Lymph Node Size Predicts for Asymptomatic Brain Metastases in Patients With Non–small-cell Lung Cancer at Diagnosis

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Abstract

We questioned the National Comprehensive Cancer Network recommendation for staging brain magnetic resonance imaging in patients with stage IB and above non–small-cell lung cancer (NSCLC), and report a 5.7% prevalence of asymptomatic brain metastases in stage I to III NSCLC, with the highest prevalence in lymph node-positive patients. Two stage I patients had asymptomatic brain metastases (adenocarcinoma), whereas no stage II patients had brain metastases, suggesting potential overutilization of brain magnetic resonance imaging staging in this cohort.

Background: We questioned whether the National Comprehensive Cancer Network recommendations for brain magnetic resonance imaging (MRI) for patients with stage ≥ IB non–small-cell lung cancer (NSCLC) was high-yield compared with American College of Clinical Pharmacy and National Institute for Health and Care Excellence guidelines recommending stage III and above NSCLC. We present the prevalence and factors predictive of asymptomatic brain metastases at diagnosis in patients with NSCLC without extracranial metastases. **Materials and Methods:** A retrospective analysis of 193 consecutive, treatment-naïve patients with NSCLC diagnosed between January 2010 and August 2015 was performed. Exclusion criteria included no brain MRI staging, symptomatic brain metastases, or stage IV based on extracranial disease. Univariate and multivariate logistic regression was performed. **Results:** The patient characteristics include median age of 65 years (range, 36-90 years), 51% adenocarcinoma/36% squamous carcinoma, and pre-MRI stage grouping of 31% I, 22% II, 34% IIIA, and 13% IIIB. The overall prevalence of brain metastases was 5.7% (n = 11). One (2.4%) stage IA and 1 (5.6%) stage IB patient had asymptomatic brain metastases at diagnosis, both were adenocarcinomas. On univariate analysis, increasing lymph nodal stage ($P = .02$), lymph nodal size > 2 cm ($P = .009$), multi-lymph nodal N1/N2 station involvement ($P = .027$), and overall stage ($P = .005$) were associated with asymptomatic brain metastases. On multivariate analysis, increasing lymph nodal size remained significant (odds ratio, 1.545; $P = .009$). **Conclusion:** Our series shows a 5.7% rate of asymptomatic brain metastasis for patients with stage I to III NSCLC. Increasing lymph nodal size was the only predictor of asymptomatic brain metastases, suggesting over-utilization of MRI in early-stage disease, especially in lymph node-negative patients with NSCLC. Future efforts will explore the utility of baseline MRI in lymph node-positive stage II and all stage IIIA patients.

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Introduction

In 2017, lung cancer accounted for 155,870 deaths in the United States.[1] Intracranial disease remains a primary site of metastatic spread, and early detection of asymptomatic brain metastases has been linked with decreased morbidity and mortality.[2-4] Currently, the National Comprehensive Cancer Network (NCCN) recommends brain magnetic resonance imaging (MRI) with contrast in the workup of patients with clinical stage II or greater non–small-cell lung cancer (NSCLC), and optional for patients with clinical stage IB NSCLC.[5] We sought to evaluate the prevalence of asymptomatic brain metastases, which is especially relevant for preoperative planning of resectable patients wherein additional information from predictive clinical factors, along with overall stage, might improve the diagnostic yield of brain MRIs.[6]

Despite the NCCN recommendations noted above, at least 12% of stage IA patients underwent brain MRI staging as part of their workup in the 2011 National Lung Screening Trial.[7] In 2013, the Choosing Wisely campaign released a statement recommending against brain MRI staging in stage IA lung cancer.[8] Further, patients with stage III or above disease undergoing definitive or radical treatment are recommended to undergo staging brain imaging according to The American College of Chest Physicians (ACCP), the National Institute for Health and Clinical Excellence (NICE), and a joint update from the British Thoracic Society and Society for Cardiothoracic Surgery in Great Britain and Ireland.[9-11] However, data regarding the diagnostic yield of brain MRI in an optimally staged population of newly diagnosed NSCLC defined by timely fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET/CT) imaging and invasive mediastinal procedures (endobronchial, mediastinoscopy, or surgical) is lacking.

With specific relevance to this early-stage population diagnosed at a National Cancer Institute (NCI)-designated cancer center using standardized staging procedures, we sought to analyze the prevalence of asymptomatic brain metastases at initial diagnosis. Further, we explore a comprehensive list of clinical and pathologic factors that may be associated with the detection of asymptomatic brain disease. The overall objective of the study is to identify factors that improve the diagnostic yield of brain MRI, which could have implications on cost-effectiveness and prevent unnecessary delays in initiation of timely treatment. This has implications not only for patients planned for upfront surgery, but also for medically inoperable patients planned for stereotactic body radiation therapy, wherein FDG PET/CT staging and endobronchial invasive staging is a common practice.

Materials and Methods

Patient Selection

The study population for this institutional review board-approved retrospective analysis included all patients with newly diagnosed NSCLC who completed their entire staging workup, including pathologic diagnosis, at our institution between January 1, 2010 and August 1, 2015. Patients who underwent their initial diagnosis at outside institutions were excluded to accurately define the denominator for our study and limit the potential bias of stage migration for patients referred to our tertiary care facility. Patients were identified through an electronic medical record system query for International Classification of Diseases, Ninth Revision (ICD-9) codes of a primary lung malignancy excluding tracheal and bronchial primaries (162.3-162.9). Only patients undergoing brain MRI within 4 weeks of a pathologic diagnosis were included. At initial electronic medical record query with above criteria, 707 consecutive patients were identified. Individual patient charts were reviewed to exclude patients in whom a brain MRI did not include contrast, those who had neurologic signs or symptoms prompting brain imaging (ie, symptomatic brain metastases), histologic review did not confirm NSCLC, or if patients had stage IV disease based upon extracranial metastases on CT or FDG PET/CT imaging.

Patient and tumor characteristics were collected including age at diagnosis, gender, smoking status, smoking pack-years, race, tumor (T) stage, T size (cm), (N) stage was clinical (including endobronchial ultrasound/mediastinoscopy staging) unless surgical staging demonstrated clinically occult lymph nodal metastases, metastatic (M) staging (without MRI), M staging (with MRI), overall stage, histology, mutational status, and grade of tumor. To evaluate the burden of lymph nodal disease on risk of asymptomatic brain metastases, we also collected number of lymph nodal stations involved and largest mediastinal lymph nodal diameter.

Staging and Workup

All patients were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) excluding brain imaging. Initial staging was performed based upon detailed history and physical examination and imaging, including neurologic examination, chest radiography, CT of the chest and upper abdomen, FDG PET/CT imaging, bronchoscopy (including navigational bronchoscopy and endobronchial ultrasound), and mediastinoscopy when appropriate for lymph nodal staging. Staging was performed clinically and/or pathologically on the basis of whether the patient was managed with surgery versus definitive radiation ± chemotherapy. Brain imaging consisted of brain MRI with gadolinium contrast enhancement.

Statistical Analysis

Continuous variables are presented as medians, whereas categorical variables are presented as numbers (percentages). Using SPSS statistical software version 22, χ^2 testing, univariate and multivariate logistic regression was performed to identify factors associated with the prevalence of asymptomatic brain metastases. We evaluated the following factors as continuous variables: smoking pack-years and largest mediastinal lymph node size. We looked at the largest mediastinal lymph node diameter and performed an odds ratio (OR) for brain metastases as a continuous variable. We evaluated predefined lymph nodal cut points and also identified an optimal cut point for largest lymph node diameter that is predictive of developing asymptomatic brain metastases. We further stratified patients into a priori defined lymph nodal size groupings of ≤ 1 cm, 1 to 2 cm, and > 2 cm. A P-value $< .05$ was used for statistical significance. Binary logistic regression with forward conditional modeling was used for univariate and multivariate analysis (MVA) of predictors of asymptomatic brain metastases. Sequential MVA was then completed to avoid over-adjustment of results.

Results

Patient Characteristics

This study evaluated 707 consecutive patients who had an ICD-9 diagnosis of lung malignancy along with pathologic confirmation and brain MRI performed within 4 weeks of biopsy. Of these, 193 patients fit the eligibility criteria. Table 1 summarizes patient and tumor characteristics of the patients analyzed in this study. The median age at diagnosis of this cohort was 65 years (range, 36-90 years), and there was a slight female predominance (53.4%). Race was predominately white (50.3%), and 81 (42.0%) patients were current smokers at time of diagnosis. AJCC seventh edition staging of patients, excluding brain MRI staging, found 21.7% of patients to be stage IA, 9.3% IB, 10.9% IIA, 10.9% IIB, 34.2% IIIA, and 13.0% IIIB.

Eleven (5.7%) patients had asymptomatic brain metastases at time of diagnosis. On χ^2 testing, T stage ($P = .010$), N stage ($P = .012$), and overall stage ($P = .002$) were significantly different between patients with NSCLC with and without brain metastases (Table 1). Table 2 outlines patient and tumor characteristics in patients with asymptomatic brain metastases, as well as treatment rendered to these patients. A representative picture of a patient with lymph node positive (N2) disease and asymptomatic brain metastasis at diagnosis is shown in Figure 1.

Table 1 Patient and Tumor Characteristics

	No Brain Metastases (n = 182), n (%)	Brain Metastases (n = 11), n (%)	*P* Value
Median age at diagnosis, y (range)	65 (36-90)	65 (44-76)	.386
Gender			
Male	83 (45.6)	7 (63.6)	.244
Female	99 (54.4)	4 (36.4)	
Race			
White	92 (50.5)	5 (45.5)	.654
Black	84 (46.2)	5 (45.5)	
Other	6 (3.3)	1 (9.0)	
Cigarette use			
Never-smoker	13 (7.2)	2 (18.2)	.605
Current smoker	79 (43.4)	3 (27.3)	
Quit ≤1 year ago	24 (13.2)	1 (9.0)	
Quit >1 year but ≤15 years	29 (15.9)	2 (18.2)	
Quit >15 years	34 (18.7)	3 (27.3)	
Unknown	3 (1.6)	0 (0.0)	
Primary histology			
Adenocarcinoma	91 (50)	8 (72.8)	.289
SCC	67 (36.8)	2 (18.2)	
Large-cell	8 (4.4)	0 (0.0)	
NOS	16 (8.8)	1 (9.0)	
Stage			
T stage			
0	6 (3.3)	1 (9.0)	**.010**
1	66 (36.3)	5 (45.5)	
2	57 (31.3)	2 (18.2)	
3	41 (22.5)	0 (0.0)	
4	12 (6.6)	3 (27.3)	
N stage[a]			
0	86 (47.3)	2 (18.2)	**.012**
1	30 (16.4)	1 (9.0)	
2	54 (29.7)	4 (36.4)	
3	12 (6.6)	4 (36.4)	
Overall stage			
I	58 (31.9)	2 (18.2)	**.002**
II	42 (23.1)	0 (0.0)	
IIIA	62 (34.1)	4 (36.4)	
IIIB	20 (10.9)	5 (45.4)	

All significant *P* values are represented in bold.
Abbreviations: NOS = not otherwise specified; SCC = squamous cell carcinoma.
[a]Nodal stage as defined by either clinical or pathologic when available. If pathologic evaluation upstaged nodal burden, the pathologic staging took precedence over clinical staging for our analysis.

Disease Characteristics

Among patients with asymptomatic brain metastases, 8 (8.1%) had adenocarcinoma, 2 (2.9%) had squamous cell carcinoma (SCC), and 1 (6.3%) had NSCLC not otherwise specified histology (Table 1). This difference did not achieve statistical significance. Among stage I patients, 1 patient each of stage IA (2.4% of all stage IA patients) and stage IB (5.6% of all stage IB patients) had an asymptomatic brain metastasis at diagnosis (both patients had adenocarcinoma histology). The prevalence of asymptomatic brain metastases was 6.1% (4/66) in stage IIIA and 20% (5/25) in stage IIIB patients. Mutational status was reviewed and, when available, recorded for adenocarcinoma histology. Eight patients had an epidermal growth factor receptor (EGFR) mutation, 2 patients had an anaplastic lymphoma kinase (ALK) mutation, and 2 patients had a KRAS mutation. One patient with an EGFR mutation had an asymptomatic brain metastasis at diagnosis. Grade of tumor was not associated with a significant increase in risk of asymptomatic brain metastases.

Prevalence of Brain Metastases on the Basis of T, N, and M Staging

When analyzing patients with asymptomatic brain metastases stratified by T-stage, 1 (9.0%) patient had T0 disease, 5 (45.5%) patients had T1 disease, 2 (18.2%) had T2 disease, and 3 (27.3%) had T4 disease. T size as a continuous variable did not have a statistically significant impact on the development of asymptomatic brain metastases ($P = .214$). Stratifying according to lymph nodal staging, 2 (18.1%) patients had N0 disease, 1 (9.1%) had N1 disease, 4 (36.4%) had N2 disease, and 4 (36.4%) had N3 disease. Lymph nodal staging was statistically significantly correlated with increased risk of asymptomatic brain metastases overall ($P = .020$). Specifically, patients with N3 lymph nodal positivity had a much higher risk of asymptomatic brain metastases compared with patients with N0 disease (OR, 14.333; 95% confidence interval [CI], 2.365-86.853; $P = .004$). Finally, overall stage grouping of the patients with asymptomatic brain metastases showed 2 (18.1%) patients with stage I disease, 4 (36.4%) with stage IIIA disease, and 5 (45.5%) with stage IIIB disease. Increasing overall stage on univariate analysis was significantly predictive of asymptomatic

Table 2 Asymptomatic Brain Metastases Characteristics

Stage Before MRI	Histology	No. Metastases	Location of Metastases	Treatment for Metastases
T1bN0 IA	Adenocarcinoma	1	Right temporal	WBRT, SRS
T2aN0 IB	Adenocarcinoma	3	Right parietal, left frontal, left tentorium	WBRT, SRS
T0N2 IIIA	Adenocarcinoma	3	Right temporal, left cerebellum (×2)	Chemotherapy
T1aN2 IIIA	Adenocarcinoma	6	Left cerebellar, right cerebellar, left frontal (×2), right frontal (×2)	WBRT
T1bN2 IIIA	Squamous cell carcinoma	2	Midline cerebellum, left cerebellum	SRS
T4N1 IIIA	Adenocarcinoma	6	Bilateral cerebral hemispheres	WBRT
T2bN3 IIIB	Adenocarcinoma	1	Right parietal lobe	Chemotherapy
T1aN3 IIIB	Squamous cell carcinoma	4	Left frontal, right thalamus, right occipital, right parieto-occipital	Chemotherapy
T1bN3 IIIB	Adenocarcinoma[a]	1	Left frontal	SRS
T4N2 IIIB	Not Otherwise Specified	1	Left cerebellum	WBRT
T4N3 IIIB	Adenocarcinoma	1	Right occipital	Chemotherapy

Abbreviations: MRI = magnetic resonance imaging; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.
[a]Epidermal growth factor receptor mutation.

brain metastases (hazard ratio [HR], 1.464, 95% CI, 1.013-2.116; $P = .042$).

Lymph Nodal Burden and Lymph Nodal Size Association With Asymptomatic Brain Metastases

The median size of involved lymph nodes in our series was 1.1 cm, with a mean of 1.35 cm (range, 0-8.3 cm). We looked at the largest mediastinal lymph node diameter and performed an OR for brain metastases as a continuous variable (OR, 1.546; 95% CI, 1.114-2.146; $P = .009$). Subsequently, we identified the optimal cutpoint for largest lymph node diameter at 2.0 cm (Table 3). Patients with lymph nodes > 2 cm were statistically significantly more likely to have asymptomatic brain metastases at diagnosis (OR, 11.2; 95% CI, 2.826-44.392; $P = .001$). We further stratified patients into a priori defined lymph nodal size groupings of ≤ 1 cm, 1 to 2 cm, and > 2 cm (Table 4). Compared with lymph nodes ≤ 1 cm, there was no significant increase in asymptomatic brain metastases in patients with lymph node size of 1 to 2 cm ($P = .997$), but there was a significant increase in patients with lymph nodes > 2 cm (OR, 7.010; 95% CI, 1.758-27.941; $P = .006$). Multiple lymph nodal station positivity (defined as more than one N1 or N2 lymph nodal station) was also associated with an increased risk of asymptomatic brain metastases (OR, 2.250; 95% CI, 1.139-4.446; $P = .020$). An additional category of multilymph nodal mediastinal lymph node positivity (≥ 2 N2 lymph nodal stations involved) was evaluated, and was not associated with an increased risk of asymptomatic brain metastases (OR, 0.890; 95% CI, 0.402-1.756; $P = .644$) (Table 5). Largest lymph node diameter as a continuous variable remained the only significant variable on MVA (OR, 1.545; 95% CI, 1.114-2.143; $P = .009$) associated with an increased the risk of asymptomatic brain metastases.

To further evaluate multivariable factors associated with asymptomatic brain metastases, we performed a sequential MVA of 2 to 3 covariates to avoid over-adjustment given the small number of events (n = 11) in our series (Table 6). This yielded findings consistent with lymph nodal size being the biggest driver of asymptomatic brain metastases. When evaluating T versus N stage, N3 status was significantly associated with asymptomatic brain

Figure 1 Example of a Patient With Bulky Multi-station N2 Lymph Node Positivity and Asymptomatic Brain Metastases at Diagnosis. Brain MRI Shows the Largest Incident Lesion, but the Patient Was Noted to Have 4 Discrete Lesions Among the Bilateral Cerebral Hemispheres and Was Treated With Initial Stereotactic Radiosurgery Prior to Initiation of Treatment to the Thorax With Concurrent Chemoradiation

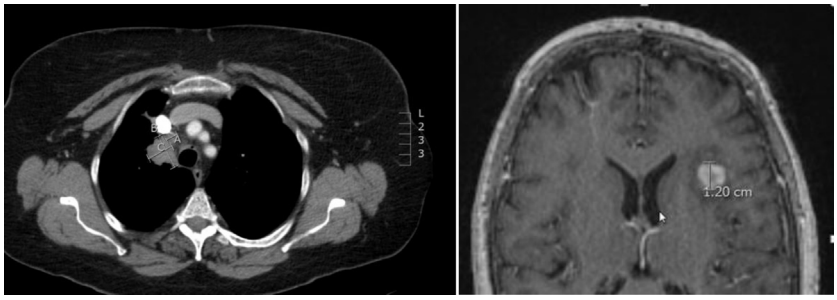

Table 3 Risk of Asymptomatic Brain Metastases by Nodal Size Using the Optimal Cutpoint

Nodal Size, cm	No Brain Metastases	Brain Metastases	Odds Ratio	*P* Value
≤2 (n = 150)	147	3	Reference	Reference
>2 (n = 43)	35	8	12.098	**<.001**

All significant *P* values are represented in bold.

Table 4 Risk of Asymptomatic Brain Metastases by Nodal Size Using Predefined Size Groupings

Nodal Size, cm	No Brain Metastases	Brain Metastases	Odds Ratio	*P* Value
≤1 (n = 95)	92	3	Reference	Reference
1-2 (n = 55)	55	0	0.000	.997
>2 (n = 43)	35	8	**9.511**	**.006**

All significant *P* values are represented in bold.

metastases (OR, 14.333; 95% CI, 2.365-86.853; $P = .004$). When MVA was performed adding in lymph nodal size to N staging, lymph nodal size > 2 cm was the only significant predictor of asymptomatic brain metastases (OR, 9.511; 95% CI, 2.575-35.125; $P = .001$), and remained significant when entered into an MVA with T stage, multi-station lymph nodal positivity, and nodal size (OR, 9.511; 95% CI, 2.575-35.125; $P = .001$). Finally, in order to compare N staging, lymph nodal size, and multi-station lymph nodal positivity, these 3 factors were entered into the model, and lymph nodal size > 2 cm was most correlated with asymptomatic brain metastases (OR, 9.511; 95% CI, 2.575-35.125; $P = .001$).

Discussion

We found a 5.7% prevalence of asymptomatic brain metastases at diagnosis (2.4% of stage IA, 5.6% of stage IB, 6.1% of stage IIIA, and 20% of stage IIIB) for FDG PET/CT- and invasive mediastinal procedure-staged patients with non-metastatic NSCLC at our institution between 2010 and 2015. On univariate analysis, T stage, N stage (and with further stratification, lymph nodal size > 2 cm as well as multilymph nodal station positivity), and overall stage were associated with increased likelihood of asymptomatic brain metastases. On MVA, increasing lymph nodal size was the most consistently significant factor associated with development of asymptomatic brain metastases, and was confirmed by sequential MVA.

In the 1980s and 1990s, the utility and cost-effectiveness of brain MRI for patients with lung cancer was analyzed. Tanaka et al evaluated 755 patients with clinical T1-2N0 NSCLC fully staged with contrast enhanced computed tomography (CT) chest/abdomen imaging, bone scan, and contrast-enhanced MRI or CT of the brain and found rates of asymptomatic extrathoracic metastases of < 1% for T1 and T2 patients, deeming MRI unnecessary in this subset of patients owing to cost and delay of care.[12] Another Japanese study of 332 patients with potentially operable NSCLC staged with CT or MRI found new brain metastases in 3.4% of the MRI group and 0.6% of the CT group.[13] Hochstenbag and colleagues performed neurologic testing as well as baseline brain MRI imaging and found a 14% rate of asymptomatic brain metastases in patients with large-cell carcinoma or adenocarcinoma of the lung, although 29% of patients had stage IV extracranial metastases.[14] In the modern era of FDG PET/CT-based staging with further improved MRI, Lee et al identified a 7% improvement in the detection of brain metastases with the addition of MRI brain imaging to FDG PET/CT in patients with newly diagnosed lung adenocarcinoma.[15] Specifically, in surgically resected patients with NSCLC, a study from Nottingham University Hospitals in the United Kingdom observed a 6.3% risk of detection of brain metastases within 12 months of surgical resection. Using presumed volume doubling time calculations, the authors estimated that up to 5.3% of the patients could have been detected with preoperative MRI with a 2-mm detection threshold. As reported in previous experiences, patients with adenocarcinoma subtype were most likely to be detected with brain metastases. The authors recommended that all patients should undergo MRI brain imaging as part of the presurgical workup, regardless of stage.[16] Patients with SCC NSCLC have demonstrated a lower prevalence of brain metastases,[17-19] suggesting a histologic stratification that may further define which patients benefit most from brain MRI staging.

Review of the literature shows a paucity of data regarding the prevalence of asymptomatic brain metastases at diagnosis to date. Barnholtz-Sloan et al found a 19.9% rate of brain metastases in patients with lung cancer between 1973 and 2001 in a Detroit population-based study.[20] These patients included those with stage IV disease extracranially, which may act as a confounder to explain the much higher prevalence of brain metastases. MRI imaging was also not available for a portion of their study, and imaging may have been prompted by symptoms, again accounting for a higher likelihood of finding brain metastases in their population. Prior studies evaluating the utility of brain MRI imaging in early-stage patients have shown conflicting information, with one study recommending all patients undergoing brain MRI imaging regardless of preoperative stage and others advocating reserving brain MRI for patients with more advanced disease.[7,12,14,16] Although this information is useful, these studies were a heterogeneous population, and therefore our study sought to further evaluate the influence of TNM staging as well as histologic and molecular classifications on the development of asymptomatic brain metastases.

More recently, a population-based study evaluating brain metastases in NSCLC using the Kentucky Cancer Registry and Alberta Cancer Registry in the MRI era found an approximate 8% prevalence of brain metastases for patients with all stages of NSCLC,[21] with adenocarcinomas comprising the largest number of asymptomatic brain metastases. This is consistent with our reported findings in the present study. However, the proportion of patients with adenocarcinoma was also the highest in both cohorts. As such, histologic subtype was not predictive of increased likelihood of asymptomatic brain metastases when undergoing optimal extracranial staging. Finally, Korean investigators found a 5% risk of brain metastases (symptomatic or asymptomatic) at diagnosis for patients with SCC.[17]

Our series differed from the above studies in several ways. First, we did not include patients with symptomatic brain metastases, as these symptoms would prompt imaging, skewing the data we were attempting to collect. Second, patients with stage IV disease based on extracranial metastases were excluded to evaluate patients

Table 5 Univariate Analysis

Characteristic	Odds Ratio	95% CI	*P* Value
Median age at diagnosis, y (range)	0.987	0.932-1.045	.648
Gender			
Male	2.087	0.591-7.378	.253
Female	REF	REF	REF
Race			.629
White	1.095	0.306-3.917	.889
Black	3.067	0.307-30.599	.340
Other	REF	REF	REF
Cigarette use			.372
Never or quit >15 years	REF	REF	REF
Current smoker	0.357	0.082-1.562	.171
Quit ≤15 years ago	0.532	0.121-2.347	.405
Primary histology			
Adenocarcinoma	REF	REF	REF
Squamous cell carcinoma	0.340	0.070-1.651	.181
Other	0.474	0.056-3.976	.491
Stage			
Tumor stage			.226
1	REF	REF	REF
2	0.463	0.087-2.479	.369
3	0.000	0.000	.999
4	3.300	0.695-15.671	.133
Nodal stage			**.020**
0	REF	REF	REF
1	1.433	0.125-16.382	.772
2	3.185	0.564-17.987	.190
3	14.333	2.365-86.853	**.004**
Multinodal N1 or N2 station			**.027**
0	REF	REF	REF
1	0.000	0.000	.998
≥2	8.640	1.798-41.523	**.007**
Mediastinal multinodal N2 Station			.644
0	REF	REF	REF
1	1.632	0.395-6.750	.499
≥2	0.771	0.192-3.104	.715
Overall stage			**.005**
I	REF	REF	REF
II	0.000	0.000	.998
IIIA	1.871	0.330-10.604	.479
IIIB	7.250	1.302-40.358	**.024**

All significant *P* values are represented in bold.
Abbreviations: CI = confidence interval; REF = reference.

planned for treatment with curative intent and to determine the true upstaging of patients based on neuroimaging. Flannery et al have described 21% 5-year overall survival in patients with synchronous brain metastases managed with gamma knife stereotactic radiosurgery.[22] With increasing data that select patients with otherwise

Table 6 Sequential Multivariate Analysis

Covariates	Significant Co-variable[a]	Odds Ratio	95% Confidence Interval	*P* Value
MVA Grouping 1				
T grouping				
T ≤ 2				
T ≥ 3				
N grouping	N grouping			**.020**
N0	N0	REF	REF	REF
N1	N1	1.433	0.125-16.382	.772
N2	N2	3.185	0.564-17.987	.190
N3	N3	14.333	2.365-86.853	**.004**
MVA Grouping 2				
N grouping				
N0				
N1				
N2				
N3				
N size	N size			**.003**
0-1 cm	0-1 cm	REF	REF	REF
1.1-2 cm	1.1-2 cm	0.000	0.000	.998
>2 cm	>2 cm	9.511	2.575-35.125	**.001**
MVA Grouping 3				
N multistation				
None				
1 stations				
≥2 stations				
N size	N size			**.003**
0-1 cm	0-1 cm	REF	REF	REF
1.1-2 cm	1.1-2 cm	0.000	0.000	.998
>2 cm	>2 cm	9.511	2.575-35.125	**.001**
MVA Grouping 4				
T grouping				
T ≤ 2				
T ≥ 3				
N grouping	N grouping			**.020**
N0	N0	REF	REF	REF
N1	N1	1.433	0.125-16.382	.772
N2	N2	3.185	0.564-17.987	.190
N3	N3	14.333	2.365-86.853	**.004**
N multistation				
None				
1 stations				
≥2 stations				
MVA Grouping 5				
T grouping				
T ≤ 2				
T ≥ 3				
N grouping				
N0				
N1				

Table 6 Continued

Covariates	Significant Co-variable[a]	Odds Ratio	95% Confidence Interval	*P* Value
N2				
N3				
N size	N size			**.003**
0-1 cm	0-1 cm	REF	REF	REF
1.1-2 cm	1.1-2 cm	0.000	0.000	.998
>2 cm	>2 cm	9.511	2.575-35.125	**.001**
MVA Grouping 6				
N multistation				
None				
1 stations				
≥2 stations				
N grouping				
N0				
N1				
N2				
N3				
N size	N size			**.003**
0-1 cm	0-1 cm	REF	REF	REF
1.1-2 cm	1.1-2 cm	0.000	0.000	.998
>2 cm	>2 cm	9.511	2.575-35.125	**.001**

All significant *P* values are represented in bold.
Abbreviations: MVA = multivariable analysis; REF = reference.
[a]This multivariate analysis included only 2 to 3 variables as the prevalence of asymptomatic brain metastases was low in our group, and multiple variables in MVA would lead to over-adjustment and less interpretable results. We therefore completed binary logistic forward conditional modeling including 2 to 3 factors with the endpoint of asymptomatic brain metastases at diagnosis. As shown above, nodal disease is significant, but within the 3 analyses of nodal disease performed which include N staging, N size, and multistation nodal positivity, nodal size remained the most significant predictor of the development of asymptomatic brain metastases at diagnosis.

limited disease who have brain metastases can have prolonged survival, the findings of a relatively low prevalence of asymptomatic brain metastases and the associated staging factors predicting for asymptomatic brain metastases at diagnosis may be of great value to practitioners.

Mujoomdar et al found that T size, cell type (adenocarcinoma and undifferentiated), and increasing lymph node stage were most predictive for brain metastases.[18] Our series did not corroborate the T size findings but did find that increasing lymph nodal size on multivariate analysis predicted for asymptomatic brain metastases at diagnosis. This knowledge can be used to help stratify the patients who are most likely to benefit from MRI staging at initial workup, and, as future data emerge, it may serve as a guide for identifying patients least likely to benefit and for whom brain MRI may be unnecessary.

Lee et al previously reported no evidence supporting the use of brain MRI staging in patients with stage I SCC and advocated only staging with brain MRI those patients who were stage II or greater.[17] Our findings agree with their study with regard to SCC. However, in our series, patients with adenocarcinomas were at higher risk for occult brain disease, even with extracranial stage I disease, thus, brain MRIs in this cohort may be beneficial. This did not achieve statistical significance, possibly owing to the size of our study.

Based on our findings, increasing lymph nodal size is the primary factor associated with having asymptomatic brain metastases at diagnosis. Although histologic subtype was not statistically significant for predicting asymptomatic brain metastases, adenocarcinoma histology was more likely to have brain metastases at an earlier stage, supporting Lee et al's recommendation to avoid staging brain MRI in patients with stage I SCC.

Our analysis was limited to patients who underwent MRI brain with contrast and had complete workup performed at our institution. We intentionally excluded patients with known extrathoracic disease and symptomatic brain metastases to not artificially increase the rate of brain metastases identified, and to avoid the bias associated with referral of patients for treatment to our tertiary care center. Doing so resulted in our analysis of a relatively limited numbers of patients compared with our overall lung cancer program, which could affect our power to find statistically significant findings. Additional large studies are needed to validate our findings, likely in a multi-center analysis.

Conclusion

Our study is one of the largest single institutional experiences evaluating the prevalence of asymptomatic brain metastases in patients with NSCLC undergoing FDG PET/CT, invasive mediastinal staging, and contrast-enhanced brain MRI as part of their initial staging workup. The overall prevalence of brain metastases for all stage I to III patients was 5.7%, with the highest diagnostic yield (20%) in stage IIIB patients. Although larger analyses are needed to validate our findings, this study is hypothesis-generating regarding possible overutilization of brain MRI in the workup of early-stage (I/II) disease, especially patients with lymph node-negative NSCLC who have undergone optimal extra-cranial staging. For patients with lymph node-positive disease, increasing size of lymph node diameter was correlated with a significantly higher risk of asymptomatic brain metastases at diagnosis, which agrees with current NCCN recommendations of which patients should undergo MRI staging. Future efforts should explore the utility of baseline MRI in lymph node-positive stage II and all stage IIIA disease.

Clinical Practice Points

- The guidelines for which patients are optimally staged with brain MRI with contrast range from optional for stage 1B and recommended for ≥ stage II (NCCN guidelines) to stage III or above (ACCP, NICE, and British and Irish Cardiothoracic guidelines).
- Brain MRI with contrast is still performed in some early-stage cases with the intention of avoiding a futile local treatment strategy if an asymptomatic brain metastasis were identified at diagnosis, despite the cost consideration of the number needed to screen to find an asymptomatic brain metastasis in this population. Prior studies evaluating utility of brain MRI staging have been confounded by including patients with extracranial metastases and/or symptomatology that prompted imaging to find a brain metastasis. The data regarding diagnostic yield of brain MRI in an optimally staged population of newly diagnosed NSCLC defined by timely FDG PET/CT imaging and invasive

mediastinal procedures (endobronchial, mediastinoscopy, or surgical) is lacking.

- Our study shows the extremely low risk of asymptomatic brain metastases in patients with early stage, lymph node-negative NSCLC at diagnosis (3.3% in stage I and 0% in stage II), suggesting overutilization in this population. Lymph nodal size was the most significant predictor of asymptomatic brain metastases at time of diagnosis, which supports the recommendation of brain MRI staging in patients with stage III or above disease.
- Future work will evaluate the utility of screening in lymph node-positive stage II and stage IIIA patients.

Disclosure

The authors have stated that they have no conflicts of interest.

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