Intracranial Metastases in the Initial Staging of Bronchogenic Carcinoma

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We evaluated the effectiveness of neurologic examination, electroencephalography (EEG), and computed tomography (CT) in the initial staging of patients with nonsmall cell carcinoma. Eight of 66 patients had evidence of intracranial metastases. Three of these had no other metastases and would otherwise have been surgical candidates. Thus, thorough investigation for evidence of intracranial metastases is warranted at the time of initial staging. The CT proved to be more effective than clinical evaluation or EEG, alone or in combination, in detecting intracranial metastases. The CT screening of patients prior to curative resection should increase the success rate for such procedures by eliminating patients with preexisting metastases.

Despite advances in radiotherapy and in chemotherapy, surgical resection represents the only real chance for long-term survival of the patient with nonsmall cell carcinoma of the lung. Candidates for curative procedures must be free of metastases, yet, in patients thought to have resectable tumors, the cure rate approximates only 25 percent. The CNS represents a frequent site of metastatic disease. Brain metastases are present in 17 percent to 38 percent of non-small cell lung carcinoma patients at autopsy.1 So far, no consensus exists as to the appropriate form of preoperative evaluation to exclude this possibility. If the patient presents with obvious signs or symptoms referable to the CNS, as approximately 10 percent of patients do, the question is debatable. The asymptomatic patient presents a more difficult problem. The current study was undertaken to investigate the best method of staging patients with newly diagnosed bronchogenic carcinoma. Skull roentgenography, radionuclide (RN) brain scanning, computed tomography (CT) of the head, electroencephalography (EEG), as well as neurologic examination have been used to detect brain metastases. Skull roentgenography is of limited value and has generally been discarded as a screening test. Prior to the advent of CT, the radionuclide brain scanning was considered to be the best method for the detection of brain metastases. The RN brain scanning rarely produces false positives, but can miss small lesions.14 The reported incidence of positive RN scans in asymptomatic lung cancer patients ranges from 0 percent to 7 percent.7 Although early studies comparing CT with RN scanning showed them to be of equal efficacy, more recent studies have demonstrated the increased sensitivity of CT. Lusins et al4 examined 32 patients with known brain metastases and found nine falsely negative RN scans, while only two CT scans were falsely negative. Similarly, Jacobs et al5 examined 50 patients with negative RN scans and no symptoms of CNS disease and found three patients to have metastases. Since RN scanning cannot add to the yield of CT scanning in identifying intracranial metastases,6 it was not included in this study.

In a retrospective analysis of 23 patients with lung carcinoma, Rowan et al6 found the EEG useful in detecting brain metastases. In 13 of the 14 patients found to have evidence of supratentorial lesions, the EEG was diagnostic. The other patient was found to have multiple metastases, but none larger than 1.5 cm in diameter. The 13 patients with diagnostic EEGs had lesions 2 cm or larger in diameter at autopsy. Three EEGs were considered positive in the group of ten patients without metastases at autopsy. In a retrospective review of 116 patients with intracranial mass lesions, Culebras et al10 found the CT diagnostic in 90 percent of the patients examined and the EEG diagnostic in only 60 percent, but 6 percent of the patients had positive EEGs and negative CT scans. Bolles et al11 studied clinically apparent metastases in patients with carcinoma of the lung and concluded that RN scan was more effective than the EEG in identifying metastases. However, some patients had normal RN scans but abnormal EEGs.12 The EEG appears useful in detecting CNS metastases. Though not as sensitive or specific as the CT scan, it is noninvasive and readily available and is included in the present study.

The purpose of the current study is first to determine if it is necessary to specifically evaluate the CNS for evidence of metastases in staging patients with newly diagnosed bronchogenic carcinoma. Secondly, by comparing the relative and combined efficacies of

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neurologic examination, EEG and CT in the preoperative evaluation of lung cancer patients the best method of evaluation will be determined.

METHODS AND MATERIALS

Between June 1, 1962, and May 1, 1963, 79 patients admitted to the Beth Israel Medical Center came to the attention of the Pulmonary Division because of a newly diagnosed lung mass, thought to represent carcinoma. These patients were evaluated by percutaneous needle aspiration, or bronchoscopic or open lung biopsy. If a malignancy was found, a metastatic workup, including a radionuclide bone scan, chest and abdominal CT scan, as well as a head CT scan and EEG, was performed. Cranial CT was obtained with a scanner unit with 10 mm scan thickness. All studies except two were carried out with intravenous injection of 150 ml (42.3 g) iodine. In some cases, precontrast CT scans were obtained. When indicated, follow-up study was pursued. Medical histories and neurologic evaluation were obtained on each patient by one of us (B. J. M. or S. T.). Each patient was classified as neurologically intact, showing signs or symptoms referable to previous CNS pathology, or showing signs suggestive of intracranial metastases. The EEG was read without knowledge of any of the other findings, as was the head CT scan.

RESULTS

Four patients were excluded from consideration because they left the hospital prior to the completion of their evaluation. A fifth died before the evaluation could be completed. Three patients were excluded because they were found not to have pulmonary malignancies. A patient with carcinoid tumor was also excluded. Of the remaining 74 patients, four were found to have small cell carcinoma and three patients' tumors could be classified only as poorly differentiated. Since surgical intervention was not contemplated in the small cell carcinoma patients, they were not considered further.

In the remaining 66 patients, intracranial metastases were found on CT scan in eight. One asymptomatic patient was found to have a cerebellar lesion adjacent to

Table 2—Medical History and Physical Exam*

<table>
<thead>
<tr>
<th>Diagnosis of metastatic disease made on the basis of history and physical examination</th>
<th>CT Evidence of Metastases</th>
<th>No CT Evidence of Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal neurologic examination</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Normal neurologic examination</td>
<td>5</td>
<td>58</td>
</tr>
</tbody>
</table>

*χ² (corrected for continuity) = 18.7 (p < 0.001).

The tentorium cerebelli which may have been a meningioma. Since the patient had other evidence of extrapulmonary metastases, no further evaluation was pursued. Five of the eight had normal clinical neurologic examinations (Table 1). Two of these five had abnormal EEGs, one showed focal slowing ipsilateral to the lesion on CT scan, the other showed bilateral cerebral dysfunction. Only two of the three patients with abnormal neurologic examinations had complained of symptoms referable to their intracranial lesions prior to examination. Two of the six asymptomatic and none of three symptomatic patients had evidence of extracranial metastases (Table 2).

Three of the patients with single metastatic lesions on CT scan had focally abnormal EEGs (Table 3). All abnormalities were on the side of the lesion. The one patient with two lesions, both in the right parietal region, had evidence of bilateral cerebral dysfunction on EEG. Four patients with a lesion on CT scan had a normal EEG, while 11 patients with abnormal EEGs had no metastatic brain lesion.

Patients with CT evidence of metastases could be reliably distinguished from those who did not on the basis of history and neurologic examination, but not by EEG (Table 4).

DISCUSSION

This study is unique in that an unselected group of newly diagnosed lung cancer patients was evaluated by a neurologist as well as by CT and EEG (Table 5). Two of the eight patients found to have intracranial metastases came to medical attention at least in part because of symptoms referable to their brain lesions. Their metastases would have been diagnosed prior to surgery. However, of the 66 patients evaluated, five (8 percent) asymptomatic patients with brain metastases evident on CT scan and a sixth who may have had a metastasis were identified. This is a slightly higher percentage than has been reported previously. 6, 11 Three patients had no other evidence of metastatic

Table 3—EEG Results

| Focal abnormal EEG | 3 | 2* |
| Focal abnormal EEG | 1 | 1* |
| Normal EEG | 4 | 3* |

*Low density nonenhancing lesion consistent with CVA.
†Hydrocephalus with mild cerebral atrophy.

Table 4—Diagnosis by EEG*

| Abnormal EEG | 4 | 11 |
| Normal EEG | 4 | 36 |

*χ² (corrected for continuity) = .0015 (p > 0.10).
Asymptomatic
Left
Asymptomatic
Right
Dysfunction
Metastasis
Right
Symptomatic
Right
Asymptomatic
Asymptomatic
Symptomatic
Asymptomatic
Focus

Table 5—Patient Summary

<table>
<thead>
<tr>
<th>Patient</th>
<th>Neurologic Evaluation</th>
<th>EEG</th>
<th>CT Scan</th>
<th>Histology</th>
<th>Extracranial Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic neurologic exam within normal limits</td>
<td>Left temporal delta-wave focus</td>
<td>Left frontal lobe metastasis</td>
<td>Adenocarcinoma</td>
<td>Absent</td>
</tr>
<tr>
<td>2</td>
<td>Asymptomatic neurologic exam within normal limits</td>
<td>Normal</td>
<td>Right frontal lobe metastasis</td>
<td>Adenocarcinoma</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>Asymptomatic neurologic exam within normal limits</td>
<td>Normal</td>
<td>Right cerebellar mass</td>
<td>Adenocarcinoma</td>
<td>Present</td>
</tr>
<tr>
<td>4</td>
<td>Asymptomatic neurologic exam within normal limits</td>
<td>Normal</td>
<td>Left parietal lobe metastasis</td>
<td>Poorly differentiated large cell carcinoma</td>
<td>Absent</td>
</tr>
<tr>
<td>5</td>
<td>Asymptomatic neurologic exam within normal limits</td>
<td>Bilateral cerebral dysfunction</td>
<td>Two right parietal lobe metastases</td>
<td>Squamous cell carcinoma</td>
<td>Present</td>
</tr>
<tr>
<td>6</td>
<td>Symptomatic right hemiparesis aphasia</td>
<td>Left cerebral dysfunction</td>
<td>Left frontoparietal metastasis</td>
<td>Adenocarcinoma</td>
<td>Absent</td>
</tr>
<tr>
<td>7</td>
<td>Symptomatic left homonymous hemianopsia</td>
<td>Right cerebral dysfunction</td>
<td>Right occipital metastasis</td>
<td>Adenocarcinoma</td>
<td>Absent</td>
</tr>
<tr>
<td>8</td>
<td>Asymptomatic ataxic gait left upper and lower extremity hyperreflexia</td>
<td>Normal</td>
<td>Right cerebellar metastasis</td>
<td>Adenocarcinoma</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Disease and would have been considered candidates for surgical resection. Clinical neurologic evaluation identified one of these patients, the EEG was focally abnormal in a second, but one patient's metastases would have been unrecognized without CT scan. No patient with a normal CT scan had a symptom or focal abnormality on neurologic examination which could not be accounted for on the basis of previous history. Two patients had focally abnormal EEGs with no history to explain their findings and a normal clinical evaluation and CT scan. Follow-up at one year failed to disclose symptoms referable to the CNS. Within the limits of the study design, CT scan appears not to have missed any intracranial lesions identified by other methods.

The findings that three of 66 patients had metastases only to the brain and that two of these had normal neurologic examinations suggest that careful evaluation of the CNS should be included in the initial staging of the patient with bronchogenic carcinoma. The combination of neurologic examination and EEG appears to do this effectively, but routine CT scanning of the head with contrast enhancement may be the most effective and efficient way to evaluate the patient. The CT scanning will detect abnormalities when EEG and neurologic examination are normal as was seen in this study and can elucidate the nature of other lesions which may produce findings mimicking metastases on EEG and neurologic examination. In the event that a CT scanner is not available, staging with detailed neurologic evaluation and EEG is warranted, with referral of all patients with positive findings for CT scan. In rare instances, angiography or biopsy may be necessary. Following such a protocol would probably result in a higher success rate for curative thoracotomy since some patients with already definable metastases would be identified prior to surgery. Patients so identified would be saved the attendant risk, cost and discomfort.

References
5. Gutierrez SC, Vincent BG, Bakshi L, Tahita H. Radioisotope scans in the evaluation of metastatic bronchogenic carcinoma. J

Intracranial Metastases in Staging of Bronchogenic Carcinoma (Mintz et al)
Big Sky Pulmonary/Ski Conference

The American Lung Association of Montana will present this course February 20-23 at the Big Sky of Montana resort, located near Bozeman. For information, contact Mr. Earl W. Thomas, 825 Helena Avenue, Helena, Montana 59601 (406:442-6556).

2nd International Symposium: Current Topics in Infectious Diseases

The University of California, San Francisco, will present this symposium in Grindelwald, Switzerland, February 9-16. For information, contact: Extended Programs in Medical Education, University of California School of Medicine, Room 569-U, San Francisco 94143 (415:666-4251).

References:
6 Bolles F, Patten DH, Howe P. Correlation of brain scan results with neuropathological findings. Lancet 1973; 1:1143-46
8 Jacobs L, Kinkel W, Vincent R. Silent brain metastases from lung carcinoma determined by CT. Arch Neurol 1977; 34:990-93