Staging of Non-small Cell Bronchogenic Carcinoma*

Relationship of the Clinical Evaluation to Organ Scans

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Organ scans are generally performed on patients with bronchogenic carcinoma only when clinical evaluation is suspicious for metastases. However, it is not clear whether the clinical abnormalities will direct attention to the single organ which should be scanned, or if all three organs (bone, brain, liver) should be evaluated if any clinical abnormality is present. We investigated the use of triple organ radionuclide scanning and computerized tomography (CT) of the brain in the initial staging of patients with non-small cell bronchogenic carcinoma with no obvious metastases. Of 122 patients with newly diagnosed lung cancer, 53 met our criteria for further study. Thirty-three (62 percent) of these had at least one clinical abnormality suggestive of metastasis. Bone scanning detected metastases in seven (21 percent) and head CT in two additional patients (6 percent). Brain and liver scanning had no yield. In only five of these nine patients did the clinical abnormality direct attention to the organ with detectable metastases. Twenty of the 53 (38 percent) patients had a negative routine clinical evaluation, yet bone scanning showed metastases in three (15 percent). We concluded that clinical abnormalities are not specific for the organ in which metastases may be detected, so three scans (bone, liver, CT of the brain) should be obtained if there is any suspicion of metastasis based on history, physical examination, and laboratory tests. The value of bone scanning in clinically normal patients deserves further study.

The increasing incidence and poor five-year survival rates in lung cancer patients have made this neoplasm the number one oncologic problem in the United States.1 Seventy-five percent of lung cancers are non-small cell and are best treated by surgical resection.2 In localized (stage 1 or stage 2) non-small cell carcinoma, surgery results in a five-year survival rate of approximately 35 percent.3 Patients with metastases rarely survive five years, regardless of the therapy employed.4,4 In view of the 5-15 percent mortality associated with pulmonary resection, the latter group should not undergo lobectomy or pneumonectomy since survival will not be prolonged.5 Therefore, after diagnosing non-small cell bronchogenic carcinoma, a patient must be accurately staged to determine appropriate therapy and to provide information on prognosis. The first step in staging is to determine the presence (M1) or absence of (M0) of detectable metastases; the second step involves intrathoracic staging (T, N status).6

To determine the M status of patients, most authors have stated that a thorough history and physical examination with routine laboratory studies will detect almost all cases of distant metastases which multiorgan scanning (brain, bone, liver) would uncover.7-9 This approach is supported by the studies of Ramsdell et al10 and Hooper et al.11 However, these two groups reached somewhat different conclusions about which specific scan should be obtained when clinical abnormalities are present. Ramsdell et al found that the abnormality on clinical examination indicated which organ should be scanned (organ-specific scanning). Hooper et al concluded "signs and symptoms do not necessarily direct attention to the involved organ, so all scans should be used when metastases are suspected." In light of the modest number of patients in the studies by Hooper et al and Ramsdell et al, and the disagreement over which scan should be obtained in a given clinical situation, we have performed a prospective study to answer the following two questions: (1) does the clinical abnormality direct attention to the specific organ with detectable metastases (organ-specific scanning), or should all scans be obtained when any clinical abnormality is present? (2) what is the yield from multiorgan scanning in patients without clinical abnormalities?

This study was designed to compare clinical indicators of possible metastases with multiorgan nuclear scanning and computerized tomography (CT) of the

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head in patients with non-small cell bronchogenic carcinoma without obvious metastases at presentation.

METHODS

Patients

In the period from November, 1981 through February, 1984, there were 122 patients seen on a pulmonary consultation service with newly diagnosed bronchogenic carcinoma. Twenty-three of these patients had small cell carcinoma, and are not included in this analysis (Fig 1).

No attempt was made to further stage patients with extremely obvious evidence of unresectability on presentation. There were 32 such patients who presented with either: (1) palpable and/or visible evidence of extra-thoracic tumor as their chief complaint (eg, supraclavicular adenopathy, skin nodules, hard nodular liver), or (2) firm radiographic evidence of extrathoracic metastases demonstrated prior to discovery of the primary bronchogenic carcinoma. This latter group included cases where CNS abnormality had prompted a head CT showing metastases, or who had primarily complained of bone pain and had plain film abnormalities considered diagnostic of malignant bone metastases. Fourteen other patients were not included for the following reasons: died in hospital, three; time constraints or patient discharge, three; previous squamous cell carcinoma of head and neck, two; massive malignant pleural effusion, one; emergent surgery for hemoptysis, one; prior workup elsewhere, one. Thus, there were 53 patients included in our study of multiorgan scanning (Fig 1).

There were 40 men and 13 women. Ages ranged from 40-82, with a mean of 62 years. Cell types were: squamous, 21; adenocarcinoma, 20; large cell undifferentiated, 12.

Diagnostic Workup

All patients were seen by a pulmonologist who obtained a history and performed physical examination. Every patient had a CBC and complete blood chemistry study, including calcium and liver function tests. Non-organ specific clinical factors suggestive of metastases are indicated on Table 1, which is modified from Hooper et al. Organ-specific findings are defined in Table 2.

All 53 patients had bone and liver-spleen scans. Brain scans were performed in 51 cases. The use of head CT was added during the investigation, and 38 patients had head CT (including the two who missed brain scans).

Equipment and Technique

The radionuclide scans were accomplished using modern, state of the art, gamma cameras. The scans were done using a Picker 4/15 Dynacamera with either a ¼ inch crystal and 37 photomultiplier tube or a ¼ inch crystal with 61 tubes.

The bone scans were full length images done on a moving table, three hours after administration of 20 mCi (739 MBq) of $^{99m}$Tc-mdp. The liver scans were done with routine 2-second flow images and static scans done 90 minutes after injection of 20 mCi (739 MBq) of $^{99m}$Tc-glucopentonate. The liver-spleen scans were accomplished 15 minutes after injection of 6 mCi (222 MBq) of $^{99m}$Tc-sulfur colloid.

The computerized tomographic brain scans were done on a third generation, high resolution, GE 8800 scanner. All scans were done after intravenous contrast enhancement, utilizing 1 cm slice thickness at 1 cm increments through the brain.

Interpretation of Scans

Liverspleen scans were interpreted as positive for metastatic disease if there were single or multiple photopenic defects within the liver or spleen. Scans were also considered positive if correlated studies were recommended for questionable abnormalities such as "prominent porta hepatitis" or "prominent gallbladder fossa" or "probable rib impressions." All positive studies were followed by some combination of CT, ultrasound or liver biopsy to differentiate true from false positive liver-spleen scans. Patchy uptake of the radionuclide indicative of hepatocellular disease was considered negative for metastases.

The brain scans were called positive for metastatic disease if there were any abnormal areas of increased uptake or activity consistent with metastatic disease, or if corroborative studies were requested for confirmation of suspicious areas not diagnostic of metastatic disease.

The bone scans demonstrated abnormal uptake more commonly than the other examinations. Any scans with multiple nongeographic defects or areas of increased uptake were listed as true positive for metastatic disease if the abnormalities were not proven benign by additional studies. Any abnormal scan findings which required additional evaluation, such as plain film, CT scan, or biopsy, were also listed as positive for metastatic disease. However, if all bone scan abnormalities proved benign on further study, the scan was labeled false positive. If only one abnormality on scan had no explanation, the scan was indeterminant positive. Finally, if abnormalities were recognized as benign conditions on the scan themselves, such as obvious degenerative arthritic changes or traumatic aligned rib fractures, the scans were interpreted as negative for metastatic disease.

RESULTS

Overall Results (Fig 1)

Twelve of the 53 patients were found by scanning to have unresectable tumors. Ten cases had bone involvement, two had brain metastases, and none had documented liver metastases. No patient had documented metastases in two organs.

Thirty-three of the 53 patients had at least one clinical indicator suggestive of metastasis. Nine of these patients had documented metastases by scan-
Bone Scan Results (Table 3)

Results of 32 of 53 bone scans were positive, including ten true positive (31 percent), nine indeterminant positive (28 percent), and 13 false positive bone scans (41 percent).

Twenty patients had organ-specific clinical indicators suggesting possible bone metastases; five of these had true positive bone scans. There were three patients with true positive bone scans but all clinical factors negative. The clinical characteristics of the three patients with negative clinical evaluations but true positive bone scans are given in Table 4. Each patient had at least two bone scan abnormalities which showed lytic defects on the confirmatory study (bone CT or plain film). These were considered characteristic of bony metastases, and biopsies were not performed. Standard staging procedures, including history, physical examination, laboratory and chest x-ray film, gave no indication of unresectability. We performed chest CT and gallium scan in each case as part of a study to compare these two modalities for staging. As shown in Table 4, each of these three patients had a positive chest CT scan (a lymph node > 1.5 cm diameter). Thus, using chest CT these patients had clinical stage N1 disease; we do not have surgical/pathologic staging information on the mediastinum, since the patients were unresectable due to bone metastases.

In addition, two patients with bone metastases had no positive organ-specific indicators for bone, but did have other clinical abnormalities (non-organ specific): one had anemia, the other had weight loss (10 lbs), nausea and right upper quadrant pain. Therefore, use of organ-specific clinical factors to determine which patients needed bone scans would have missed five of ten patients detected on bone scan. Hence, the sensitivity of bone-specific clinical indicators was 50 percent (5/10) when compared to scanning, and the specificity was 65 percent (28/43) if we consider indeterminant positive scans as not indicative of metastases.

Liver Scan Results

Results of ten of 53 liver scans were positive, though none was thought highly characteristic of tumor. On

Table 4—Clinical Characteristics of Patients with Negative Clinical Evaluation and True Positive Bone Scans

<table>
<thead>
<tr>
<th>Age</th>
<th>Cell Type</th>
<th>T-Status</th>
<th>N-Status</th>
<th>CT</th>
<th>N-Status</th>
<th>Study Confiming Bone Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>Squamous</td>
<td>T1</td>
<td>N0</td>
<td>N1</td>
<td>N1</td>
<td>Bone CT</td>
</tr>
<tr>
<td>64</td>
<td>Adenocarcinoma</td>
<td>T1</td>
<td>N0</td>
<td>N1</td>
<td>N1</td>
<td>Plain films</td>
</tr>
<tr>
<td>51</td>
<td>Squamous</td>
<td>T1</td>
<td>N0</td>
<td>N1</td>
<td>N1</td>
<td>Bone CT</td>
</tr>
</tbody>
</table>

Figure 1. Outcome in 122 newly diagnosed patients with lung cancer. Results of scanning work-up are indicated as metastases present (M+) or metastases absent (M-).

Table 3—Bone Specific Clinical Indicators vs Bone Scan Results

<table>
<thead>
<tr>
<th>Clinically Positive</th>
<th>Clinically Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive scan</td>
<td>5</td>
</tr>
<tr>
<td>Indeterminant positive scan</td>
<td>3</td>
</tr>
<tr>
<td>False positive scan</td>
<td>6</td>
</tr>
<tr>
<td>Negative scan</td>
<td>6</td>
</tr>
</tbody>
</table>
further studies, all ten were judged to be false-positive. Thus, liver scanning had zero yield for metastases. Seventeen of the 53 patients had some liver-specific clinical indicator positive. However, since no metastasis was documented, the positive predictive value of liver-specific clinical indicators was zero (0/17).

CNS Scan Result

Four of 51 brain scans were interpreted as positive for metastases, though three of the four were only mildly abnormal. None of these three patients had positive neurologic findings, and all three had negative head CTs. These were interpreted as false positive brain scans. The fourth patient had no neurologic findings, a definitely positive brain scan, and a head CT showing a meningioma. Thus, brain scanning found no metastases.

Thirty-eight head CT scans were performed. Two patients had evidence of metastases: both had positive non-organ specific clinical factors (elevated alkaline phosphatase), but normal neurologic findings at presentation, and negative brain scans. Both had adenocarcinoma. Four other patients had unsuspected abnormalities on head CT, including the meningioma.

There were seven patients with CNS-specific clinical indicators positive, yet none of these had CNS metastases by any scan.

Discussion

The American Cancer Society has estimated that 139,000 new cases of lung cancer were diagnosed in the United States in 1983.1 Physicians practicing chest medicine must decide how to stage these cases in a cost-effective and expeditious manner. The scans and other staging procedures should be tailored to the individual patient, since every patient will not need every available staging study. If metastases are discovered, the patient is saved from an unnecessary surgical procedure (mediastinal exploration, thoracotomy). It is accepted that some number of “excess” scans and other studies will be performed for each patient found to have metastases; this is part of the cost incurred for the benefit of avoiding fruitless surgery. Two studies have been published which provide data on the yield of various scanning strategies in different clinical situations.8,10 Our study provides more data in this regard. We will conclude our discussion with suggestions for a staging workup based on our data and previously published reports.

Hooper et al10 reported 111 patients studied prospectively. All patients underwent liver, brain and bone scans. All cell types were included, and they did not mention exclusion for obvious metastatic disease. They concluded that: (1) all three scans should be ordered if there is any clinical suspicion of metastatic disease; and (2) “routine scanning . . . of patients with limited disease and without clinical evidence of spread does not identify a significant number of patients with unsuspected metastatic disease.”

Ramsdell et al10 performed the same three scans in 52 patients with a non-small cell bronchogenic carcinoma. They excluded patients who had obvious metastatic disease. They concluded that routine scanning was not indicated in patients “in whom the history, physical examination and serum chemistry give no evidence of metastases.” They further stated that the clinical abnormality pointed to the organ which was involved and should be scanned (organ-specific scanning).

Our study encompassed 122 patients with newly diagnosed lung cancer. We excluded 23 patients with small cell carcinoma, and saw no need to evaluate scanning in 32 patients who presented with obvious metastases. Eliminating the 14 who could not participate, we were left with 53 patients with non-small cell bronchogenic carcinoma without obvious metastases. This represented the patient population in whom the need for multiorgan scanning may arise.

We found 33 patients with clinical suspicion of metastases. Scanning documented metastases in nine of the 33 patients; however, in only five of the nine did the abnormality point to the organ involved (organ-specific). Our data support the conclusion of Hooper's group that clinical indicators of possible metastatic disease are not sufficiently organ-specific to justify limitation of scanning to clinically suspect organs.11

Our results further indicate that bone scanning may have a significant yield in patients without clinical indicators of metastases. We had 20 clinically negative patients and found three true-positive bone scans in this group. In each of these cases, the chest x-ray examination showed no mediastinal abnormality, but chest CT scans detected one lymph node >1 cm in the mediastinum of two patients, and several lymph nodes of this size in the third. Hence, the clinical-diagnostic (prethoracotomy) stage of each case was N0. We did not perform surgical-pathologic staging of the mediastinum since each case was already M1 (distant metastases). The false-positive rate for CT of the mediastinum is reported as 36 percent,12 so at our institution each patient would have undergone a mediastinal exploration prior to resection if bone metastases had not been found. These additional data on the mediastinum do not alter the finding that standard workup (history, physical examination, laboratory, and chest x-ray film) missed distant metastases in three of 20 clinically negative patients. Furthermore, some authors advocate neither CT nor mediastinal exploration in favorable operative candidates with normal mediastinum on chest x-ray,13 so these three patients might have undergone thoracotomy and even attempts at radical resection if the results from bone scanning were not availa-
This finding is at variance with the conclusions of both Hooper et al. and Ramsdell et al. Data from both studies showed a small yield on occult metastases detected by bone scanning; 1/14 (2.5 percent) and 2/49 (4 percent), respectively. Neither study found any occult metastases by liver or brain scanning. As noted earlier, these authors believed that this yield was too low to justify routine scanning in asymptomatic patients. Our finding of a 15 percent yield for discovery of occult bone metastases by bone scanning is not disproportionate compared to previously published results. The range in reported yields for bone scanning is probably due to a combination of random variation, use of different clinical criteria to suggest metastases, and different methods of patient selection. In view of our results and the earlier reports, we feel that the use of bone scanning in clinically negative patients may prove useful. However, a larger study will be needed to define the cost-benefit ratio before any firm recommendations can be made.

An unresolved issue is management of the patient whose bone scan shows only one unexplained abnormality (indeterminate positive). Corcoran et al. reviewed 172 cases where a solitary bone scan abnormality was present among 1,129 consecutive patients with various extraskeletal primary malignancies. Adequate data, including follow-up, were available in 90 cases: 32 were benign, 58 malignant. Among the 58 with malignancy, 21 (36 percent) became obvious only on follow-up, as the initial film did not show metastasis. We had nine patients with solitary unexplained bone scan abnormalities. Six of these patients were medically operable, but only one underwent resection; 3/6 had mediastinal nodes involved with tumor, one had tumor erode into the pulmonary artery and died, and one had metastasis on head CT. The remaining three patients were medically inoperable. Though no patient was denied resection of the primary carcinoma based on a solitary unexplained bone scan abnormality, in retrospect, the large burden of disease in these cases makes us suspect that many of the scan abnormalities were actually metastases. We believe this issue needs further investigation.

In our study, 51 brain scans detected no evidence of metastases and missed the two found by use of head CT. Both of these patients had normal neurologic findings at presentation, but a non-neurologic clinical indicator of metastasis was noted in each case (elevated alkaline phosphatase). This finding is in accordance with the conclusions of Hooper et al. concerning the nonorgan specificity of clinical abnormalities. It does not refute the findings of Ramsdell et al. that brain scanning has no yield if result of the neurologic examination is normal; instead, it confirms the poor sensitivity of brain scanning. Our findings point out the greater sensitivity of head CT in detecting cerebral metastases. Other authors have come to similar conclusions.

Lusin et al. reported 30 patients with various tumors who had brain metastases by head CT; only 23 were positive by brain scans. Jacobs et al. studied 50 patients with lung cancer who were neurologically normal. Every patient had a brain scan and a head CT. Three patients showed brain metastases by CT, but none was detected by brain scan.

More recently, Hooper et al. reported that 7/16 patients with lung cancer and abnormal head CT scans had normal neurologic findings. Each of these seven patients had at least one non-neurologic clinical abnormality to suggest metastasis.

We did not find liver scans to be at all useful in 53 cases without obvious metastases. This may be due to the low incidence of detectable liver metastases at presentation in non-small cell carcinoma. Margolis et al. performed liver scans and peritoneoscopy with biopsy in 92 patients with non-small cell lung cancer; only two had liver metastases. Another problem is the inability of liver scans to detect lesions less than 2 cm in diameter. Furthermore, all cases of liver metastases seen during the study period occurred among the 32 patients who had obvious metastases at presentation, reflecting the advanced stage of disease in patients with large (2 cm) liver metastases.

When our 85 evaluable patients with non-small cell bronchogenic carcinoma are viewed as a group, it is apparent that most detectable metastases are obvious at presentation. Thirty-two of 85 (38 percent) patients had obvious metastases, including most cases of CNS spread and all cases of liver tumor seen during the study period. In these 32 patients, the chest x-ray examination revealed the primary when the extrathoracic metastasis had already drawn attention to itself with such presentations as seizures or severe bone pain with confirmatory radiographic studies. Further workup with multiorgan scanning in the remaining 53 patients detected an additional 12 cases of metastases. Overall, 41/85 (48 percent) patients were found to be free of metastases prior to detailed intrathoracic staging (for T, N status). This is comparable to most published studies on the fate of patients with newly diagnosed lung cancer.

We have not addressed the problem of the true incidence of metastases in these patients. Based on the 35 percent five-year survival in patients resected for cure, it is obvious that many metastases are subclinical at time of presentation. Our study defined the presence or absence of metastases based on organ scanning and ancillary studies (eg, plain film, CT, biopsy). Until more sensitive and specific indicators of metastasis are developed, this approach will remain the standard for clinical practice despite its inadequacies.
In conclusion, we studied 53 patients with non-small cell bronchogenic carcinoma without obvious metastases. We found that the clinical abnormality which was present did not necessarily direct attention to the organ in which metastases were found. Bone scanning had the greatest value in detecting metastases, even in clinically negative patients (15 percent yield). Head CT was useful in clinically positive patients even if neurologic examination was normal. Brain and liver scanning were not useful in our limited patient population.

Based on our data and the earlier reports, we recommend the following diagnostic work-up to determine the M status of patients having non-small cell bronchogenic carcinoma without obvious metastases:

1. Perform history, physical examination, and order routine laboratory studies and chest x-ray films.
2. If no clinical indicators of malignancy are present, no further scanning studies are mandatory. Bone scanning may have some value in this situation, but more data are needed to determine the yield and cost/benefit ratio.
3. If any clinical indicator is positive, a bone scan and a head CT should be done first. If negative scan results are obtained, a liver scan should be ordered.
4. If all studies are negative for metastases (M status), proceed with intrathoracic staging (T, N status).

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