Does Initial Staging or Tumor Histology Better Identify Asymptomatic Brain Metastases in Patients with Non–small Cell Lung Cancer?

Ann A. Shi, MD, Subba R. Digumarthy, MD,* Jennifer S. Temel, MD,† Elkan F. Halpern, PhD,* Landon B. Kuester,* and Suzanne L. Aquino, MD**

Background: To determine whether the distribution, staging features, or tumor histology of non–small cell lung cancer (NSCLC) distinguishes neurologically symptomatic from asymptomatic patients initially diagnosed with lung cancer, and to determine whether these factors may predict the presence of brain metastasis.

Methods: We performed a retrospective review of 809 patients with NSCLC and brain metastases who were treated in our institution between January 1996 and March 2003. Patients who had brain metastasis on initial staging were included. Thoracic computed tomographic scans were reviewed for lung tumor features and staging. Neurological computed tomographic or magnetic resonance image scans were assessed for distribution of brain metastases. Medical records were reviewed for comprehensive staging, tumor histology, and neurological symptoms. Fisher's exact test was used to determine any differences among tumor histology, staging, and imaging features among patients with or without neurological symptoms.

Results: Of the 809 patients, 181 had brain metastasis at initial staging. Among these 181 patients, 120 (66%) presented with neurological symptoms (group 1); 61 (34%) patients were asymptomatic (group 2). Patients with adenocarcinoma and large-cell carcinoma had greater odds of brain metastases than patients with squamous cell carcinoma ($p = 0.001$). There were 106 (58.6%) patients with adenocarcinoma, 32 (17.7%) with large cell carcinoma, and 18 (9.9%) with squamous cell carcinoma. In both groups, most lung cancers were in the right lung with upper lobe dominance. No significant difference in tumor histology or T stage was found between groups, although group 2 was more likely to have a higher N stage. Of the 181 patients with brain metastasis, 60 (33.1%) had N0 disease, 51 (28.2%) had T1 disease, and 23 (19.2%) had no other metastasis. There was no correlation between number/distribution of brain metastases and tumor histology, although patients with disease in the cerebellum or temporal lobes had a greater likelihood of neurological symptoms (odds ratio 3.7).

Conclusion: There was no significant difference in tumor histology, staging, or distribution between symptomatic or asymptomatic patients with NSCLC with brain metastases. The odds of brain metastases were greater in those with adenocarcinoma or large-cell carcinoma.

Key Words: Non–small cell lung cancer, Imaging, Brain metastasis, Staging.

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Lung cancer is a leading cause of cancer death. Approximately 170,000 cases of non–small cell lung cancer (NSCLC) are diagnosed annually in the United States.[1] Although the initial staging of NSCLC is essential for determining treatment approach, there is no consensus regarding whether a full examination should be routinely performed. In particular, the necessity of preoperative screening for distant metastases in the brain remains a controversial topic.[2–18] The most recent joint statement of the American Thoracic Society and the European Respiratory Society[2] on pretreatment evaluation for NSCLC advocates no preoperative imaging of the brain in patients with NSCLC who have no symptoms or other evidence of distant metastases.

NSCLC does not follow a set pattern to metastasize, and occult brain metastasis may exist in the absence of neurological symptoms.[6,7,11,19] Many investigators[12–18] believe the low incidence of brain metastasis in asymptomatic patients—particularly in those with early, local disease—renders routine screening cost-ineffective. Others argue that detection of occult brain metastasis will avoid increased morbidity either by allowing earlier treatment of the brain or by avoiding futile thoracotomies.[4–9]

Several prospective and retrospective studies have examined the incidence of brain metastasis. The results vary greatly depending on the modality, size of study group, tumor histology, size and nodal disease, and inclusion of patients with positive or negative neurological symptoms.[4–11,14–17] Knowledge of factors that may identify the presence of brain metastasis from NSCLC may help to identify a subgroup of patients likely to benefit from central nervous system (CNS) imaging during initial staging. We conducted a retrospective review of patients with NSCLC with brain metastasis on

Departments of *Radiology and †Medical Oncology, Massachusetts General Hospital, Boston, Massachusetts.
Address correspondence to: Suzanne L. Aquino, MD, Department of Radiology, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114. E-mail: saquino@partners.org

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initial staging to investigate any association between thoracic computed tomography (CT) features of NSCLC, i.e., distribution and staging features, tumor histology, and the presence of symptomatic or asymptomatic CNS metastases.

PATIENTS AND METHODS

This study was approved by our institution's Human Research Committee, and patient consent was waived. We conducted a database search of our institution's Cancer Registry and identified 809 patients with NSCLC and brain metastases who were treated at our institution between January 1996 and March 2003. These patients' medical records, including radiology, pathology, surgery report, clinical notes, and discharge summaries, were reviewed.

Institutional lung cancer staging procedure during this time interval included the acquisition of the following noninvasive diagnostic studies: a contrast-enhanced CT of the thorax and abdomen, magnetic resonance (MRI) or CT of the head, bone scan, physical and neurological examination, and blood chemistries. Invasive diagnostic procedures included percutaneously needle biopsy of lung nodules and masses unless a suspected metastatic site was found on imaging, which alternatively would be biopsied for both diagnosis and staging. Fluorodeoxyglucose positron emission tomography (FDG-PET) scan was not a routine study during this time period but is now routine in our institution. All surgical candidates underwent mediastinoscopy before curative resection. The histological cells types that were considered consistent with NSCLC included: adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, poorly differentiated non–small-cell carcinoma, and non–small-cell carcinoma not otherwise specified. When both intrathoracic and extrathoracic pathologies were obtained but discordant, final diagnosis was based on intrathoracic pathology. Patients with a concurrent secondary primary cancer were excluded from the study.

Among the 809 patients, we selected two groups of patients who had brain metastasis at initial staging. The first group included 120 patients who presented with neurological symptoms and were subsequently diagnosed with lung cancer. The second group included 61 patients who were neurologically asymptomatic but had brain metastasis shown by CT or MRI at initial staging. Only patients whose neurological imaging was performed within 1 month of the diagnosis of chest abnormality were included in the second group.

In group 1, 70 patients underwent brain biopsy, and one patient had cerebrospinal fluid (CSF) cytology consistent with NSCLC. In group 2, 13 patients underwent brain biopsy, and one patient received CSF cytology. Of the 181 patients, 96 did not undergo brain biopsy. There were 95 patients in group 1 and 55 patients in group 2 who had pathological data from lung, pleural fluid, adrenal gland, or bone. Seven patients with non-pathologically proven lung cancer were included, as they are clinically considered to have lung cancer.

Thoracic CT scans, radiology and pathology reports, and surgical and clinical notes of these 181 patients were reviewed for lung tumor features and staged according to the International System for Staging Lung Cancer adopted by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer.[20] Mediastinal lymph nodes larger than 1 cm in short axis were considered to be pathological by CT criteria. Non-pathologically enlarged nodes were considered metastatic if pathologically proven from surgical resection or positive by FDG-PET. Only nine patients underwent PET. Two patients' nodal staging was altered because of PET findings. PET did not affect tumor staging for the other seven patients. Eleven patients did not receive a chest CT; staging data were derived from surgical results or plain radiograph findings if available. There was no information regarding tumor size for 37 patients, tumor location was unknown for 18 patients, and there was no information regarding nodal disease for 8 patients. Limited clinical data were available for several reasons: (1) chest CT was not performed at our institution; (2) outside CT was not available for review and tumor size or presence of mediastinal lymph nodes was not mentioned in the radiology report; (3) multiple lung nodules were present, and the primary lesion could not be determined.

Neurological CT or MRI scans were assessed for the number and distribution of brain metastases. A significant number of patients underwent both CT and MRI; in these cases, the MRI scan was evaluated

The presence of non-CNS extrathoracic disease was determined by abdominal and pelvic CT, bone scan, FDG-PET imaging, and biopsy results. Five patients also underwent musculoskeletal MRI for evaluation of various skeletal metastases.

Fisher's exact test was used to determine any differences among tumor histology, staging, and imaging features among patients with or without neurological symptoms. Histological data were compared with the rates calculated from the patients included in the Surveillance, Epidemiology, and End Results (SEER) Program from 1975-1999.

RESULTS

We identified 120 neurologically symptomatic patients (group 1) and 61 neurologically asymptomatic patients (group 2) with brain metastasis at initial staging. The demographic information of the two study groups is listed in Table 1. There was no significant difference in the age and gender ($p = 0.87$) distribution between the two groups.

Of the 181 patients studied, 106 (58.6%) had adenocarcinoma, 32 (17.7%) had large-cell carcinoma, and 18 (9.9%) had squamous cell carcinoma (Table 2). Based on an incidence of 37.3 % adenocarcinoma, 30.9 % squamous cell carcinoma, 19.9 % small-cell lung cancer, and 11.9 % large-cell carcinoma in the SEER lung cancer patient population between 1975–1999,[21] patients with adenocarcinoma and

TABLE 1. Gender and Age of Symptomatic (Group 1) and Asymptomatic (Group 2) Patients with Brain Metastases

	Number	Men	Women	Mean age (yr)	Age range (yr)
Total	181	90	91	61.3	35–85
Group 1	120 (66%)	59	61	61.9	35–85
Group 2	61 (34%)	31	30	60.1	41–81

TABLE 2. Histology and Distribution of Primary Lung Tumor in Symptomatic (Group 1) and Asymptomatic (Group 2) Patients with Brain Metastases

	Adenocarcinoma	Squamous	Large cell	NSCLC NOF	Poorly differentiated	Unknown	Left	Right	Upper/middle lobe	Lower lobe
Total $n = 181$	106 (58.6%)	18 (9.9%)	32 (17.7%)	9 (5%)	9 (5%)	7 (3.9%)	64 (35.4%)	103 (56.9%)	131 (72.4%)	42 (23.2%)
Group 1 $n = 120$	71 (59.2%)	10 (8.3%)	22 (18.3%)	5 (4.2%)	8 (6.7%)	4 (3.3%)	40 (33.3%)	68 (56.7%)	75 (62.5%)	30 (25.0%)
Group 2 $n = 61$	35 (57.4%)	8 (13.1%)	10 (16.4%)	4 (6.6%)	1 (1.6%)	3 (4.9%)	24 (39.3%)	35 (57.4%)	46 (75.4%)	12 (19.7%)

NSCLC, non–small cell lung carcinoma; NOF, not otherwise specified.

large-cell carcinoma had greater odds of brain metastases than patients with squamous cell carcinoma ($p < 0.001$). There was no statistically significant difference in tumor histology between groups 1 and 2 ($p = 0.56$).

There was no significant difference in T stage between the two groups ($p = 0.28$), although group 2 was more likely to have a higher N stage ($p < 0.001$) (Table 3). The most common tumor stage was T2 (38.7%), followed by T1 (28.2%), T3 (7.7%), and T4 (5%). The tumor stage was not available for 37 of 181 patients (20.4%).

Among the patients studied, 33.2% had N0 disease, which was the most common; 7.2%, 31.5%, and 23.7% had N1, N2, and N3, respectively (Table 3). Nodal status could not be determined in eight (4.4%) patients.

Of the 181 patients, 56 (30.9%) had no distant metastasis other than the brain. Of these, 20 symptomatic patients (group 1) and 3 asymptomatic patients (group 2) had no evidence of nodal metastasis (N0) on imaging. Another 79 (43.6%) had additional non-CNS metastases. The remaining 46 patients (25%) had imaging findings suspicious for metastasis, but no biopsy or follow up imaging was available for confirmation.

Information regarding laterality (right versus left lung) of the tumor was available for 167 patients, and the lobar distribution was available for 173 patients. In both groups, most lung cancers were in the right lung (61.7% overall) with an upper and middle lobe dominance (75.7% overall) (Table 2). No significant distribution differences were found in laterality ($p = 0.25$) and lobar distribution ($p = 0.16$) of the primary tumor between symptomatic and asymptomatic patients.

Patients with squamous cell tumor and NSCLC not otherwise specified were less likely to have CNS spread in the absence of nodal metastases(Table 4). On the contrary, patients with large-cell tumors had greater odds of brain metastasis regardless of nodal disease ($p = 0.01$).

We reviewed head CT and MRI scans and found the pattern of CNS involvement of NSCLC by histology was very similar between the two groups. There were a nearly equal number of patients with a single brain metastasis and those with multiple brain metastases by all cell types (Table 5). Multiple metastatic foci just as frequently caused neurological symptoms as a single focus: 57 of 91 patients (62.6%) with multiple metastases were neurologically symptomatic versus 63 of 90 patients (70%) with single brain metastasis ($p = 0.35$). When examining the location of single brain metastases (Table 6), we found that tumors in the cerebellum and temporal lobes had a higher correlation with neurological symptoms (odds ratio 3.7, $p = 0.046$).

DISCUSSION

The brain is a frequent site of metastasis from NSCLC. Although early detection of brain metastasis will alter surgical management and avoid unnecessary thoracotomy,[4–9] preoperative screening of neurologically asymptomatic patients has not been advocated. Many investigators consider the incidence of occult brain metastasis to be quite low, particularly among patients with early disease,[14–16] and view the routine use of MRI and CT in asymptomatic patients as not cost-effective.[2,12,13,18]

Toloza et al.[22] pooled data from 17 studies and found a 13% average prevalence of brain metastasis by CT among patients with NSCLC, but the prevalence rate ranged widely from 0 to 32%. Advocates of preoperative screening for brain metastases argue that studies demonstrating a low prevalence are often skewed by a high proportion of patients with stage 1 disease, who are at lower risk of metastases.[10] Contributing to this controversy is the poorly understood pattern of NSCLC spread. Although it is generally acknowledged that metastases to the brain are more frequent with tumors staged greater than T1[10,14–16] or the presence of nodal metasta-

TABLE 3. T and N Stages of Symptomatic (Group 1) and Asymptomatic (Group 2) Patients with Brain Metastases

	T1	T2	T3	T4	Unknown	N0	N1	N2	N3	Nx
Total $n = 181$	51 (28.2%)	70 (38.7%)	14 (7.7%)	9 (5%)	37 (20.4%)	60 (33.2%)	13 (7.2%)	57 (31.5%)	43 (23.7%)	8 (4.4%)
Group 1 $n = 120$	38 (31.7%)	48 (40.0%)	8 (6.7%)	4 (3.3%)	22 (18.3%)	51 (42.5%)	9 (7.5%)	37 (30.8%)	21 (17.5%)	2 (1.7%)
Group 2 $n = 61$	13 (21.3%)	22 (36.1%)	6 (9.8%)	5 (8.2%)	15 (24.6%)	9 (14.7%)	4 (6.6%)	20 (32.8%)	22 (36.1%)	6 (9.8%)

TABLE 4. Breakdown of Patients with Brain Metastases with and without Nodal Metastases Based on Cell Type of Primary Tumor at Staging

Tumor Type	*N*	Patients without lymph node metastasis	Patients with lymph node metastases
Adenocarcinoma	106	32 (30.2%)	74 (69.8)
Squamous cell	18	2 (11.1%)	16 (88.9%)
Large cell	32	17 (53.1)	15 (46.9%)
NSCLC NOF	9	1 (11.1%)	8 (88.9%)
Poorly differentiated	9	4 (44.4%)	5 (55.6%)
Unknown	7	4 (57.1%)	3 (42.9%)

NSCLC, non–small cell lung carcinoma; NOF, not otherwise specified.

TABLE 5. Correlation between Plurality of Brain Metastases in Symptomatic (Group 1) and Asymptomatic (Group 2) Patients and Tumor Type

	Total	Adenocarcinoma	Squamous	Large cell	NSCLC NOF	Poorly differentiated	Unknown
Multiple brain mets	91 (50.3%)	55 (30.4%)	12 (6.6%)	14 (7.7%)	5 (2.8%)	2 (1.1%)	3 (1.7%)
Group 1	57 (47.5%)	35 (29.2%)	12 (6.6%)	6 (5.0%)	2 (1.7%)	1 (0.8%)	1 (0.8%)
Group 2	34 (55.7%)	20 (32.8%)	2 (3.3%)	6 (9.8%)	3 (4.9%)	1 (1.6%)	2 (3.3%)
Single brain mets	90 (49.7%)	51 (28.2%)	6 (3.3%)	18 (9.9%)	4 (2.2%)	7 (3.9%)	4 (2.2%)
Group 1	63 (52.5%)	36 (30.0%)	10 (8.3%)	4 (3.3%)	3 (2.5%)	7 (5.8%)	3 (2.5%)
Group 2	27 (44.3%)	15 (24.6%)	8 (13.1%)	2 (3.3%)	1 (1.6%)	0	1 (1.6%)

Mets, Metastases; NSCLC, non–small cell lung carcinoma; NOF, not otherwise specified.

TABLE 6. Distribution of Single Brain Metastasis in Symptomatic (Group 1) and Asymptomatic (Group 2) Patients

Anatomic location	Group 1 $n = 120$	Group 2 $n = 61$
Cerebellum/spine	16	4
Frontal lobe	17	12
Parietal lobe	6	7
Temporal lobe	9	0
Occipital lobe	4	2
Frontal/parietal lobe	3	0
Parietal/occipital lobe	4	1
Other	5	0

sis,[11,17] metastases have been reported to spread from even small primary tumors in the absence of other metastases.[3,4,6] To date, there has been no comprehensive study that evaluates the factors associated with brain metastasis in asymptomatic patients compared with those who are symptomatic. Therefore, the purpose of this study was to determine whether there are any specific tumor features, such as location, size, stage at diagnosis, or tumor cell type, that could help to distinguish which patients are likely to have asymptomatic brain metastases.

In terms of primary tumor distribution on CT scan, we found that most lung cancers in both the symptomatic and asymptomatic groups occurred in the right upper lobe. Our results are in keeping with previous studies that have shown that most lung cancers occur in the upper lobes, with a typical upper to lower lobe ratio of roughly 2.5:1.0.[19,23] Therefore, we could not conclude that a tumor's lobar site of origin correlated to any increased likelihood of brain metastases.

In terms of the evaluation of T stage, we found brain metastases in patients with all T stages. Of note, 31.7% of patients in group 1 and 21.3% of patients in group 2 had tumors smaller than 3 cm (T1 stage). When we evaluated our patient population based on N stage, patients with N0 disease formed the largest group (33% of all patients). Although group 2 (asymptomatic patients) had a higher N stage, we speculate that this reflects an inclination of clinicians to perform additional imaging examinations when there is evidence of nodal spread. Taken together, a large proportion of patients, both neurologically symptomatic and asymptomatic, had early, local lung cancer. We did not have data regarding the tumor staging of all NSCLC patients treated at our institution during the study period to examine the likelihood of brain metastasis based on tumor staging; thus, we can only speculate as to the importance of this finding. The SEER data show that 18.2% of patients had local disease, and 29% of patients had regional disease at diagnosis.[21] Because our institution is a referral center for lung cancer, our patient base may have more advanced disease than that reflected in national statistics. The high proportion of patients with T1 or N0 disease in our study suggests a higher prevalence of brain metastasis than previously thought. Our data also question the current understanding that patients with local disease are much less likely to have brain metastasis than those with more advanced disease. Further research is needed to understand NSCLC tumor behavior with regard to CNS spread.

There was no correlation between the number and distribution of brain metastases and tumor histology. We also found no significant difference in primary tumor histology

between asymptomatic and symptomatic patients. There was a significant increase in the occurrence of brain metastases in patients with adenocarcinoma and large-cell carcinoma histology. Our results are in accordance with a study by Salvatierra et al.,[6] who reported that non-squamous cell lung cancer histology was a risk factor for brain metastasis. We found that squamous cell tumors less frequently spread to the CNS than other histological subtypes, particularly in the absence of lymph node metastases. On the contrary, large-cell tumors spread to the CNS regardless of lymph node status. Therefore, screening for brain metastasis may not be as cost-effective in patients with localized squamous cell tumor, whereas it will provide a higher yield in all patients initially diagnosed with large-cell lung cancer.

A significant proportion of patients (19.2%) in our study had isolated brain metastases and an absence of nodal involvement. Studies have shown that those patients with early stage lung disease in the thorax and an isolated brain metastasis have better survival rates after resection of both lesions.[24–27] This fact, along with our results, suggests that patients with resectable lung cancers, especially those with local disease and adenocarcinoma or large-cell carcinoma histology, should receive a staging neurological CT or MRI. Among our patients with CNS metastases, 30.9% had no other extrathoracic metastasis. Therefore, the absence of distant metastases to the abdomen, pelvis, or skeleton should not be used to preclude the absence of a brain metastasis.

There are several limitations of this study. Because of its retrospective design, tumor, node, metastasis and histological distribution of the study population was not completely available. In addition, our patient group was largely derived from a referral group to a lung cancer multidisciplinary oncology and surgical clinic. Consequently, the true prevalence of brain metastasis of lung cancer could not be assessed. In addition, both CT and/or MRI were used for imaging the brain for metastases. Studies have shown that MRI is more sensitive than CT in detecting brain lesions[28,29]; therefore, the detection of brain metastasis at initial staging may not be as accurate for patients who underwent CT alone.

Although surgical and clinical information was used to modify tumor, node, metastasis staging whenever available, staging information was largely derived from CT. The detection of hilar and mediastinal nodal disease by CT is insufficiently sensitive and specific,[30] yet CT is the best method available for patients who do not undergo surgical staging. With the increased use of PET or combined PET-CT,[31] more information may become available in the future regarding the relationship between nodal disease and brain metastasis.

CONCLUSION

In conclusion, no specific T or N staging features of lung cancer on CT helped to distinguish which patients had asymptomatic brain metastases on initial staging. We encountered a large number of patients with early disease (N0 and T1) who had asymptomatic metastatic spread to the CNS. This was more likely in patients with adenocarcinoma and large-cell carcinoma. A large number of patients with brain metastases had no other evidence of distant metastases. Our results raise questions regarding the current practice recommendation of limiting brain imaging to those patients with neurological symptoms. Further research is recommended to evaluate the use of CNS imaging for routine staging in all patients with NSCLC.

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