

Revisiting Indications for Brain Imaging During the Clinical Staging Evaluation of Lung Cancer



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ABSTRACT

Introduction: Available guidelines are inconsistent as to whether patients with newly diagnosed clinical stage II NSCLC should receive routine brain imaging.

Methods: The National Cancer Database was queried for the prevalence of isolated brain metastases among patients with newly diagnosed NSCLC in 2016 and 2017. Patients with metastases in locations other than the brain were excluded. The prevalences were then stratified by clinical T and N classifications and further stratified into a summary stage, which was calculated based on T and N classifications. The summary stage represents the clinical stage that would have been available at the time of decision for brain imaging.

Results: A total of 6,949 of 149,958 patients (4.6%) with clinical stages I, II, III, or brain-limited stage IV NSCLC had dissemination limited to the brain. As T and N stages increased, prevalence of brain metastases generally increased. Among patients with node-negative (N0) NSCLC, the prevalence of brain-only metastases increased from 1.2% in patients with T1a to 3.8% among patients with T4 ($p < 0.001$). Among patients with T1a, the prevalence of brain-only metastases increased from 1.2% for patients with N0 to 7.9% for patients with N3 ($p < 0.001$). The prevalence of brain-limited metastases generally increased with increasing summary stage. The prevalence of brain-only metastases among patients with stage IA was 1.7% whereas that among patients with stage IIIA was 6.7% ($p < 0.001$). Of note, the prevalence of brain-limited metastases was approximately 6% for both summary stages II and III.

Conclusions: Considering the similarity in prevalence of isolated brain metastases and the potential hazards

associated with brain imaging in early stage NSCLC, practitioners may consider a more liberal use of brain imaging when interpreting conflicting guidelines.

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Introduction

Non-small cell lung cancer (NSCLC) has a tendency to metastasize to the brain, often without symptoms and commonly as the only site of metastatic disease. As a

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result, brain imaging is an important part of the staging evaluation for many NSCLC subsets, with eligibility based on tumor (T) and nodal (N) staging status. Many clinicians design their clinical staging evaluations to align with published NSCLC staging guidelines. Nevertheless, for patients without neurologic symptoms, there is discrepancy between the National Comprehensive Cancer Network (NCCN), which recommends brain imaging in clinical stage II disease or greater,¹ and the American College of Chest Physicians, which recommends brain imaging in clinical stage III disease or greater.² We evaluated the prevalence of brain-limited metastatic NSCLC across different categories of T and N variables. Our goal was to better understand the probability of brain-only metastases associated with specific T and N staging attributes and potentially clarify the role of brain imaging in patients with NSCLC.

Materials and Methods

The National Cancer Database was queried for patients diagnosed with having NSCLC as their first and only malignancy during 2016 and 2017.³ Stage was evaluated using the seventh edition of the American Joint Committee on Cancer guidelines.⁴ This study focused on metastases limited to the brain (i.e., brain-only metastases), as the role of brain imaging is less clear in this population. Therefore, patients with stage IV disease involving metastatic sites other than the brain were excluded. The Yale School of Medicine institutional review board approved this study with a waiver of informed consent.

Results

Overall, 149,958 patients with clinical stage I, II, III, or brain-limited stage IV NSCLC were analyzed. Of these, 6,949 patients (4.6%) had dissemination limited to the brain. The prevalence of brain-only metastases was stratified by clinical T and N status (Table 1). There was a general trend toward increasing prevalence of brain metastases with increasing T and N status. For example, among patients with node-negative (N0) NSCLC, the prevalence of brain-only metastases increased from 1.2% in patients with T1a to 3.8% among patients with T4 ($p < 0.001$). Increasing nodal status was also associated with a greater prevalence of brain-only metastases. Among patients with T1a NSCLC, the prevalence of brain-only metastases increased from 1.2% for patients with N0 to 7.9% for patients with N3 ($p < 0.001$). For the less common scenarios, such as T4 and N3, the pattern was less consistent.

In an attempt to mirror the structure of brain imaging recommendations within NCCN and the American College of Chest Physicians staging guidelines, the

Table 1. Prevalence of Patients With Brain-Only Metastases Among Those Diagnosed With NSCLC in the NCDB Based on Clinical T and N Classification

	N0, %	N1, %	N2, %	N3, %
T1A	1.2	6.0	7.1	7.9
T1B	2.4	6.5	8.1	5.7
T2A	3.7	7.2	7.6	6.2
T2B	6.0	10.3	9.2	6.8
T3	5.1	6.6	6.7	5.4
T4	3.8	5.2	4.8	3.5

Note: Classification is based on seventh edition NSCLC staging guidelines corresponding to guidelines in practice during 2016 to 2017. T and N stages are the clinical stages listed in NCDB. Percentages in bold correspond to stage III lesions that meet both ACCP and NCCN criteria for brain MRI imaging.

ACCP, American College of Chest Physicians; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database.

prevalence of brain-only metastases was also stratified by summary stage (i.e., stage I, II, or III). Summary stage was determined based only on T and N staging variables, to reflect available information at the time the decision is made whether or not to obtain brain imaging (Table 2). There was a general trend toward an increase in the prevalence of brain-limited metastases with increasing summary stage. For example, the prevalence of brain-only metastases among patients with stage IA was 1.7%, whereas the prevalence among those with stage IIIA was 6.7% ($p < 0.001$). Interestingly, the relationship is not completely linear, as there is a dip in prevalence from IIIA to IIIB.

Discussion

Our results suggest a general increase in the likelihood of brain-only metastases associated with increasing

Table 2. Prevalence of Brain-Only Metastases According to Stage With Stage Calculated From Clinical T and N Classification^a

Stage	Brain Metastases (N)	Without Brain Metastases (N)	Prevalence Brain Metastases (%)
IA	625	37,330	1.7
IB	561	14,432	3.7
IIA	644	9,384	6.4
IIB	560	9,140	5.8
IIIA	2,845	39,963	6.7
IIIB	1,714	32,760	5.0

^aIn other words, what the stage would have been—before the brain being imaged. Classification is based on seventh edition AJCC staging guidelines. T and N classification are the clinical stages listed in the NCDB. Percentages in bold correspond to stage III lesions that meet both ACCP and NCCN criteria for brain MRI imaging.

ACCP, American College of Chest Physicians; AJCC, American Joint Committee on Cancer; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database.

T and N status and increasing summary stage. There was some variability among stage III determinates, which could reflect our restriction to brain-only metastases, as these subgroups may be at higher risk to have multi-organ involvement (which were excluded from this study). These findings are not surprising and reflect a correlation between increasing stage status and events associated with mortality risk (i.e., systemic progression).

Perhaps the more intriguing aspect of the findings is the range of prevalence. More specifically, clinical stage III is a consensus indication for brain imaging across different clinical guidelines, and the average prevalence of brain-only metastases was approximately 6%. For the stage II designations, the prevalence was also 6%, which could support brain imaging in this population (i.e., consistent with the NCCN guidelines). Nevertheless, for the stage I subcategories, the prevalence ranged from 1.7% to 3.7%, suggesting there may be subsets of patients with stage I disease in whom brain imaging was reasonable. If the benchmark pretest probability to image the brain is 6%, at what prevalence does brain imaging become unreasonable?

The rationale behind any threshold for brain imaging during the clinical staging evaluation for primary lung cancer must balance the hazards of over or under-imaging the brain. We reflected on the risks and benefits associated with imaging versus not imaging the brain in Table 3. Delays in detecting an asymptomatic brain metastasis (either by not imaging brain or a false-negative examination) may ultimately compromise local control of the metastasis when treated and may lead to increased mortality—though published studies are unable to control for lead-time bias and tumor aggressiveness.^{5,6} In contrast, any broadening of the indications for brain imaging would include patients with a lower pretest probability, which tends to increase the

false-positive rate. Although a false-positive rate could cause substantial anxiety for the patient and even unnecessary workup and treatments, the potential for loss in survival and neurologic symptom control associated with undiagnosed metastases provides significant counterbalance. Clinicians would have to thoughtfully consider positive studies in these groups to minimize treatment delays or treatment of benign lesions.

A number of recent advances in lung cancer management could impact brain imaging consideration. Phase 2 trial results support a more liberal use of local therapy to treat oligometastatic NSCLC.¹⁰ Support for local therapy in this setting may lessen the impact of an indeterminate finding in the brain, as many may consider it reasonable to proceed with definitive treatment and follow the brain lesion. In addition, immunotherapy, which is increasingly playing a role in patients with locoregionally confined lung cancer, seems to have better activity in the brain.^{11,12} Although these innovations are certainly factors in the management of brain-limited metastatic lung cancer, it is unclear if and how these would affect decision-making around brain imaging. Ultimately, patients are best served by the most accurate clinical stage determination, recognizing the tradeoffs between timeliness and cost and staging accuracy.

Perhaps the most challenging and potentially biasing aspect in this study is the inability to know why brain imaging was ordered. If we consider that approximately 25% to 50% of brain metastases are asymptomatic, the rationale for acquiring the brain imaging would almost certainly affect the prevalence of brain-only metastases.^{5,13} More specifically, hospitals that routinely imaged the brain in all patients with clinical stage II would likely have a higher prevalence of brain-only metastases than hospitals that only imaged symptomatic patients with stage II. Although we cannot mitigate the bias, we can

Table 3. Potential Hazards of Brain Imaging Patients Who Are Diagnosed With Early Stage NSCLC

	Theoretical Hazard	
	No Brain Mets Present	Brain Mets Present
No imaging	None	Delays in diagnosis of brain metastases associated with increased mortality and less effective neurologic symptom control ^{5,6}
Scan = no metastases	TN Cost for tests that did not change treatment (e.g., 37,000 patients with stage IA × \$800 per brain MRI) ⁷ , Decreased survival if NSCLC surgery delayed 50 d ⁸	FN Delays in diagnosis of brain metastases associated with increased mortality and less effective neurologic symptom control ^{5,6}
Scan = suspicious for metastases	FP False-positive rate of 7.6% for stage I vs. 1.4% for stage III, ⁹ leading to delays in treatment, unnecessary biopsy/definitive treatment	TP Desired result for patients with brain metastases

Note: The cost of imaging varies by imaging modality (CT vs. MRI), hospital, and insurance status. The listed cost is a median price paid by all public/private insurers in a large medical group in the Northeast United States. Imaging costs are incurred with all four outcomes (TP/FP/TN/FN). CT, computed tomography; FN, false negative; FP, false positive; MRI, magnetic resonance imaging; TN, true negative; TP, true positive.

estimate the direction of the bias. We expect that approximately one-fourth to one-half of patients with early stage NSCLC received invasive mediastinal staging based on previous reports and that the vast majority received a positron emission tomography-computed tomography scan based on the NCCN guidelines; however, imaging the brain of patients with stage I NSCLC was not a part of any staging guideline, and as such, it is likely that most of these brain-imaged patients had symptoms.^{1,14,15} For reference, an analysis of all patients with stage IA NSCLC in the National Lung Screening Trial found that 12% of the participants were screened for brain metastases whereas an analysis of the Surveillance Epidemiology and End Results Program found that 25% of patients with stage IA were imaged.^{14,15} As a result, asymptomatic brain-only metastases were likely under-detected in the stage I population. Therefore, it is quite likely that the true prevalence of brain metastases in clinical stage I is actually higher and the range between stages I and III is even more narrow.

Ultimately, we provide evidence of clear differences in the prevalence of brain-only metastases in NSCLC across staging attributes. It is less clear whether these differences are of sufficient magnitude to differentiate reasonable from unreasonable indications for imaging. These data could be interpreted as supporting a more liberal threshold to brain imaging, either by adopting the NCCN guidelines (clinical stage \geq II) or performing brain imaging at potentially even earlier stages. Further work is justified to understand the true prevalence of brain-only metastases within the various staging subgroups in the NSCLC population and potentially refine the clinical staging recommendations.

CRedit Authorship Contribution Statement

Matthew D. Pichert: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

Maureen E. Canavan: Software, Validation, Formal analysis, Writing - review & editing.

Richard C. Maduka, Andrew X. Li, Theresa Ermer, Peter L. Zhan, Michael Kaminski, Justin D. Blasberg, Vincent J. Mase Jr, Andrew P. Dhanasopon: Conceptualization, Methodology, Writing - review & editing.

Brooks V. Udelsman: Conceptualization, Writing - review & editing.

Daniel J. Boffa: Conceptualization, Methodology, Writing - review & editing, Project administration.

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