GENERAL THORACIC SURGERY

INTRAOPERATIVE LYMPHATIC MAPPING FOR NON-SMALL CELL LUNG CANCER: THE SENTINEL NODE TECHNIQUE

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Background: The purpose of the study was to determine the accuracy and role of the sentinel node technique in patients with non-small cell lung cancer. **Methods:** This study was carried out on 36 consecutive patients undergoing lung resection. Peritumoral tissue was infiltrated with isosulfan blue dye and the first lymph node to stain was identified as a sentinel node. Sensitivity and specificity of the sentinel node in predicting the status of other lymph node stations were determined. **Results:** Seventeen patients had sentinel lymph nodes. In 9 of these 17 cases neither the sentinel node nor any other lymph node contained metastatic carcinoma. In 5 cases the sentinel node was in the mediastinum and documented unexpected N2 disease. In 19 patients no sentinel node was found. Final lymph node statuses were N0 in 13 patients, N1 in 5, and N2 in 1. **Conclusions:** The use of isosulfan blue for intraoperative lymphatic mapping is feasible. The specificity in our experience was good; 9 of 9 patients with negative sentinel nodes were found to be N0 on the final pathology report. Unexpected N2 disease was found in 5 patients. The accumulation of further experience will determine the role of the sentinel node technique in patients with non-small cell lung cancer. (J Thorac Cardiovasc Surg 1999;117:220-4)

The prognosis of the patient with non-small cell lung cancer (NSCLC) is closely related to the pathologic stage of the disease, with the pattern of regional lymph node involvement a major determinant. Accurate staging information is therefore essential in developing therapeutic strategies. These data also provide patients with a realistic appraisal of prognosis so that they can plan for the future. Nonetheless, consensus is lacking in the thoracic surgical community with respect to the benefits associated with performing regional lymphadenectomy during lung resection. When mediastinal

lymph nodes are not routinely sampled or harvested, understaging can occur.¹

A technique for intraoperative mapping of the pattern of regional lymph node drainage for patients with a variety of solid tumors has been developed. Original investigators infiltrated peritumoral tissues with a lipophilic vital dye that spreads rapidly into the lymphatic channels. Experience with melanoma² and breast cancer³ demonstrated that selective dissection of the lymph node that stained first was accurate with respect to prediction of the statuses of more distant lymph node stations. This early-staining node has been referred to as the *sentinel lymph node*. Our group used this sentinel node lymphatic mapping technique in a group of patients undergoing lung resection for NSCLC to determine its accuracy and usefulness in these patients.

Patients and methods

Our study was carried out in a group of 36 patients with NSCLC, 23 men and 13 women with an age range of 48 to 74 years and a mean age of 60.1 years. The final histologic classifications were squamous cell carcinoma in 13 patients, adenocarcinoma in 19 patients, and other histologic type in 4

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Fig 1. Photograph of resected right upper lobe. Parenchymal blue dye is visible, as well as a blue-stained lymph node to the left of the bronchial stump. This sentinel node was tumor negative, as were all other lymph nodes in this patient.

patients. In addition to history and physical examination, all patients were evaluated before the operation by computed tomographic scanning of the chest and the upper abdomen to include the liver and the adrenal glands. No metastatic disease was found. Seven of these patients underwent cervical mediastinoscopy for paratracheal mediastinal lymph nodes with a diameter between 1.0 and 1.5 cm. No biopsy specimens revealed the presence of metastatic NSCLC. Five of the 7 were pathologically N0 and 2 had a pathologic N1 status. Results of final preoperative clinical staging were stage I in 29 patients and stage II in 7 patients.

The intraoperative techniques were similar for all patients. All operations were performed through a lateral thoracotomy, with or without a muscle-sparing approach. The incision was extended posteriorly for the 5 patients with involvement of the chest wall. In these patients a 3-rib segment of chest wall was resected in continuity with the lung and the primary tumor. The lung was collapsed as contralateral ventilation was continued through a double-lumen endotracheal tube. Visual and manual inspections of the lung and the mediastinum were performed. Except for the primary tumor, no significant abnormalities were seen in any patient. A total of 5 ml isosulfan blue dye was injected in divided doses into each quadrant of lung tissue immediately surrounding the tumor. The pleura was then circumferentially incised around the lung hilum and routine lung resection was carried out. Ultimately, lobectomy or bilobectomy was performed in 28 patients and pneumonectomy was performed in 8. At the completion of the lung resection, paratracheal (American Thoracic Society [ATS] level 4), subaortic (ATS level 5), subcarinal (ATS level 7), and inferior pulmonary ligament (ATS level 9) lymph node groups were

all resected en bloc. During performance of the lung resection the first lymph node to stain blue, if any, was considered the sentinel lymph node and sent separately for permanent histologic examination.

This study was approved by the Institutional Review Board of University Medical Center of Southern Nevada. Informed consent was obtained from the patients.

Results

Postoperative pathologic staging was as follows: (1) Twenty-one patients (58.3%) had stage I disease, T1 N0 M0 in 11 (30.6%) and T2 N0 M0 in 10 (27.8%). (2) Seven patients (19.4%) had stage II disease, T1 or T2 N1 M0 in 6 (16.7%) and T3 N0 M0 in 1 (2.8%). (3) Eight patients (22.2%) had stage IIIA disease, T2 N2 M0 in 4 (11.1%), T3 N2 M0 in 2 (5.5%), and T3 N1 M0 in 2 (5.5%).

A sentinel lymph node was found in 17 of the patients (47%). An example of the typical appearance of a sentinel node is shown in Fig 1. In 9 of these 17 cases neither the sentinel lymph node nor any other lymph node contained metastatic NSCLC, so nodal staging was N0. The sentinel nodes in the other 8 patients were positive for tumor. In 3 patients the sentinel or blue lymph node was either intraparenchymal or interlobar and contained metastatic tumor (N1 disease) but all mediastinal nodes were negative. Two of these 3 patients had a negative mediastinoscopic result. In 5 of the 17 patients the sentinel node was in the

36 Patients

Fig 2. Schematic depiction of results. Approximately half of the patients had a sentinel lymph node (SN) found. The final pathologic stages (*Path*) of all lymph nodes are given.

mediastinum, paratracheal in 3 and subcarinal in 2, and its examination documented unexpected N2 disease. No other lymph nodes containing metastases were found in any of these 5 patients.

In 19 of the patients (53%) no sentinel node was found despite a careful intraoperative search. Diffuse staining of the lung was observed, but no blue staining of mediastinal tissues was seen. Among these 19 patients, final lymph node pathologic evaluation was N0 in 13 cases, N1 in 5 cases, and N2 in 1 case.

These results are schematically depicted in Fig 2. In several patients mediastinal lymph nodes were sectioned before submission for histologic examination and blue staining of the central part of several nodes, which could not be detected on the node surface, was found.

Discussion

This initial experience with the use of isosulfan blue—which is lipophilic and is therefore quickly and selectively taken up by the lymphatic system—for intraoperative lymphatic mapping is encouraging. Sentinel lymph nodes could be found in only approximately half of the patients, but these results are consistent with early experiences with use of this technique in patients with melanoma or breast cancer. Increased experience has since resulted in detection of sentinel nodes in more than 90% of patients on a regular basis.^{2,3}

Two potential benefits of the sentinel node technique have emerged from these experiences. Previous investigators demonstrated that an upward staging of disease occurs when this selective lymphatic mapping technique is employed.⁴ It appears that allowing the pathologist to focus on either a single lymph node or relatively few nodes aids in finding micrometastases. With

only a single node to examine, the use of specialized techniques, including polymerase chain reaction and immunohistochemical tests directed toward appropriate antigens, may increase the ability to detect only a few metastatic cells.⁵⁻⁷ The second, and more controversial, benefit of this technique is its ability to predict a pathologic N0 staging status when no metastases are present in the sentinel node. If this hypothesis is valid, patients are spared more extensive lymph node dissection. If it is invalid, patients lose the potential benefits of lymphadenectomy.

In our experience the specificity was excellent. All 9 patients with tumor-negative sentinel nodes were found to have N0 disease on final pathologic examination after a systematic mediastinal lymphadenectomy. Interestingly, of the 19 patients without a sentinel lymph node found, 18 were either N0 or N1. Further experience will help to determine whether this is because of diffuse lymphatic drainage and therefore spread of the blue dye, so that in fact there is no true sentinel lymph node in some patients with lung cancer, or whether these results simply reflect the learning curve inherent with this technique. The goal in the case of patients with a tumor-negative sentinel lymph node is to use this information during the operation to guide the surgeon. If sufficient experience documents that frozen-section determination of sentinel node tumor status is a sufficiently accurate predictor of the status of mediastinal nodes, then additional lymph node sampling or dissection would not be necessary. We have begun obtaining frozen-section pathologic assessment of the sentinel node, both to determine overall accuracy and to document the reliability of frozen-section analysis, because this would be simpler than obtaining multiple frozen-section assessments of several lymph nodes.⁸

We did find unexpected N2 disease in 5 patients. Routine harvesting of all mediastinal lymph node groups would presumably have provided equally accurate staging information, but this is not a routine aspect of pulmonary resection operations for many, indeed probably most, thoracic surgeons. This may be because of the modest but real associated morbidity.¹ However, lymphadenectomy for staging, and arguably for therapeutic benefit, remains the gold standard for mediastinal staging.

We do believe that it is likely that sensitivity of this technique will improve in time, because surgeons showed a learning curve with this technique in melanoma and breast cancer.^{2,3} Further, accumulation of the blue dye in the central portion of lymph nodes implies that radioimmunologically guided techniques could add to the sensitivity, although that approach could also reduce the specificity by identification of a node that does not truly represent a predominant or exclusive lymphatic spread pattern.⁹ Evaluation of this option is necessary.

Acquisition of sufficient tissue to determine the status of both the N1 and N2 lymph node basins is an essential responsibility of the operating thoracic surgeon. Although therapeutic benefit arguably may result,¹⁰ the inarguable benefit relates to staging¹¹ because increasingly effective multimodal therapies are available for patients with N2 disease. With the knowledge that N1 node status does not reliably predict N2 node status,¹² either routine lymphadenectomy, lymph node sampling, or the sentinel node technique should be routinely employed.

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Discussion

Dr Douglas Wood (Seattle, Wash). Dr Morton and his colleagues introduced lymphatic mapping 8 years ago for melanoma, and it has quickly demonstrated its utility, primarily in such superficial malignancies as melanoma, breast, vulvar, testicular, and thyroid cancer. Unfortunately, lymphatic mapping has to date made little impression on the staging of visceral malignancies, for obvious reasons of accessibility of the tumor and its draining lymph nodes. Dr Little and colleagues are to be congratulated for their straightforward and elegant study examining the feasibility of the sentinel lymph node technique in NSCLC. To my knowledge this is the first presentation of lymphatic mapping for lung cancer. It is a well-constructed pilot study of 36 patients with apparent clinical stage I and II disease undergoing lymphatic mapping at thoracotomy with anatomic hilar and mediastinal lymph nodes dissections serving as each patient's control lymphatic staging. Some of the results are intriguing, with a 100% specificity seen in the 9 patients with a negative sentinel node. Other results were predictable, with 6 of 36 patients (17%) showing occult N2 disease, which is comparable to the published false-negative rate for chest computed tomographic staging of mediastinal lymph nodes in patients with lung cancer. One of the results was disappointing, with fewer than 50% of patients having a sentinel lymph node discovered. I agree with Dr Little that this low number will probably improve significantly with experience and with the addition of radioisotope mapping combined with the vital blue dye, as the teams experienced with this approach in melanoma and breast cancer have discovered. Unfortunately, however, because of the low rate of sentinel node identification, 6 of 36 patients (17%) had N1 or N2 positive nodes that were not discovered by lymphatic mapping.

Lymph node status certainly is the most important predictor of prognosis in patients with NSCLC, and this study is an important contribution that may take us another step toward accurate preoperative staging, for which even computed tomographic and positron emission tomographic scans have limitations. If we could reliably find and sample sentinel

lymph nodes *before* thoracotomy in patients with lung cancer, we could potentially avoid the morbidity associated with thoracotomy in patients with stage IIIA or IIIB disease who would not be expected to benefit significantly from surgical treatment, as well as directing these patients to appropriate clinical trials.

Dr Little, do you think that the future of this technique is computed tomography-guided tumor injection directing prethoracotomy lymph node sampling by mediastinoscopy, mediastinotomy, or thoracoscopy? Do you think that it will find a significant number of N2-positive nodes that would be missed by routine mediastinoscopy? What were the anatomic locations of the N2 nodes found by lymphatic mapping in your patients? In retrospect, do you think that the lymphatic mapping found N2-positive nodes that could not have been discovered by mediastinoscopy before thoracotomy?

Dr Little. I appreciate your comments, and among the benefits I hope for in presenting these early data to this group is that some of you will be intrigued and will go back and use it. That is certainly what happened with the melanoma and breast cancer patients and how a role for lymphatic mapping was eventually identified.

Taking your questions in reverse order, in the 5 patients with sentinel nodes that were in the mediastinum, 1 was subaortic, 2 were paratracheal, and 2 were subcarinal. None of those nodes would have been removed with a routine lobectomy. Depending on one's approach, whether simply performing lobectomy or going to the trouble of excising those lymph node stations, those nodes would or would not have been detected.

I think that the future is going to be interesting. I was exposed to this technique by a coauthor, Dr Kirgan, who was a coauthor with Dr Morton on his first paper. Not believing that we have a consensus for the ideal approach for intraoperative staging, I thought that the blue node technique was worth trying. I remain intrigued by it. Either the learning curve has to be a real phenomenon though, and we have to be able to detect sentinel nodes in considerably more than half the patients, or we need to add to the sensitivity with a radioimmunologically guided approach, which theoretically might increase the sensitivity but decrease the specificity. Looking at the sentinel node pathologically with more sensitive techniques than just the eyeball by staining for some of the tumor antigens that have been described in recent years might add to the sensitivity.

Dr Wood. I agree that those lymph nodes that you mentioned would not have been excised with a standard lobectomy or pneumonectomy. My question relates to 4 of those 5 that would have been easily sampled by mediastinoscopy. I wonder whether routine mediastinoscopy before thoracotomy would have discovered those lymph nodes, even without the sentinel lymph node technique.

Dr Little. I guess my position is that the key issue is that we stage the disease in our patients well, not so much how we stage it. It is worth pointing out, though, that results of mediastinoscopy were negative in 7 patients who had nodes seen on computed tomographic scan between 1 and 1.5 cm in diameter, and 2 of these patients had sentinel nodes that were different lymph nodes from those sampled in the mediastinoscopy. I think that these techniques are all complementary. These are computed tomographic scanning, positron emission tomographic scanning, and mediastinal node dissection. This is another technique that can be considered, depending on your approach right now to lymphatic mapping and staging. I hope that this approach can have a role in the future, particularly if the sensitivity data hold up so that if in fact there is a sentinel node that is tumor negative it can clearly be shown to accurately correlate with distant lymph nodes.

Dr Wood. One technical question that we have to deal with that the others doing sentinel lymph node mapping do not is whether anthracosis in intrathoracic lymph nodes causes a problem in identifying the blue node. Did you find that?

Dr Little. Yes. It seems as though everything is bluish gray. It is a little tricky, and it may turn out that this technique is not as good as one would like in this setting and for this patient population. When the node is there, though, there really is no question between blue and black; it is extremely clear.

Dr Wood. I congratulate you on this innovative and pioneering work. It is really intriguing, and I hope that it does give us some progress in staging the disease in our patients better.

Dr James B. D. Mark (*Stanford, Calif*). Certainly this is making good use of a technique that has been established in other areas. I want to look ahead to see what you are going to gain from it, however. You have made the point that systematic node dissection is really an important part of lobectomy and pneumonectomy in lung cancer, and only in some circumstances do I think that this technique is going to be worthwhile. If the negative sentinel node is really as good as you hope it is going to be but the patient has still had a thoracotomy, you have not saved much by preventing the node dissection. I think that the only way that this is going to be really important is if you can somehow use this or a similar technique to determine that a patient should not have a thoracotomy at all, otherwise I am afraid that we have not saved much.

Dr Little. I think that if everyone practiced thoracic surgery the way you do, that would be true, and in the setting in which a true mediastinal lymph node harvest is going to take place the value of this technique is limited. I suggest, however, that most practicing thoracic surgeons do not do what you do, or even come close to it. This technique is additive, it is complementary, it is another option. I do agree with you, however, that the benefit of this technique is limited if you are going to do a mediastinal node harvest in every patient.