21%). Ten (91%) of the 11 patients with lung cancer had SN involvement. In the 33 patients with metastatic melanoma, SN involvement significantly reduced the rate of 2-year survival (0% vs 48%).

**Conclusions:** Lymphatic mapping and sentinel lymphadenectomy of intrapulmonary malignancies is technically challenging but feasible. Blue dye is most useful for in vivo identification of SNs; ex vivo radioactivity can confirm that excised nodes are SNs. Lymphatic mapping and sentinel lymphadenectomy can provide important prognostic information for patients with melanoma and lung metastases, and it may improve the staging of primary lung cancer.

*Arch Surg. 2004;139:870-877*
SNs were examined by routine histologic examination. Staining for melan-A was used in more recent cases. Non-HMB-45–staining was used to identify metastatic melanoma. Cytokeratin staining was used to identify metastatic lung, colon, and breast carcinomas; S100-staining and by IHC. Cytokeratin staining was used to identify more distally located SNs. All blue-stained or radioactive SNs that could be identified were removed approximately 10 to 15 minutes of injection. Additional dissection was performed along the pulmonary artery and bronchi to identify more distally located SNs. All blue-stained or radioactive SNs that could be identified were removed. Since background activity from the heart and major vessels created so much radioactive signal, SNs frequently could not be identified in vivo using radioactivity alone. However, radioactivity was useful ex vivo to distinguish SNs from non-SNs. This examination of excised lymph nodes was performed by the operating surgeon away from the operative field after conclusion of the operative procedure. Lymph nodes with the highest radioactivity ex vivo were considered sentinel. All patients with primary lung carcinoma underwent anatomical resection and complete hilar and mediastinal lymph node dissections.

Sentinel nodes were examined by routine hematoxylin-eosin staining and by IHC. Cytokeratin staining was used to identify metastatic lung, colon, and breast carcinomas; S100- and HMB-45–staining was used to identify metastatic melanoma. Staining for melan-A was used in more recent cases. Non-SNs were examined by routine histologic examination.

RESULTS

Sixty-seven patients were evaluated using LM/SL. Twenty-eight patients had primary lung carcinomas and 39 had metastatic lesions in the lung. The 2 groups were similar in terms of age, sex, and tumor distribution within the lung (Table 1). Mean tumor diameter was 3 cm for primary lung tumors and 3.3 cm for metastatic lesions. Most primary lung tumors (20 of 28) were adenocarcinoma and most metastatic lesions (33 of 39) were melanoma.

Of the 28 patients with primary lung cancer, 22 underwent lobectomy, 2 underwent bilobectomy of the right middle and right lower lobes, 3 underwent anatomical segmentectomy, and 1 patient did not undergo pulmonary resection. In this patient, palpation through the diaphragm identified a small hepatic lesion not demonstrated on preoperative images, and the resection was aborted after a biopsy specimen confirmed the presence of metastasis.

Of the 39 patients with metastatic lesions, 16 underwent lobectomy, 12 underwent a single segmentectomy, and 7 had multiple segmentectomies to preserve lung parenchyma. Three other patients underwent bilobectomy and 1 underwent pneumonectomy. All mapping procedures were unilateral, although 3 patients had either simultaneous or staged resections of contralateral metastatic lesions. There were no intraoperative complications related to the mapping procedure and no operative deaths.

A blue-stained and/or radioactive SN was identified in all cases. The median number of SN specimens was 2 (Table 2). In several cases, SN specimens contained more than 1 node when examined pathologically so that the number of pathologically identified nodes was greater than the number of surgical specimens. All nodes in the surgically defined SN specimen were treated pathologically as SNs.

Close examination of the pleural surface surrounding the tumor injection site generally revealed dye visibly marking the primary lymphatic drainage pattern and directed examination of pertinent lymph node stations (Figure 1B). Blue coloration of the SN was most easily detectable in vivo, but the rapid fading of the blue dye as well as the anthracotic nature of lymph nodes in this setting made the color harder to visualize than is the case in other anatomic sites (Figure 1C and D).

A radiotracer was used concomitantly in 47 cases. There was significant background radioactivity or “shine through” owing to the closeness of the tracer injection site and central vascular structures. The combination of mapping agents facilitated technical completion of the procedure. Additionally, once the pulmonary lesion had been resected, lymph node stations could be reexamined for residual radioactivity. After removal of the source of much of the background radioactivity, a thorough survey of the remaining nodal stations was possible to ensure that no SN had been missed. More SNs were removed in cases mapped with both agents (mean, 4.1) than in those using isosulfan blue dye alone (mean, 2.7; P = .01, 2-tailed t test).

Sixty-eight percent of the SNs were located in N1 positions; 32% were in N2 positions. Lower lobe lesions drained to upper mediastinal lymph nodes in 3 of 24 cases; all were on the left side (Figure 2). The SNs contained tumor from 10 (36%) of 28 primary lung lesions and 8 (22%) of 37 metastatic lesions.

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In 17 of 18 patients who had primary lung tumors and negative SNs, all lymph nodes removed during complete lymph node dissection also were negative for metastasis. The one false-negative SN was from a patient who had undergone neoadjuvant chemotherapy. This SN demonstrated a cystic change that was pathologically consistent with regression of tumor after systemic treatment. In this patient, the tumor-involved non-SN was replaced with tumor, decreasing the likelihood of tracer uptake.

In 5 (45%) of 11 patients who had primary lung tumors and positive SNs, all non-SNs were negative. In 1 case, SN metastasis was identified only by IHC. A total of 93 SNs were identified of which 21 (23%) contained metastasis. A total of 163 non-SNs were identified 23 (14%) of which contained metastasis. The difference in positive node rate between SNs and non-SNs approaches statistical significance ($P = .08$, $\chi^2$ test) even with this limited sample size.

The number of patients with nonmelanoma metastatic lesions was too small to provide meaningful data specific to those diagnoses. For this reason, no survival analysis was performed for those patients. However, since the lymphatic anatomy should theoretically not be changed by the pathologic features of the mapped lesion, they were included in assessments of the locations and numbers of SNs.

Analysis of the subgroup of 33 patients with melanoma revealed the prognostic importance of SN status. Sentinel node metastasis was identified in 5 (16%) of these patients and its presence significantly decreased survival (median survival, 10.4 vs 22.6 months; $P = .009$, log rank test [Figure 3]). All patients with SN metastasis died of melanoma within 2 years, whereas 24% of pa-

Figure 1. Mapping technique. A, Peritumoral injection of radiotracer with palpation of tumor; B, subpleural lymphatic channel staining with isosulfan blue dye; C, blue-stained lymph node in vivo; and D, sentinel lymph node after excision.
Patients with SN-negative tumors were alive more than 3 years after resection.

**COMMENT**

Lymph node staging is critical to determine the prognosis and appropriate treatment for patients with non–small cell carcinoma of the lung. The presence, location, and number of tumor-positive nodes are powerful predictors of outcome and can be used to identify and stratify candidates for clinical trials of adjuvant treatment.

However, the fact that more than half of the patients without evidence of nodal metastases have disease recurrence and die of lung cancer indicates that current methods of lymphatic staging are not optimally accurate. There are 2 possible sources of inaccuracy: surgery and pathology. Surgical lymphadenectomy may be inadequate if limited to nodes in the resection specimen and randomly sampled hilar and mediastinal nodes. Examination of more nodes and systematic dissection of lymph node stations have been associated with improved outcomes but are often not performed, probably because of fears they might increase the duration and potential morbidity of lymphadenectomy.

Immunohistochemistry and PCR assessment of lymph nodes can increase diagnostic information. A study of 588 lymph nodes from 60 patients with lung cancer reported a 63% incidence of occult metastases visible by IHC but missed on routine pathologic examination. Patients with occult metastases had significantly lower survival, a finding that has since been confirmed in other studies of lung cancer. However, as Goldstein et al pointed out, the application of these labor-intensive techniques to multiple lymph node sections may exceed the clinical value of the additional information they provide.

One strategy that allows the use of intensive pathologic techniques without overtaxing the pathologist is to select a few nodes for evaluation using LM/SL. This has allowed the practical application of IHC and even PCR techniques in malignancies in other locations. Subsequent improvements in lymphatic staging have been documented in melanoma as well as in breast and colorectal cancer.

Lymphatic staging in the lung has previously been investigated in both preclinical and clinical settings. In a canine model, Nwogu et al identified an SN in 5 of 6 dogs whose nodes were mapped with technetium TC 99m sulfur colloid and in 3 of 6 dogs whose nodes were mapped with isosulfan blue dye. Initial clinical studies also used only 1 mapping agent, either a blue dye or a radiotracer. Little et al used blue dye to identify an SN in 17 of 36 patients, a rate of identification similar to that reported for the dog model of dye-directed mapping. The negative predictive value of the technique was excellent in the 9 cases with a negative SN; no additional disease was found in higher-echelon nodes.

In a more recent series of 100 consecutive patients, LM/SL with radiotracer alone was undertaken.
ex vivo after pulmonary resection and hilar and mediastinal lymph node dissection. Sentinel nodes were identified in 86% of the cases, again quite similar to the rate reported for a radiotracer in the dog model. No lymph node metastases were found in patients whose SN was free of tumor. A recently reported series used a combination of isosulfan blue dye and radiotracer but did not report considerable difficulty with this phenomenon, which was improved by decreasing the amount of radiotracer. Neither mapping agent is entirely satisfactory in isolation, but their combination tends to overcome the weaknesses of each.

The other important factor in successful identification of the SN is experience with LM/SL. Earlier reports noted refinements in technique after completing a preliminary series of cases. Because our group developed LM/SL for lymphatic staging of primary melanoma and subsequently extended it to breast and colorectal carcinomas, we began our investigation of LM/SL for nodal staging of pulmonary tumors at a point well along the learning curve. We expect that SN identification rates will improve at other centers as their overall experience with LM/SL for malignancy increases.

To our knowledge, our study is the first to consider LM/SL as a prognostic tool for lymph node staging in patients with melanoma metastatic to the lungs. Although single-agent mapping can be acceptable in some clinical situations when the surgeon is experienced in LM/SL, anatomical considerations suggest that a combination of mapping agents is preferable in the lung. Isosulfan blue dye is generally visible within subpleural lymphatic channels but may fade rapidly from anthracotic pulmonary lymph nodes ex vivo. This means that close inspection of the lung surrounding the peritumoral injection site is important to identify the pertinent lymphatic channels and thereby follow them to the SN stations. In addition, the confined space and physical proximity of both the tumor and central vascular structures guarantee a fairly high level of shine-through or background radioactivity. This tends to obscure any signal within the SN. Indeed, 1 series reported considerable difficulty with this phenomenon, which was improved by decreasing the amount of radiotracer. Neither mapping agent is entirely satisfactory in isolation, but their combination tends to overcome the weaknesses of each.

LM/SL in other solid tumors. Although single-agent mapping can be acceptable in some clinical situations when the surgeon is experienced in LM/SL, anatomical considerations suggest that a combination of mapping agents is preferable in the lung. Isosulfan blue dye is generally visible within subpleural lymphatic channels but may fade rapidly from anthracotic pulmonary lymph nodes ex vivo. This means that close inspection of the lung surrounding the peritumoral injection site is important to identify the pertinent lymphatic channels and thereby follow them to the SN stations. In addition, the confined space and physical proximity of both the tumor and central vascular structures guarantee a fairly high level of shine-through or background radioactivity. This tends to obscure any signal within the SN. Indeed, 1 series reported considerable difficulty with this phenomenon, which was improved by decreasing the amount of radiotracer. Neither mapping agent is entirely satisfactory in isolation, but their combination tends to overcome the weaknesses of each.

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To our knowledge, our study is the first to consider LM/SL as a prognostic tool for lymph node staging in patients with melanoma metastatic to the lungs. Although these patients did not undergo complete lymph node dissection, 16% rate of SN metastasis in this subgroup suggests that these metastases were derived from the lung lesions. Our group's previous studies in patients with intrathoracic melanoma lesions support the utility of LM/SL in the metastatic setting. In the present study, patients with SN metastases from pulmonary le-
sions clearly belonged to a different risk category than patients whose SNs were negative for tumor. The use of such prognostic information is important in the design of adjuvant therapy trials for stage IV melanoma. The substantial fraction of patients with negative SNs who enjoy long-term survival should also underline the need to consider resection as a treatment option for properly selected patients with stage IV melanoma.

In addition, this remarkable evidence of the ability of metastatic lesions to continue to metastasize should have an important effect on our understanding of the biological behavior of melanoma. Pulmonary metastases are clinically important not only because of their direct effect on the patient’s pulmonary function, but also as a source of ongoing disease dissemination. Early removal of such lesions may stem or even interrupt the cascade of metastatic cells derived from metastatic sites.34 In other words, effective local treatment of metastatic lesions through surgery may be an important form of systemic therapy. Moreover, the presence of metastatic disease in such a large proportion of patients suggests complete hilar and mediastinal lymph node dissections should be considered during resections for pulmonary metastases.

Overall, the technique of LM/SL is a feasible and accurate method of evaluating patients for the presence of regional lymphatic disease in the setting of intrapulmonary malignancies. When combined with modern techniques in pathology, it will prove to be a practical method of improving lymphatic staging in primary lung cancer.

Accepted for publication April 15, 2004.

This study was supported by grant CA29605 from the National Cancer Institute, Bethesda, Md, and by funding from the Amyx Foundation Inc, Boise, Idaho; Alice Johnson McKinney, Nancy and Carroll O’Connor, Los Angeles, Calif; the Harold J. McAlister Charitable Foundation, Los Angeles; the George Hoag Family Foundation, Los Angeles (Dr Essner); and the Saban Family Foundation, Los Angeles (Dr Essner).

This paper was presented at the 75th Annual Meeting of the Pacific Coast Surgical Association; February 17, 2004; Maui, Hawaii; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

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REFERENCES

Frederic W. Grannis, Jr, MD, Duarte, Calif: Isaac Newton once said, “If I have seen farther, it is by standing on ye shoulders of Giants.” While Newton invented calculus, and I just barely passed the course, I too had the distinct pleasure of standing on the shoulders of giants this morning, and the opportunity to ask them some questions about their experience with SN techniques in the treatment of lung tumors. This is not hyperbole; Donald Morton is a true giant in our field and his place in history is secure. He and his colleagues have helped thousands of people by facilitating curative treatment of breast cancer and melanoma by developing, testing, and standardizing methods of accurate staging nodal metastasis that avoid the necessity of debilitating radical nodal dissections.

Before proceeding, I would like to remind members of the Pacific Coast Surgical Association that their former member, Joseph A. Weinberg, MD, of Long Beach, Calif, was the first person to use vital dye technology in the evaluation of mediastinal nodal metastasis in lung cancer, and that both Drs Weinberg (J Thorac Surg. 1953;25:582-599) and John F. Higginson, MD, (J Thorac Surg. 1953;25:582-599) have emphasized that as many as 30% of mediastinal lymph nodes may be involved with disease before proceeding to a mediastinal node dissection. As we know, there is a just completed American College of Surgeons Oncology Group study completed at the same time. If, indeed, your indication for a lymph node dissection is a positive SN, have you tried intraoperative node biopsy? In the case of axillary and groin nodal dissections, the complications do you think can be avoided by averting mediastinal node dissection?

Richard J. Finley, MD, Vancouver, British Columbia: I enjoyed this paper very much because the authors are exploring new methods of accurate intraoperative staging. Right now in staging in lung cancer, most patients undergo an enhanced CT scan and a PET (positron emission tomographic) scan, so my first question for the authors is did these patients undergo a PET scan prior to their surgical intervention? What other staging procedures did they have? Did they have mediastinoscopes before the thoracotomy? Did all of these patients have preoperative diagnosis of their lesions?

In the future of lung cancer staging will be CT and PET. Are you using CT and PET in both primary lung cancer and in metastatic cancer?

Ralph W. Aye, MD, Seattle, Wash: This paper makes a very important contribution in an area that we continue to struggle with in the surgical staging of lung cancer. The practical question is whether this approach would make a difference in management. Specifically, I would ask the authors how often they believe that the SNs that were identified would not have been removed in the course of routine lobectomy and mediastinal node dissection. As we know, there is a just completed American College of Surgeons Oncology Group study comparing routine nodal dissection to node sampling, and if we are all moving toward node dissection as a routine, perhaps these are nodes we would have identified at any rate. Of course, we still are not quite sure what to do with IHC-positive, histologically negative nodes.

The other question is whether mediastinoscopy potentially interferes with node drainage patterns enough to invalidate the sentinel node technique with regard to mediastinal nodes. Could the authors please comment on that?

Stanley P. L. Leong, MD, San Francisco, Calif: In melanoma and breast cancer, we tend to wait for the permanent section result and reschedule the patient for a completion lymph node dissection if, indeed, an SN is positive. Of course, in your situation, you would like to have the entire procedure completed at the same time. If, indeed, your indication for a lymph node dissection is a positive SN, have you tried intraoperative RT-PCR (reverse transcription–PCR) to give you a rapid diagnosis of metastatic disease in the SNs before proceeding to a lymph node dissection in the same setting?

Dr Essner: I will try to proceed with all of them. All of these questions were very good. Dr Grannis, the concept of sentinel lymphadenectomy certainly for lung cancer is not a new concept and others have tried to use this technique of identifying the lymph nodes to better stage these patients’ diseases.

DISCUSSION

In a procedure such as this it is unlikely that we would go back and reoperate on these patients certainly at this point but the concept of being able to better stage patients may allow us to better segregate which patients should be candidates for adjuvant therapy. Recently, there was a study by Gajra as Dr Faries alluded to demonstrating that patients who have had increasing number of lymph nodes removed were better staged and translated into a better survival advantage certainly for the early stage-patients. This has been done in other diseases such as colon cancer and we wrote a paper about that in melanoma, and it is probably not regarding the total number of nodes but actually better staging in which we segregate patients better into their groups.

The concepts of complications regarding mediastinal node dissection: at least in our hands it is rare and again the idea of SN dissection was not to avoid mediastinal node dissection but rather to identify where the sites of metastases and certainly, ultimately, when this technique is validated by larger groups, it perhaps could avoid mediastinal node dissection in those patients who are found to have disease limited to N1 stations. In fact, from our study the suggestion was that 32% of our patients had N2 nodes and it may be that the old concepts of where these nodes are in these patients may be altered by the technique of SN dissection.

Is this practical? It simply is very simple. Using the blue dye, the blue dye travels quickly and, in fact, we would recommend that the thoracic surgeons have their general surgical oncology colleagues teach them how to use this technique. When we first developed SN dissection for melanoma in the early 1990s, in our first paper we published that the accuracy rate of SN dissection was only 80% and at that point, when we presented the paper, a number of individuals said, “Well, why bother if we are only 80% accurate.” But the reality is with increased experience and increasing numbers at individual centers the technique can be accomplished. One of the other problems that is unique to lung cancer is the anthracotic lymph nodes that make it difficult to identify the blue dye and so the addition of the radiopharmaceuticals is helpful, although it can be somewhat impractical to have a nuclear medicine physician in the operating room with you to inject. In California there is only a rare individual surgeon who has a license to use radiopharmaceuticals in the operating room.

Regarding the number of lymph nodes again, we had an average of 10 total lymph nodes removed and from the Gajra paper, his upper quartile number of lymph nodes removed was 9, so although the number of lymph nodes appears small, the reality is that it is not a low number. At this point we do not think that this procedure is going to change surgery again until it is validated. Certainly our concepts are is trying to identify the patterns of metastases in patients with melanoma, and over 100 years ago Padgett came up with the idea of seed-and-soil so the concept is is metastasis seeding other metastases and so the reality is in our patients with metastatic disease, indeed, if we can prevent subsequent metastasis or at least identify them in these patients, perhaps we can improve outcome as Dr Faries has alluded to. Certainly in lung cancer again it is more of a staging procedure.

Regarding the use of imaging preoperatively, these patients had CT scans. Again this was over a 10-year period and so PET scan became part of our practice back in about 1995 and then last year we have used PET and CT. I cannot tell you for sure, but I do not believe any of these patients had mediastinoscopy and it would certainly question if you did mediastinoscopy would you disrupt the lymphatics. My answer would be I would think so. As we know, our experience from breast and melanoma that anything that you do to alter the lymph node basin at risk can alter lymphatic channels.

The role of immunohistochemistry is unknown. Certainly there is a suggestion that better staging of patients may be accomplished using immunohistochemistry but the reality is none of us know if it is ultimately going to change the outcome of these patients. Dr Leong mentioned the comments about using intraoperative PCR. At this point we have not done that. Certainly we had enough trouble using it in melanoma and breast cancer that we have not used it in these lung cancers and certainly at this point it hasn’t been shown or at least our data do not show that we should alter our surgical approach.