

INTRODUCTION

Most patients with non-small-cell lung cancer (NSCLC) have locally advanced or metastatic disease at diagnosis, with an estimated 15-20% of these patients having brain metastases; thus, the National Comprehensive Cancer Network (NCCN) recommends pre-treatment brain MRI for patients with T2 NSCLC or greater, while screening is merely "optional" for stage 1B disease and not for T1N0 NSCLC. Yet the evidence supporting these guidelines is largely based on staging by CT, which is now known to be less sensitive and specific for detecting brain metastases than MRI. Despite these advances in lung cancer staging, U.S. national guidelines still do not recommend routine brain MRI for patients with T1N0 NSCLC. Using a large, contemporary national cohort, we sought to characterize the prevalence and predictors of occult brain metastases in this population and identify patient subgroups who may benefit most from upfront neuroimaging.

METHODS

The Surveillance, Epidemiology, and End Results (SEER)-Medicare database was used to identify adults with primary NSCLC between 2010-2021. The SEER dataset is a population-based, federally funded collaboration between the National Cancer Institute, state cancer registries and the US Centers for Disease Control and Prevention. Clinical and pathologic staging information is recorded using the 8th edition American Joint Committee on Cancer (AJCC) Tumor Nodes and Metastases (TNM) classifications. Patients with clinical T1a-cN0 NSCLC were first identified in the SEER-Medicare database. Patients with other cancer diagnoses or metastases were excluded. Presence of brain metastases at time of diagnosis were defined if pre-treatment MRI/CT was performed within 6 months of the initial diagnosis date. Outcomes of interest included the presence of, and factors correlated with having brain metastases. Multivariable logistic regression models adjusted for covariates including age, sex, race, comorbid conditions, clinical T stage, histology, and grade. Multivariable outcomes are reported as adjusted odds ratios (aOR) with 95% confidence intervals.

RESULTS

Among 34,810 adults with T1N0 NSCLC, 14,705 (42.2%) underwent brain MRI at diagnosis; of these, 1,683 (11.5%) were found to have brain metastases. Compared to those without brain metastases, affected patients were younger (74.7 vs. 75.7 years, $p<0.001$), less frequently female (53.3% vs 56.0%, $p=0.008$), and more likely to identify as Black (7.33% vs. 5.90%, $p=0.004$). Those with brain metastasis had larger primary tumors (19.9mm vs 18.4mm, $p<0.001$) and were more frequently characterized as T1c disease (47.0% vs. 37.2%, $p<0.001$). In terms of histology, adenocarcinoma (63.4% vs. 55.4%, $p<0.001$) and non-small cell carcinoma (4.61% vs 2.99%, $p<0.001$) were more prevalent among those with brain metastases, while squamous cell carcinoma (15.3% vs 23.7%, $p<0.001$) was less common. On multivariable analysis, independent predictors of brain metastases included younger age (aOR: 0.97/year, 95% CI: 0.97–0.98), male sex (aOR: 1.16, 95% CI: 1.07–1.26), Black race (aOR: 1.23, 95% CI: 1.05–1.44; ref: White), T1c substage (aOR: 1.81, 95% CI: 1.55–2.10; ref: T1a), adenocarcinoma (aOR: 1.78, 95% CI: 1.59–2.00; ref: squamous cell carcinoma), and non-small cell carcinoma (aOR: 2.46, 95% CI: 1.97–3.06; ref: squamous cell carcinoma).

TABLE 1: Patient and tumor characteristics stratified by presence of brain metastases. (SE: standard error)

Factor	No Mets (n=32,272)	Brain Mets (n=2,538)	p-value
Age (years, SE)	75.7 (0.04)	74.7 (0.13)	<0.001
Female (%)	18,067 (56.0)	1,352 (53.3)	0.008
Black Race (%)	1,905 (5.90)	139 (7.33)	0.004
Comorbidities (%)			
Dementia	2,253 (6.98)	154 (6.07)	0.08
CHF	10,666 (33.1)	744 (29.3)	<0.001
Interstitial lung disease	25,027 (77.6)	1,829 (72.1)	<0.001
Smoking	23,134 (71.7)	1,775 (69.9)	0.06
Histology (%)			<0.001
Adenocarcinoma	17,869 (55.4)	1,608 (63.4)	
Adenosquamous	438 (1.24)	37 (1.46)	
Carcinoid	1,618 (5.01)	79 (3.11)	
Large cell	256 (0.79)	54 (2.13)	
Non-small cell carcinoma	965 (2.99)	117 (4.61)	
Squamous cell	7,639 (23.7)	389 (15.3)	
Other	3,525 (10.9)	254 (10.1)	
Primary tumor size (mm, SE)	18.4 (0.03)	19.9 (0.13)	<0.001
Stage (%)			<0.001
T1a	3,639 (11.3)	215 (8.47)	
T1b	16,638 (51.6)	1,131 (44.6)	
T1c	11,996 (37.2)	1,192 (47.0)	

Table 2: Adjusted odds of patients with T1N0 non-small cell lung cancer having brain metastases at time of diagnosis. AOR: Adjust Odds Ratio, CI: Confidence Interval

Factor	AOR	95% CI	p-value
Demographics (%)			
Male	1.16	[1.07-1.26]	<0.001
Black	1.23	[1.05-1.44]	0.01
Age	0.97	[0.97-0.98]	<0.001
Histology (%)			
Adenocarcinoma	1.78	[1.59-2.00]	<0.001
Adenosquamous	1.79	[1.26-2.56]	0.001
Carcinoid	1.00	[0.78-1.29]	0.98
Large cell	4.06	[2.97-5.56]	<0.001
Non-small cell carcinoma	2.46	[1.98-3.06]	<0.001
Squamous cell	Ref		
T-Stage (%)			
T1a	Ref		
T1b	1.19	[1.02-1.38]	0.03
T1c	1.81	[1.55-2.10]	<0.001
Comorbidities (%)			
Interstitial lung disease	0.81	[0.73-0.88]	<0.001
Ischemic heart disease	0.87	[0.79-0.95]	0.002
Cerebellar vascular disease	1.30	[1.19-1.42]	<0.001
Smoking	1.00	[0.91-1.10]	0.97

DISCUSSION

In this contemporary national analysis, the largest to focus exclusively on T1N0 NSCLC, 11.5% of all patients and 11.5% of those who underwent brain MRI were found to have brain metastases at diagnosis. Beyond histology and T-substage, younger age, male sex and Black race emerged as independent risk factors, highlighting the need for demographic-conscious staging practices. Thus, early brain MRI may be considered in those at higher risk, including subgroups such as younger Black males and those with T1c adenocarcinoma.

CONCLUSIONS

In this national analysis of T1N0 NSCLC, the prevalence of brain metastases was 11.5%. In the setting of T1N0Mx NSCLC, evaluation with brain imaging may be considered in patients with high-risk features, such as those with T1c Adenocarcinoma.

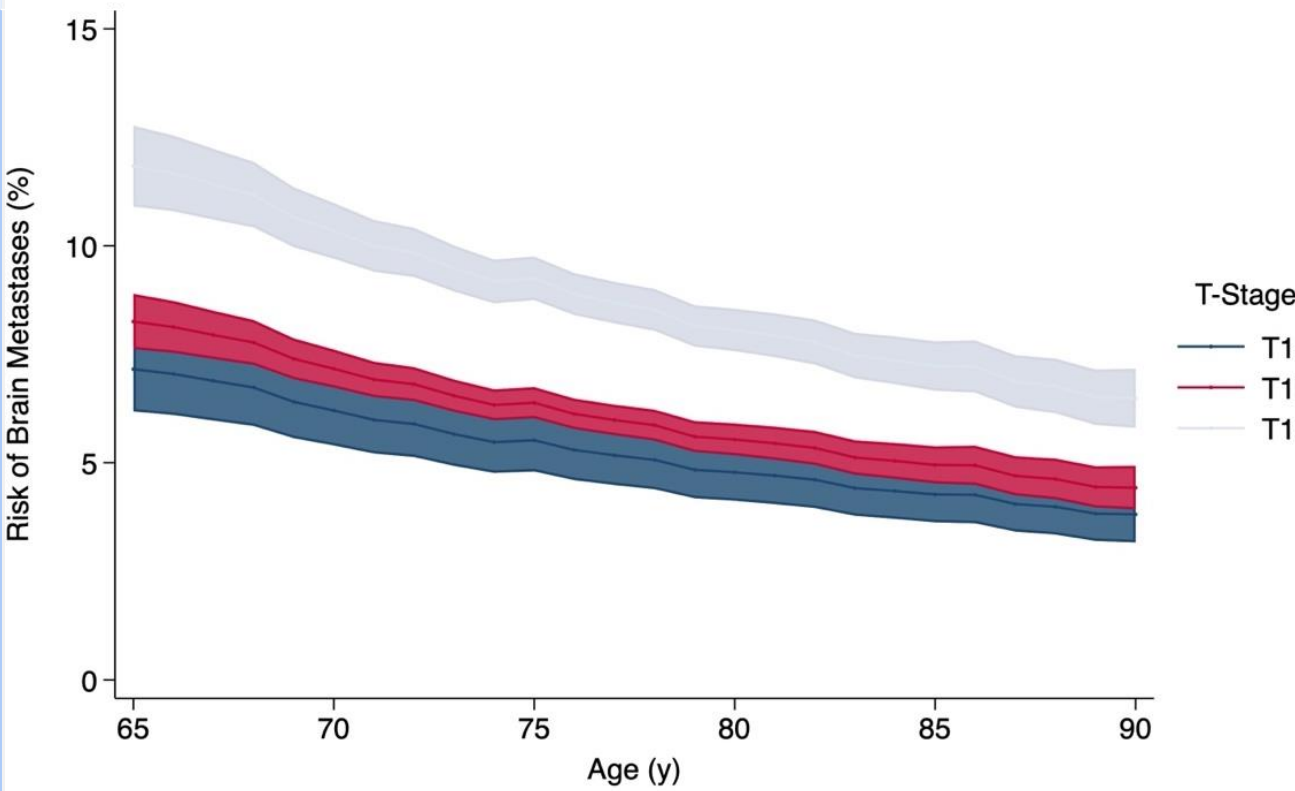


Figure 1: Predicted risk of brain metastases in T1N0 NSCLC patients at the time of diagnosis stratified by T-status

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