Search for a Primary Lung Neoplasm in Patients with Brain Metastasis: Is the Chest Radiograph Sufficient?

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OBJECTIVE. We assessed whether chest CT provided an advantage over chest radiography when diagnosing a primary lung neoplasm in a selected group of patients.

MATERIALS AND METHODS. From a retrospective evaluation of 925 patients who had a discharge diagnosis of brain metastasis, we identified 32 patients who presented without a known primary tumor site and who were investigated subsequently with both chest radiography and CT. Reports of chest radiographs were classified as showing a primary lung neoplasm (positive), as abnormal but nonspecific, or as negative. Patients were categorized as having negative chest radiograph, negative CT; positive chest radiograph, positive CT; nonspecific chest radiograph, positive CT; or negative chest radiograph, positive CT. Radiographic technique and clinical and lesion characteristics were compared among these categories.

RESULTS. We found negative chest radiograph and negative CT in one patient who ultimately proved to have breast cancer. The remaining 31 patients (97%) had primary lung carcinoma. In 19 (59%) of the 32 patients, chest radiographs and CT were positive. Twelve patients (38%) had a nonspecific or negative chest radiograph and positive CT. In the 31 patients with lung carcinoma, the mean diameter of lesions in patients with positive chest radiographs was 4.2 cm, compared with 2.5 cm in patients with normal or nonspecific radiographs ($p < .01$).

CONCLUSION. Lung cancer is by far the most common cause of a de novo presentation with brain metastasis. Chest CT is valuable to supplement chest radiography in patients with metastatic brain disease in whom a primary lesion is sought. Lesion size appears to be the most important determinant of detectability of a primary tumor on chest radiographs.

Metastasis to the brain is a frequent occurrence in patients with lung cancer [1]. Development of brain metastases in patients with lung cancer has been regarded as a poor prognostic sign because the disease has been considered unresectable [1]. Recently, a more aggressive surgical approach and newer radiotherapy techniques have raised the possibility that a cure of both the primary lung neoplasm and the brain metastases might be achieved in some instances [2–12]. Therefore, it is increasingly important to distinguish individuals with a primary lung neoplasm from those whose tumor originates at another site.

For patients whose brain metastasis is the initial manifestation of tumor, a chest radiograph is the first, and often only, technique used to assess for a primary lung carcinoma. If the chest radiograph fails to provide an unequivocal diagnosis and the patient is a candidate for a curative resection, a chest CT can be obtained. However, it is uncertain whether CT is any more likely than the chest radiograph to identify the lesion if the chest radiograph is equivocal or normal.

To determine whether chest CT provides meaningful information that is not obtained by chest radiography in this setting, we evaluated both of these studies in 32 patients who presented de novo with a metastatic brain tumor.

Materials and Methods

We obtained a computerized list from our medical records department of all patients with a discharge diagnosis of brain metastasis who presented to our institution between 1991 and 1995. The names of 925 patients who were thus identified were entered into our radiology information system. The following criteria were used to identify patients who had an initial presentation with symptomatic brain metastasis: the patient underwent a head CT or MR imaging study at our institution as part of the initial evaluation of CNS symptoms in the absence of other systemic clinical symptoms (i.e., patients referred from outside institutions were excluded), cross-sectional imaging of the brain showed one or more lesions that were judged to be suggestive of metastatic disease, and no prior neoplasm was documented.

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Eight hundred eighty-six patients were excluded using these criteria. The most common reason for exclusion was that the patient had a known primary neoplasm, most often lung carcinoma, at the time of presentation with a brain metastasis. Approximately 10% were excluded because their initial evaluation was done at an outside institution. Finally, several patients appeared on our list erroneously who did not have a brain lesion.

Of 39 patients who were identified using our three criteria, four were excluded because histopathologic examination ultimately revealed a primary brain neoplasm (n = 3) or multiple sclerosis (n = 1) and no extracerebral primary neoplasm. The remaining 35 patients had histopathologic proof of metastatic brain disease (n = 19) or histopathologic proof of an extracerebral primary carcinoma and strong evidence on imaging studies of brain metastasis (i.e., one or more brain masses associated with marked edema of the white matter) (n = 16). Three patients, all of whom had a primary lung carcinoma that was evident on chest radiographs, were excluded from our analysis because no chest CT was performed at our institution as part of the initial evaluation. The remaining 32 patients constituted the final study population.

For each study patient, the chest radiograph obtained at presentation was interpreted without knowledge of the chest CT result. The presence on cross-sectional imaging of the brain of a brain tumor or suggestive CNS symptoms was known to the radiologist who read the initial chest radiograph of 20 patients. In 12 instances, the clinical history supplied by the referring physician was unrelated (e.g., rule out pneumonia). Posteroanterior and lateral radiographs were obtained for nine patients and anteroposterior radiographs for 23 patients. Fourteen of the anteroposterior radiographs were bedside portable studies.

The report of the initial chest radiograph was reviewed to determine whether a primary lesion was identified by the original radiologist. Reports were classified as being definite (positive) for malignant disease if the official report described a mass or other abnormality for which a neoplastic cause was considered possible or likely. Reports in which an abnormality was described but was not considered by the original radiologist to be suggestive of malignant disease (e.g., infiltrate, subsegmental atelectasis) were designated as nonspecific. Reports for which no substantial parenchymal abnormality was described were categorized as negative. Any description of hilar or mediastinal lymphadenopathy and metastatic disease was documented. All available initial chest radiographs that were classified as negative were reviewed by two thoracic radiologists to ascertain whether a primary lung neoplasm was evident in retrospect.

Chest CT was performed a median of 2 days (range, 0–50 days) after both cross-sectional imaging of the head and the initial chest radiograph. Only one chest CT was obtained more than 2 weeks after the initial radiograph. The largest number of chest CT studies (n = 13) were obtained on a HiSpeed Advantage scanner (General Electric Medical Systems, Milwaukee, WI). All other examinations were done on Prospeed, Sytec, and 9800 scanners (General Electric Medical Systems) or HiQ and DRH scanners (Siemens, Iselin, NJ). Scan collimation was 5-mm-thick sections through the hila and 10 mm elsewhere in 22 patients and 10-mm-thick sections throughout the chest in 10 patients. Twenty-three patients received IV contrast media.

Each chest CT report was reviewed to determine if a primary lesion was shown. Because histopathologic confirmation was not available for both the primary lesion and the brain metastasis in all patients, a lesion was categorized as a primary lung tumor if one of the following criteria was met: Lung biopsy or surgery revealed malignant cells diagnostic of a primary lung neoplasm and initial and subsequent evaluation of other organs showed no lesion that could be interpreted as a primary lesion, or imaging characteristics (e.g., large size, marked spicules, absence of other extracerebral primary tumor) were typical of a primary lung carcinoma in the setting of brain biopsy that showed a metastatic lesion with a cell type consistent with a primary lung carcinoma.

The CT reports also were reviewed for the size and location of any primary tumor and the presence of mediastinal or hilar lymphadenopathy and intrathoracic or upper abdominal metastases. Mediastinal lymph nodes were judged to be enlarged and potentially involved with tumor if the short axis diameter of at least two nodes exceeded 1 cm. All available CT scans were reviewed by two thoracic radiologists.

The medical record of each patient was reviewed to determine patient age and sex, symptoms at presentation, smoking history, method of diagnosis of the brain and lung lesions, cell type of the tumor, and whether other organ systems were examined to assess for neoplastic involvement. Patients were categorized on the basis of reports of chest radiographs and CT into patients in whom no lesion was identified on either study (category 1), patients in whom both studies revealed a primary lung carcinoma (category 2), patients in whom the chest radiograph was nonspecific but a lesion was found on CT (category 3), and patients in whom the chest radiograph was negative and a lesion was revealed on CT (category 4).

For patients in categories 2–4, we analyzed whether radiographic technique (anteroposterior versus posteroanterior and lateral) or clinical history (relevant versus noncontributory) was related to the likelihood of detecting the primary lesion on the chest radiograph. For each category, the mean diameter of the primary lesion was calculated from the average of two representative perpendicular diameters. If more than one lesion was present, the largest lesion was measured. The lobar location and location with respect to the hilum (central versus peripheral) were also documented. We also assessed whether CT showed

TABLE 1 Categorization of Patients with Brain Metastases by Chest Radiography and CT Results

Variable	Category 1: Negative CXR/ Negative CT	Category 2: Positive CXR/ Positive CT	Category 3: Nonspecific CXR/Positive CT	Category 4: Negative CXR/ Positive CT
Number of patients	1	19	4	8
Anteroposterior radiographs only	0	13	3	7
Relevant history provided	0	12	2	4
Diameter (range) of lesion (cm)	NA	4.2 (1.2–7.0)	2.7 (1.5–4.5)	2.4 (1.0–3.7)
Lobar location of lesion (number)				
Right upper lobe	NA	9	1	2
Right middle lobe	NA	2	1	0
Right lower lobe	NA	0	1	2
Left upper lobe	NA	4	0	3
Left lower lobe	NA	4	1	1
Peripheral lesions	NA	17	3	6
Cell type of primary tumor (number)				
Breast	1			
Lung adenocarcinoma		8	1	5
Squamous cell lung carcinoma		5		
Non–small cell lung carcinoma		4	1	1
Small cell lung carcinoma		1	2	
Large cell lung carcinoma		1		2

Note.—CXR = chest radiography, NA = not applicable.

mediastinal adenopathy or metastasis that was not evident on the chest radiograph.

Fisher's exact theorem was used to test for whether a significant difference existed between proportions. The Student's *t* test was used to test whether a significant difference existed between means.

Results

The 32 patients who constituted the final study population consisted of 25 men and seven women. Their mean age was 57 years old (range, 44–84 years old). Thirty patients were smokers at the time of presentation. The most common presenting complaint was seizure. Other initial symptoms included syncope, headache, weakness, and nausea and vomiting. In one patient, neither chest radiography nor CT showed a primary lesion (category 1). Breast cancer was detected on mammography and ultimately confirmed at biopsy.

Among the remaining 31 patients (97%), all proved to have primary lung carcinoma that was shown on CT (Table 1). Nineteen (61%) had a primary lesion on both the chest radiograph and CT (category 2). Details of radiographic technique, clinical history (relevant or irrelevant), and the location of these tumors in the lung are provided in Table 1. Average diameter of these lesions was 4.2 cm (range, 1.2–7.0 cm).

In four patients (13%), the interpretation of the chest radiograph was classified as nonspecific although the CT scan showed a definite primary lesion (category 3) (Fig. 1). The abnormality was described as an infiltrate or area of atelectasis in three patients, and a tentative suggestion of left hilar enlargement was made in one patient. Data regarding radiographic technique, clinical history, and the location of these tumors in the lung are provided in Table 1. Average diameter of lesions in this group was 2.7 cm (range, 1.5–4.5 cm).

In the remaining eight patients (26%), the radiologist did not describe seeing a lesion on the initial chest radiograph, although CT showed a primary lung carcinoma (category 4) (Figs. 2 and 3). A posteroanterior radiograph was obtained in one patient and anteroposterior radiographs in seven patients. Details of radiographic technique, clinical history (relevant or irrelevant), and the location of these tumors in the lung are provided in Table 1. Average diameter of lesions in this group was 2.4 cm (range, 1.0–3.7 cm).

Among these eight patients (category 4), six radiographs were available for retrospective evaluation. The tumor was visible in retrospect in four patients (Fig. 3). Presumed reasons for the failure to diagnose these carcinomas were overpenetration of the radiograph in two patients and superimposition of the lesion on the first costochondral junction and projection of the tumor over left hilum in one patient each. In one patient with an overpenetrated radiograph, two lesions were overlooked.

We assessed several factors that might have contributed to the relatively high incidence of failure to diagnose a primary lesion on chest radiography. In particular, we evaluated whether the type of radiographic examination (posteroanterior and lateral or anteroposterior radiograph), the historical information that was provided by the referring physician, and the characteristics of the lesion itself influenced the likelihood of identifying a primary tumor.

A posteroanterior and lateral chest radiograph is preferable to an anteroposterior radiograph, but many of our study patients had neurologic symptoms or were otherwise too debilitated to cooperate with the technologist. Among patients who proved ultimately to have primary lung carcinoma, most (74%) underwent anteroposterior radiographs. Anteroposterior radiographs were obtained in only 13 (68%) of 19 patients with a primary lesion that was evident on chest radiographs (category 2) and 10 (83%) of 12 patients with negative or nonspecific radiographs (categories 3 and 4), respectively ($p > .05$). Thus, we found no significant difference between the groups with respect to radiographic technique.

We analyzed whether the historical information that was provided to the initial radiologist was relevant to presenting symptoms. Among patients with primary lung carcinoma, a history of neurologic symptoms or brain tumor was supplied to the radiologist in 12 (63%) of 19 patients with a positive chest radiograph and six (50%) of 12 patients with a negative or nonspecific

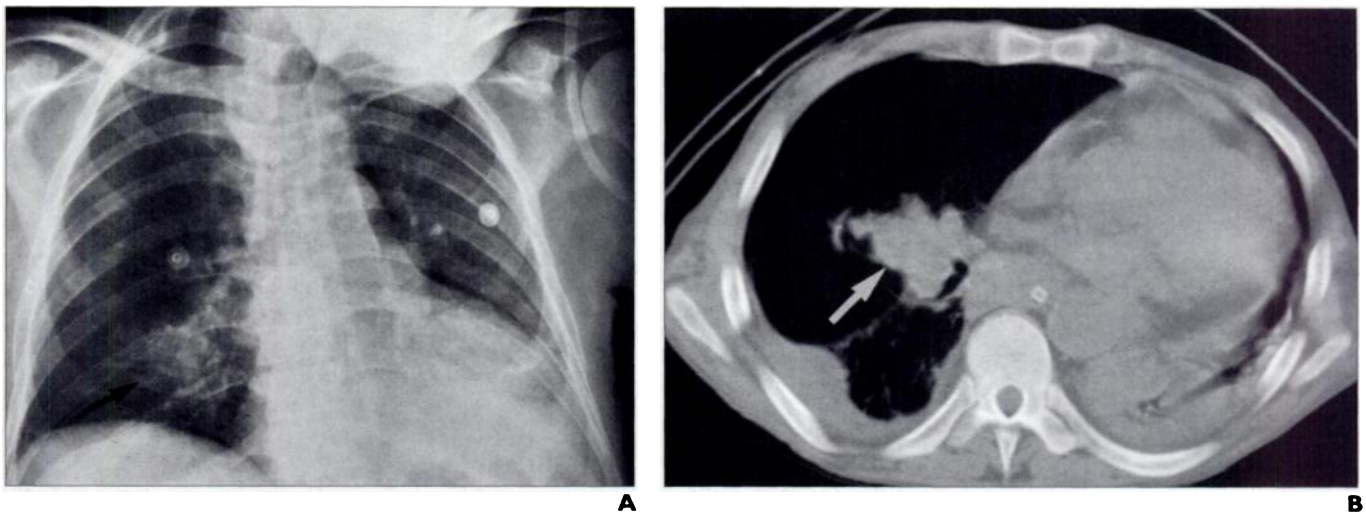

Fig. 1.—69-year-old man with primary lung carcinoma evident on CT who had nonspecific abnormality on chest radiograph.
A, Chest radiograph shows density in right lower lung (*arrow*) that was initially interpreted as area of atelectasis or pneumonia. Note consolidation at left base.
B, CT scan reveals right hilar mass (*arrow*) that corresponds to area of atelectasis and pneumonia on **A**. Note consolidation of left lower lobe. At bronchoscopy (not shown), mass proved to be lung carcinoma. Consolidation of left lower lobe was presumed due to aspiration pneumonia.

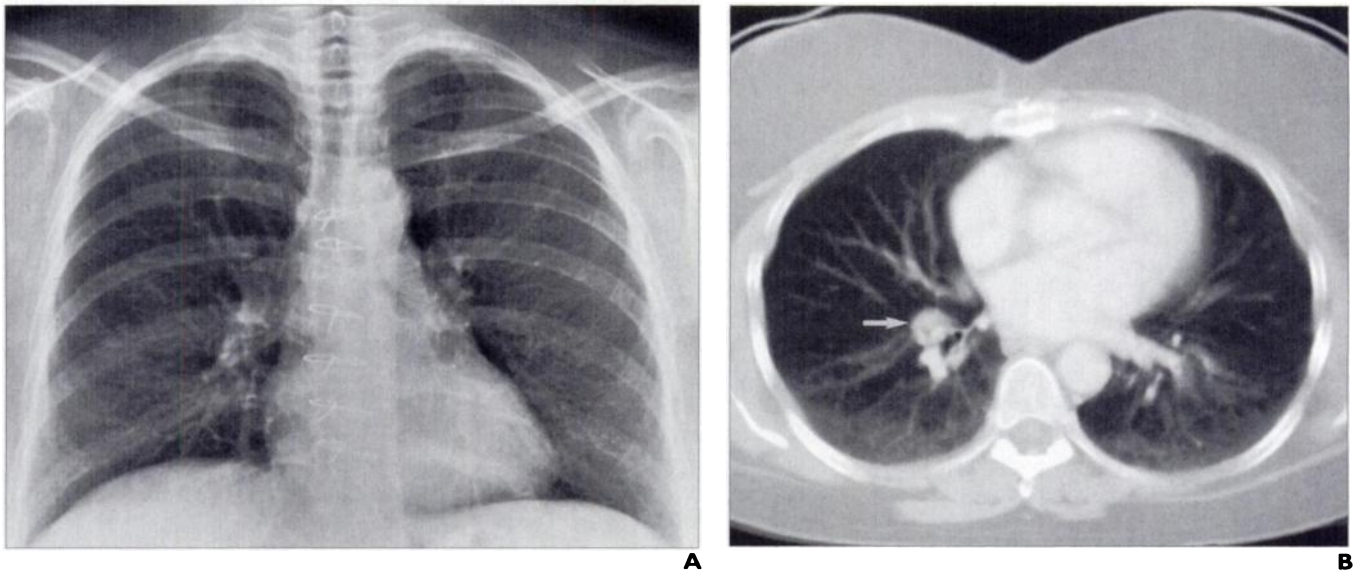

Fig. 2.—54-year-old man with primary lung carcinoma found on CT who had negative chest radiograph.
A, Anteroposterior chest radiograph shows no abnormality and was reported as negative.
B, CT scan reveals 1.7-cm lesion (*arrow*) in right lower lobe anterior to inferior pulmonary vein.

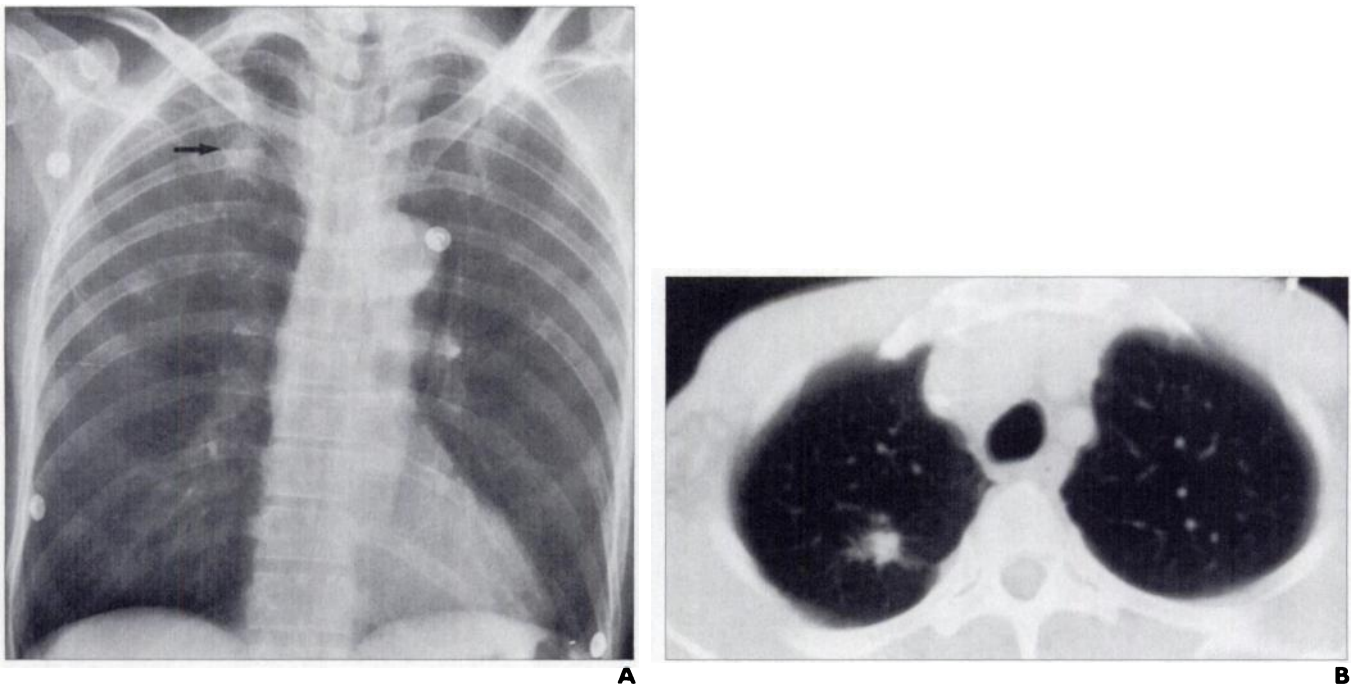

Fig. 3.—53-year-old man with primary lung carcinoma evident on CT who had chest radiograph originally read as negative. In retrospect, lesion is visible.
A, Anteroposterior chest radiograph was reported as negative. In retrospect, increased density is visible projecting over right first costochondral junction (*arrow*).
B, CT scan reveals small spicular mass in right upper lobe.

radiograph, respectively ($p > .05$). Although a relevant clinical history was provided slightly more often in patients with a positive chest radiograph, provision of appropriate clinical information appeared to have little effect on the likelihood of identifying a primary lung carcinoma.

We also evaluated whether lesion characteristics affected the likelihood of primary tumor detection. A significant difference existed in mean diameter of the primary lesion in patients whose chest radiographs were interpreted as positive (4.2 cm) as compared with those whose radiographs were normal or nonspecific (2.4 cm) ($p < .01$). We found that neither the lobar location of the primary carcinoma nor its position with respect to the hilum (central or peripheral) differed substantially between patients whose chest radiographs were interpreted as positive and those whose radiographs were nonspe-

cific or negative. Moreover, the cell type of the primary tumor appeared to be distributed similarly between the two groups of patients.

Findings other than the primary lesion that were not evident on the chest radiograph and that might preclude a curative procedure were found on chest CT in 14 patients (45%). In seven of these patients, the primary lesion was identified on chest radiography. Mediastinal or hilar adenopathy that was unsuspected on the chest radiograph occurred in 10 patients, and extrathoracic metastasis to the adrenal (n = 5) or liver (n = 1) was present in five. In two patients, a second lung nodule was found that indicated either a synchronous primary tumor or a solitary lung metastasis.

The histopathologic cell type of the 31 patients with metastatic lung carcinoma was adenocarcinoma in 14 patients, squamous cell carcinoma in five, non–small cell lung carcinoma (not otherwise specified) in six, large cell carcinoma in three, and small cell lung carcinoma in three. Tissue was obtained from the lung in 17 patients, from the brain in 10, and from both in four. Before therapy, evaluation of the brain revealed a solitary metastasis in 19 patients, from two to four metastases in four patients, and five or more metastases in eight patients. Of 19 patients for whom clinical follow-up was available, curative therapy involving both lung and brain lesions was attempted in five patients. Three of these five patients are alive between 7 and 20 months after treatment, one died 6 months after treatment from progressive disease, and one was lost to follow-up.

Discussion

The development of brain metastases in patients with lung carcinoma has long been considered to be a poor prognostic indicator. Indeed, the current staging classification of bronchogenic carcinoma categorizes such patients as having stage IV disease, the most advanced category [13]. Five-year survival for all patients with stage IV lung carcinoma is 1.7% [13].

More recently, an aggressive surgical approach to patients with lung carcinoma and solitary brain metastasis has been advocated, and results that are more favorable than palliative therapy (whole brain irradiation) alone have been reported [2–5, 7, 10–11]. In four retrospective studies published since 1988, 5-year survival rates of 13–45% have been reported [4, 7, 11, 14]. A randomized prospective trial in 48 patients with a single brain metastasis demonstrated a significantly longer mean survival (9 months) in patients treated surgically compared with those who had palliative therapy (3.5 months) [12].

A newer noninvasive therapy that has been used to treat one or more brain metastases is stereotaxic radiosurgery [6, 8]. This technique employs a focused beam of high-dose radiation to target a brain lesion and spare surrounding normal brain parenchyma. Radiosurgery has been advocated in patients with small or deep brain lesions and those who for medical reasons cannot tolerate complete surgical resection. Using radiosurgery, patients with as many as four brain metastases may be treated. In a study of 167 patients with brain metastases who underwent stereotaxic radiosurgery, 94% achieved local control of the lesions after 9 months and most lesions decreased in size, as seen on sequential imaging studies [8]. Although no large prospective trial exists that compares resection of the primary lung tumor combined with surgical brain resection or stereotaxic radiosurgery to less aggressive palliative measures, these newer approaches suggest that improved survival and cure might be achieved in selected patients with lung cancer metastatic to the brain. Thus, identification of the site of origin of a brain metastasis has assumed increased importance.

In patients who present de novo with CNS symptoms and who have metastatic disease to the brain that is proven at surgery or suggested on the basis of brain imaging studies, a search for the primary lesion typically includes a chest radiograph. Local practice varies, and further evaluation may or may not include a CT scan, particularly if the chest radiograph does not show a primary lesion. Use of CT must be justified because it entails added expense. In consideration of the high percentage of primary tumors that arise in the lung in the setting of brain metastasis and in view of the possibility of curative resection, we analyzed patients who presented initially with metastatic brain disease to determine whether chest CT provided substantial additional information when compared with chest radiography.

Our study assessed the potential additional benefit of CT from two perspectives. First, we determined whether CT identified a primary lesion in patients in whom the chest radiograph was normal or equivocal. Second, we evaluated whether CT identified nodal disease, metastases, or additional lung nodules that were not evident on the chest radiograph. The latter consideration is important because patients who have disease in addition to the primary lung lesion and metastatic brain disease usually are not candidates for an attempt at curative resection [4].

Our study provided convincing evidence that CT is useful to supplement chest radiography in locating a primary tumor. In 13 (41%) of 32 patients with a new presentation of brain metastasis, the chest radiograph was interpreted originally as negative (n = 9) or nonspecific (n = 4). In 12 (92%) of these 13 patients, chest CT revealed a primary tumor (categories 3 and 4).

We evaluated several factors that may have contributed to failure to diagnose these 12 lung carcinomas. We found that patients with unrecognized lung cancer were somewhat more likely to have undergone anteroposterior radiographs and to lack relevant history on their requests than patients in whom the lesion was diagnosed, but the differences were not statistically significant. In contrast, lesion size was significantly smaller in the former group of patients.

We also found that chest CT provided substantial additional information regarding unsuspected nodal metastasis and extracerebral metastasis in the 31 patients with primary lung carcinoma. The precise extent to which CT is useful in this situation is difficult to assess because histopathologic proof of nodal and extracerebral metastasis was usually not available.

One interesting finding of our study was the high prevalence (34/35, 97%) of lung carcinoma that was found among patients whose initial presentation resulted from symptomatic brain metastases. Although the high frequency may reflect our institutional status as a tertiary referral center, our inclusion criteria were designed to exclude patients who were transferred to our institution from elsewhere. Metastatic brain disease is most commonly caused by lung carcinoma, but a somewhat lower frequency of 40–60% is reported [7]. However, patients who present de novo with symptomatic brain metastases are more likely to have a primary lung carcinoma [15–17]. With results similar to those of our study, Zimm et al. [15] reported a 96% frequency of lung carcinoma among 59 patients who presented with symptomatic brain metastases. This high prevalence of lung carcinoma in patients who present de novo with brain metastasis underscores the value of a thorough imaging assessment of the chest.

Our study inclusion criteria introduced a small bias because three patients with lung carcinoma and a positive chest radiograph who did not have a CT scan were excluded. Nevertheless, even if these patients were added to the 31 patients with lung cancer in the study group, negative or nonspecific chest radiographs accounted for a substantial percentage (12/34, 35%) of patients with lung carcinoma. A second bias might have been introduced if patients with nonpulmonary primary tumors had brain metastases that were atypical, leading to failure to include such patients in our series. A consequence of such bias would be an apparent higher frequency of primary lung tumors among patients with a de novo presentation of brain metastasis. Another limitation is the large number of anteroposterior chest radiographs that were obtained. Possibly some of the lesions in patients with negative or nonspecific radiographs would have been evident if all patients had undergone posteroanterior and lateral chest radiographs. However, in view of the neurologic symptoms such as stroke and seizure that characterize the presentation of these patients and the difficulty in positioning them for radiographic examination, our experience probably reflects the situation that is encountered commonly in clinical practice. The frequent use of the anteroposterior technique may also account for the rather large mean diameter (2.4 cm) of lesions that were overlooked on chest radiography. A final limitation is that not all patients with metastatic lung carcinoma had histopathologic proof of both lung carcinoma and brain metastasis. Nevertheless, even in patients without such proof, the imaging appearance was highly suggestive of metastatic lung carcinoma. Moreover, each patient was treated using a protocol for metastatic lung carcinoma.

In summary, we studied a substantial number of patients with symptomatic brain metastases in whom the chest radiograph was insufficient for diagnosis of primary lung carcinoma. The tumor diameter appeared to be the most important determinant of whether a primary carcinoma was detected on radiographs. CT was useful to identify a primary lesion and to delineate additional unsuspected disease that would render the patient unresectable for cure. Based on our finding that four lesions were visible on radiographs in retrospect, we also suggest that some subtle primary lung lesions may be identified by rigorous evaluation of the chest radiograph, thereby obviating imaging investigation of other areas of the body.

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The reader's attention is directed to the commentary on this article, which appears on the following pages.