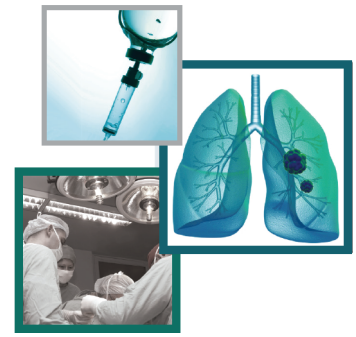
Short Communication

For reprint orders, please contact: reprints@futuremedicine.com

Lung Cancer Management



Risk of brain metastases in T1–3N0 NSCLC: a population-based analysis

Michael T Milano*[,1], James E Bates[1], Justin Budnik[1], Haoming Qiu[1], Sara Hardy[1], Michael A Cummings[1], Megan A Baumgart[2], Ronald J Maggiore[2], Deborah A Mulford[2] & Kenneth Y Usuki[1]

[1]Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY 14642, USA

[2]Department of Radiation Oncology, University of Florida, Gainesville, FL 32610, USA

*Author for correspondence: Michael_Milano@urmc.rochester.edu

Aim: Several consensus guidelines recommend against routine brain imaging at diagnosis of T1-3N0 non-small cell lung cancer (NSCLC). **Methods:** From the Surveillance, Epidemiology and End Results registry, patients with pathologically confirmed T1-3N0 NSCLC were identified. Risks of brain metastases at time of initial diagnosis were analyzed. **Results:** Patients selected to not undergo primary NSCLC resection had approximately tenfold greater incidence of brain metastases versus those who did. Younger age, adenocarcinoma histology, higher tumor stage and higher histologic grade were all significantly ($p < 0.0001$) associated with greater likelihood of presenting with brain metastases. **Conclusion:** Given the morbidity and mortality of brain metastases, routine brain screening after NSCLC diagnosis (particularly adenocarcinoma) may be justifiable, though more refined cost-benefit analyses are warranted.

First draft submitted: 3 October 2019; Accepted for publication: 10 February 2020; Published online: 25 February 2020

Keywords: adenocarcinoma • brain metastases • NSCLC • squamous cell carcinoma

Brain metastases are a common cause of morbidity and mortality, occurring in an estimated >100,000 patients per year in the USA. [1]. The incidence of brain metastases is dependent on the primary cancer site, histology and stage, with lung cancer being associated with the greatest absolute risk as well as number of patients diagnosed with brain metastases in the USA. [1–6]. More than half of patients with lung cancer (including small cell and non-small cell lung cancer [NSCLC]) present with metastatic disease [7], many with brain metastases.

A US population-based study, using data from the Surveillance, Epidemiology and End Results (SEER) program, showed that 26.8% of patients with lung adenocarcinoma and 15.9% of patients with lung squamous cell carcinoma were diagnosed with brain metastases at the time of initial presentation [5]. The risk of brain metastases from lung cancer is associated not only with histology, but also with the tumor and nodal staging of the disease [8–12]. It is estimated that 10–30% of patients with lung cancer (including those who initially present with nonmetastatic disease) will develop brain metastases during the course of their disease [13,14].

Recent National Comprehensive Cancer Network (NCCN) guidelines for NSCLC have recommended brain imaging during initial staging of patients with T2–3N0 NSCLC (as well as for those with more advanced stages of disease), but not for T1N0 NSCLC [15]. The version 7.2019 update of the NCCN guidelines explicitly considers brain imaging optional for Stage IB (i.e., T2aN0) NSCLC.

While the 2010 British Thoracic Society and 2017 European Society for Medical Oncology guidelines suggest consideration of screening for brain metastases in patients with NSCLC who are eligible for curative/radical therapy [16,17], the United Kingdom's 2019 National Institute for Health and Care Excellence (NICE) guidelines recommend against brain imaging for patients with clinical stage I NSCLC and no neurological symptoms [18].

The Society of Thoracic Surgeons (STS) Choosing Wisely campaign also explicitly recommends against routine brain imaging for patients with Stage I NSCLC [19]. Notably, the 2013 STS Choosing Wisely statement describes a 3% rate of clinically occult brain metastases from Stage I NSCLC and an 11% false-positive rate from brain

Future Medicine

imaging. These numbers were obtained from a 1997 American Thoracic Society and European Respiratory Society Consensus Report [20], though that report did not specify the NSCLC stage(s) associated with a 3% rate of occult brain metastases. Also, these numbers represent the use of head computed tomography for brain staging, and therefore are now outdated given the greater accuracy of brain MRI versus computed tomography in detecting brain metastases [21]. A 1999 study from Japan (with patients treated from 1982 to 1996) [22], also cited by STS, showed low rates of brain metastases (10 of 754) in patients with T1–2N0 NSCLC; while some patients underwent brain MRI, most had had head computed tomography for staging. A 2013 evidence-based report from the American College of Chest Physicians [23] describe a low yield (0–10%) of imaging for brain metastases in patients with NSCLC and a negative neurologic examination, and concluded that 'use of routine (brain) MRI in staging patients with NSCLC and negative clinical evaluations has not been studied adequately.'

We aimed to estimate the frequency of brain metastases in the setting of lymph node-negative T1–3 NSCLC, and to compare the tumor characteristics of this population to those without brain metastases. We hypothesized that the risk of brain metastases would be large enough to warrant consideration of brain imaging for those with T2–3N0 disease (as suggested by NCCN guidelines), and that tumor stage, adenocarcinoma histology and other patient and tumor-related factors (such as age, race, sociodemographic status and tumor grade) would impact these risks.

Methods

Patient database

The SEER Program collects information from population-based cancer registries throughout the USA. Serial registry data are de-identified and submitted to the National Cancer Institute on a biannual basis.

Patients were selected from within the SEER-18 registries using the SEER-Stat case listing session, with the following criteria: patients diagnosed from 2010 to 2016 with stage T1–3N0 (American Joint Committee on Cancer -AJCC- version 7) NSCLC primary site as the first or only cancer registered to the SEER program, with pathologically confirmed diagnosis of adenocarcinoma or squamous cell carcinoma (ICD-O-3 codes 8050-8084/3, 8140/3, 8255/3, 8260/3 or 8310/3) histology. Only patients with known surgical status (i.e., whether or not they underwent cancer-directed surgery) were included (in order to subgroup patients by this factor, as the rates of brain metastases in patients selected to undergo resection was expected to relatively low). Autopsy only/death certificate cases were excluded. Cancer-directed surgery indicates resection of the primary NSCLC (which was confirmed with the coding in the 'RX Summ–Surg Prim Site (1998+)' field). Patient, tumor and treatment characteristics were analyzed.

The SEER program captures information, at the time of initial diagnosis, on the presence or absence of metastases to the liver, lung, bone or brain. In 2016, SEER added a nonregional (distant) lymph node metastasis category; prior to 2016, information on nonregional node metastases was recorded in the 'CS mets at dx (2004–2015)' field. In 2016, SEER also added a field for 'other' metastases, which includes pleural effusions and pleural foci, pericardial effusions, metastases to nonliver abdominal organs and other sites. Prior to 2016, information on other metastases was also captured in the 'CS mets at dx (2004–2015)' field, with certain codes specifying the presence or absence of nonregional nodes and/or pleural effusions/foci and/or pericardial effusions; however among those patients diagnosed prior 2016 with brain metastases and without liver, lung, bone or nodal metastases, it cannot be determined if those registered as having 'other' sites in the 'CS mets at dx (2004–2015)' field had only brain metastases or had brain and other sites of metastases. Therefore, for this study, it was considered to have been unknown if those patients had other sites of metastases (other than brain metastases).

Patients were grouped into those without metastatic (M0) disease, those with brain metastases without known or recorded sites of other metastases, those with brain metastases who also had other sites of metastases at diagnosis, and those without known brain metastases who had other sites of metastases recorded in the SEER program.

Statistical analysis

Stata version 15.1 (StataCorp, TX, USA) was used for data analysis. For univariate comparisons between different groups, χ^2 test was used for categorical variables and t-test was used for continuous variables. Multivariable logistic regression analyses were performed to determine associations between selected variables and presence of brain metastases (with no other known metastases); odds ratios (OR) and 95% CI were reported from these regression analyses.

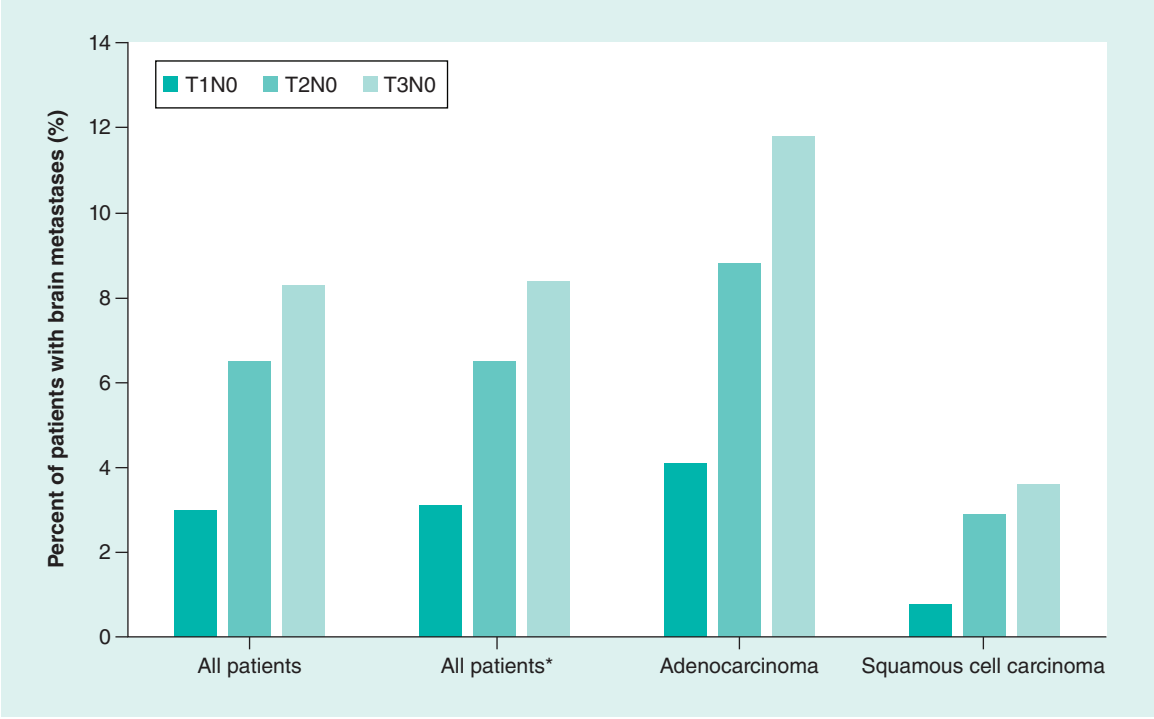


Figure 1. Percent of patients presenting with brain metastases, grouped by tumor stage.
*Excluding patients for whom the presence or absence of brain metastases was registered as "unknown".

Results

Patient & tumor characteristics

Table 1 summarizes the patient, tumor and treatment characteristics of the study patients. The median age at the time of diagnosis was 70 years. Because the patient, tumor and treatment characteristics differed greatly between the groups of patients who underwent resection of NSCLC versus those who did not (indicative of expected selection biases between these two groups), and because the incidence of brain metastases differed greatly among those selected to undergo resection of NSCLC versus those who did not (presented below), patients were grouped by this factor. Those who underwent resection of NSCLC were significantly ($p < 0.0001$) younger, more likely to be white and more likely to reside in countries with greater education and income. The tumors of those who underwent resection were significantly more likely to be adenocarcinoma, right-sided, lower tumor stage and lower histologic grade ($p < 0.0001$ for each factor). Patients who underwent resection of NSCLC were markedly and significantly more likely to have had regional lymph nodes pathologically examined, less likely to have undergone radiotherapy and more likely to have undergone chemotherapy ($p < 0.0001$ for each factor).

Rate of brain metastases

Among all 49,495 patients with T1–3N0 NSCLC, 2661 (5.4%) had brain metastases at time of initial diagnosis, of whom more than half (57.0%) had no other metastatic sites registered to the SEER program. Excluding 828 patients with metastatic disease, but with no specific metastatic sites registered in the SEER program, resulted in similar findings.

For patients with T1N0, T2N0 and T3N0 NSCLC, 650 of 21,063 (3.0%), 1244 of 19,172 (6.5%) and 767 of 9260 (8.3%) presented with brain metastases, respectively (Figure 1).

For patients with adenocarcinoma 2242 of 16,470 (13.6%) presented with brain metastases, versus 419 of 8246 (5.1%) with squamous cell carcinoma. Figure 1 shows the incidence of brain metastases grouped by tumor stage.

Table 2 summarizes the patient, tumor and treatment characteristics of patients who underwent resection of NSCLC, grouped by whether or not they presented with metastases, and what metastatic sites were involved (brain with no other known sites, brain and other sites, other sites without known brain metastases). Of 25,357 patients, 217 (0.9%) presented with brain metastases at the time of initial diagnosis; most (181 of 217; 83.4%) had no

Table 1. Patients with T1-3N0M0-1 NSCLC: patient, tumor and treatment characteristics.

Characteristics	All patients	Underwent resection of NSCLC	No resection of NSCLC	p-value
Total	49,495	25,554	23,941	not applicable
Age, mean (years)	69.9	67.8	72.0	<0.0001‡
Median	70	68	73	
<70	23,399 (47.3%)	14,031 (54.9%)	9368 (39.1%)	<0.0001
≥70	26,096 (52.7%)	11,523 (45.1%)	14,573 (60.9%)	
Year of lung cancer diagnosis				
2010–2013	27,062 (54.7%)	14,446 (56.5%)	12,616 (52.7%)	<0.0001
2014–2016	22,433 (45.3%)	11,108 (43.5%)	11,325 (47.3%)	
Race				
White	40,359 (81.5%)	21,309 (83.4%)	19,050 (79.6%)	<0.0001
Black	5336 (10.8%)	2296 (9.0%)	3040 (12.7%)	
Others	3648 (7.4%)	1842 (7.2%)	1806 (7.5%)	
Unknown	152 (0.3%)	107 (0.4%)	45 (0.2%)	
County % with <High school education				
Median	12.5%	12.5%	13.0%	
Mean	13.9%	13.7%	14.1%	<0.0001‡
County income				
Median	$61,020	$61,020	$60,800	
Mean	$62,614	$63,645	$61,514	<0.0001‡
Histology				
Adenocarcinoma	31,401 (63.4%)	17,068 (66.8%)	14,333 (59.9%)	<0.0001
Squamous cell carcinoma	18,094 (36.6%)	8486 (33.2%)	9608 (40.1%)	
Laterality				
Right	28,203 (57.0%)	15,254 (59.7%)	12,949 (54.1%)	<0.0001
Left	20,978 (42.4%)	10,283 (40.2%)	10,695 (44.7%)	
Bilateral‡	143 (0.3%)	6 (<0.1%)	137 (0.6%)	
Not reported	171 (0.3%)	11 (<0.1%)	160 (0.7%)	
T stage				<0.0001
T1	21,063 (42.6%)	13,008 (50.9%)	8055 (33.6%)	
T2	19,172 (38.7%)	9491 (37.1%)	9681 (40.4%)	
T3	9260 (18.7%)	3055 (12.0%)	6205 (25.9%)	
Grade				<0.0001
Grade 1–2	21,729 (43.9%)	15,892 (62.2%)	5837 (24.4%)	
Grade 3–4	13,896 (28.1%)	8202 (32.1%)	5694 (23.8%)	
Unknown grade	13,870 (28.0%)	1460 (5.7%)	12,410 (51.8%)	
Regional nodes examined				<0.0001
Yes	24,656 (49.8%)	22,996 (90.0%)	1660 (6.9%)	
No	24,729 (50.0%)	2525 (9.9%)	22,204 (92.7%)	
Unknown	110 (0.2%)	33 (0.1%)	77 (0.3%)	
First course of therapy: radiotherapy				<0.0001
Yes	15,394 (31.1%)	1548 (6.1%)	13,846 (57.8%)	
No/unknown	34,101 (68.9%)	24,006 (93.9%)	10,095 (42.2%)	
First course of therapy: chemotherapy				<0.0001
Yes	10,948 (22.1%)	22,020 (86.2%)	16,527 (69.0%)	
No/unknown	38,547 (77.9%)	3534 (13.8%)	7414 (31.0%)	

†t-test or χ^2 test comparing distribution of variable among patients undergoing vs those not undergoing cancer-directed surgery of primary lung cancer.
‡All 143 patients with 'bilateral' non-small cell lung cancer had metastatic disease (n = 108 with lung metastases); therefore, bilateral is likely indicative of contralateral primary and metastatic site(s). However, with correct coding for laterality, all T1-3N0M0 non-small cell lung cancer would by unilateral).

Table 2. Patients who underwent resection of T1-3N0 NSCLC: presence of absence of metastases grouped by patient, tumor and treatment characteristics.

Characteristics	M0	M1 brain (no other sites†)	M1 brain (+ other sites†)	M1 without known brain metastases
Total	24,716	181	36	424
Age, mean (years)	68.0	60.8	62.1	66.7
Median	68	61	64	67
<70	13,488 (54.6%)	149 (82.3%)	29 (80.6%)	246 (58.0%)
≥70	11,228 (45.4%)	32 (17.7%)	7 (19.4%)	178 (42.0%)
Year of lung cancer diagnosis				
2010–2013	13,927 (56.3%)	102 (56.4%)	25 (69.4%)	260 (61.3%)
2014–2016	10,789 (43.7%)	79 (43.6%)	11 (30.6%)	164 (38.7%)
Race				
White	20,624 (83.4%)	155 (85.6%)	30 (83.3%)	336 (79.2%)
Black	2202 (8.9%)	16 (8.8%)	3 (8.3%)	54 (12.7%)
Other	1785 (7.2%)	9 (5.0%)	3 (8.3%)	34 (8.0%)
County % <High school education				
Median	12.5%	11.6%	12.7%	13.0%
Mean	13.7%	13.6%	14.2%	14.1%
County income				
Median	$61,020	$61,020	$61,020	$61,020
Mean	$63,715	$63,028	$65,419	$61,056
Histology				
Adenocarcinoma	16,470 (66.6%)	157 (86.7%)	34 (94.4%)	302 (71.2%)
Squamous cell carcinoma	8246 (33.4%)	24 (13.3%)	2 (5.6%)	122 (28.8%)
Laterality				
Right	14,750 (59.7%)	114 (63.0%)	23 (63.9%)	250 (59.0%)
Left	9958 (40.3%)	67 (37.0%)	11 (30.6%)	170 (40.1%)
T stage				
T1	12,833 (51.9%)	63 (34.8%)	9 (25.0%)	85 (20.0%)
T2	9201 (37.2%)	84 (46.4%)	17 (47.2%)	167 (39.4%)
T3	2682 (10.9%)	34 (18.8%)	10 (27.8%)	172 (40.6%)
Grade				
Grade 1–2	15,556 (62.9%)	66 (36.5%)	14 (38.9%)	184 (43.4%)
Grade 3–4	7811 (31.6%)	95 (52.5%)	12 (33.3%)	184 (43.4%)
Unknown grade	1349 (5.5%)	20 (11.0%)	10 (27.8%)	56 (13.2%)
Regional nodes examined				
Yes	22,446 (90.8%)	141 (77.9%)	16 (44.4%)	238 (56.1%)
No	2238 (9.1%)	40 (22.1%)	20 (55.6%)	185 (43.6%)
First course of therapy: radiotherapy				
Yes	1197 (4.8%)	151 (83.4%)	29 (80.6%)	84 (19.8%)
No/unknown	23,519 (95.2%)	30 (16.6%)	7 (19.4%)	340 (80.2%)
First course of therapy: chemotherapy				
Yes	3096 (12.5%)	108 (59.7%)	20 (55.6%)	192 (45.3%)
No/unknown	21,620 (87.5%)	73 (40.3%)	16 (44.4%)	232 (54.7%)

† 'no other sites' implies no known metastases to bone, liver, lung, nonregional lymph nodes or other sites, while '+ other sites' implies known metastases to one or more of bone, liver, lung, nonregional lymph nodes or other sites.
Not shown: number of patients with unknown race, lung cancer laterality, bilaterality or status of regional node examination.
Also not shown are 197 patients registered as having had Stage IV disease, but with no known (or listed) sites of metastases.

Table 3. Patients who did not undergo resection of T1-3N0 NSCLC: presence of absence of metastases grouped by patient, tumor and treatment characteristics.

Characterisitcs	M0	M1 brain (no other sites†)	M1 brain (+ other sites†)	M1 without known brain metastases
Total	13,601	1335	1109	7265
Age, mean (years)	73.6	65.8	66.0	71.1
Median	74	66	66	72
<70	4508 (33.1%)	834 (62.5%)	684 (61.7%)	3098 (42.6%)
≥70	9093 (66.9%)	501 (37.5%)	425 (38.3%)	4167 (57.4%)
Year of lung cancer diagnosis				
2010–2013	6921 (50.9%)	714 (53.5%)	597 (53.8%)	4017 (55.3%)
2014–2016	6680 (49.1%)	621 (46.5%)	512 (46.2%)	3248 (44.7%)
Race				
White	11,119 (81.8%)	1011 (75.7%)	812 (73.2%)	5613 (77.3%)
Black	1632 (12.0%)	214 (16.0%)	138 (12.4%)	972 (13.4%)
Others	824 (6.1%)	108 (8.1%)	156 (14.1%)	666 (9.2%)
County % <High school education				
Median	12.6%	13.0%	12.6%	13.3%
Mean	13.9%	14.1%	13.9%	14.5%
County income				
median	$60,810	$61,020	$61,020	$60,810
mean	$61,557	$61,590	$62,723	$61,281
Histology				
Adenocarcinoma	6709 (49.3%)	1115 (83.5%)	936 (84.4%)	5261 (72.4%)
Squamous cell carcinoma	6892 (50.7%)	220 (16.5%)	173 (15.6%)	2004 (27.6%)
Laterality				
Right	7560 (55.6%)	698 (52.3%)	575 (51.8%)	3783 (52.1%)
Left	6020 (44.3%)	634 (47.5%)	500 (45.1%)	3257 (44.8%)
T stage				
T1	6012 (44.2%)	363 (27.2%)	215 (19.4%)	1399 (19.3%)
T2	5162 (38.0%)	663 (49.7%)	480 (43.3%)	3227 (44.4%)
T3	2427 (17.8%)	309 (23.1%)	414 (37.3%)	2639 (36.3%)
Grade				
Grade 1–2	4069 (29.9%)	205 (15.4%)	169 (15.2%)	1238 (17.0%)
Grade 3–4	3399 (25.0%)	413 (30.9%)	260 (23.4%)	1455 (20.0%)
Unknown grade	6133 (45.1%)	717 (53.7%)	680 (61.3%)	4572 (62.9%)
Regional nodes examined				
Yes	1345 (9.9%)	51 (3.8%)	26 (2.3%)	188 (2.6%)
No	12,211 (89.8%)	1281 (96.0%)	1079 (97.3%)	7057 (97.1%)
First course of therapy: radiotherapy				
Yes	9380 (69.0%)	1066 (79.9%)	807 (72.8%)	2320 (31.9%)
No/unknown	4221 (31.0%)	269 (20.1%)	302 (27.2%)	4945 (68.1%)
First course of therapy: chemotherapy				
Yes	2621 (19.3%)	636 (47.6%)	586 (52.8%)	3260 (44.9%)
No/unknown	10,980 (80.7%)	699 (52.4%)	523 (47.2%)	4005 (55.1%)

†'no other sites' implies no known metastases to bone, liver, lung, non\regional lymph nodes or other sites, while '+ other sites' implies known metastases to one or more of bone, liver, lung, nonregional lymph nodes or other sites.
Not shown: number of patients with unknown race, lung cancer laterality, bilaterality or status of regional node examination. Also not shown are 631 patients registered a having had Stage IV disease, but with no known (or listed) sites of metastases.

other sites of metastases; thus approximately 0.7% had T2–3N0M1 with brain metastases and no other apparent (or registered) metastatic sites.

Table 3 summarizes the patient, tumor and treatment characteristics of patients who did not undergo resection

Table 4. Univariate relationship of patient and tumor characteristics and significance of association with brain metastases in patients with no other known sites of metastases.

Characterisitcs	p-values	
	Patients who underwent resection of NSCLC	Patients who did not undergo resection of NSCLC
Age (≥70†)	$p < 0.0001$	$p < 0.0001$
Age* (older†)	$p < 0.0001$	$p < 0.0001$
Year of lung cancer diagnosis	$p = 1.0$	$p = 0.07$
Race (nonwhite†)	$p = 0.71$	$p < 0.0001$
County %<HS education*	$p = 0.74$	$p = 0.94$
County income*	$p = 0.60$	$p = 0.15$
Histology (adenocarcinoma†)	$p < 0.0001$	$p < 0.0001$
Laterality (left sided†)	$p = 0.85$	$p = 0.022$
T stage (T2–3†)	$p < 0.0001$	$p < 0.0001$
Grade (grade 3–4/unknown†)	$p < 0.0001$	$p < 0.0001$
Regional nodes examined (no†)	$p < 0.0001$	$p < 0.0001$

†Factors associated with greater risk of brain metastases.
p-values of comparison between M0 group and those with brain metastases and those no other known sites of metastases. Univariate analyses using $\chi 2$ test (for categorical variables) or t-test (for continuous variables, as denoted by *).

of NSCLC, grouped as described above for Table 2. Of 23,310 patients, 2444 (10.5%) presented with brain metastases at the time of diagnosis; the majority (1335 of 2444; 54.6%) had no other sites of metastases; thus approximately 5.7% had T1-3N0M1 with brain metastases and no other apparent (or registered) metastatic sites.

Univariate & multivariable analyses

Table 4 summarizes the significance of the comparison of patient and tumor-related factors between patients presenting with M0 disease versus those presenting with metastases to the brain and no other sites of metastases registered to the SEER program. Patients with M0 disease were significantly ($p < 0.0001$ for each factor) more likely to be older in age, with squamous cell cancer histology, lower tumor stage and lower histologic grade, for both groups (those who underwent resection of NSCLC and those who did not). Among those who did not undergo resection of NSCLC, patients with M0 disease were significantly ($p < 0.0001$ for each factor) more likely to be white race and with right-sided (versus left sided) primary NSCLC, albeit with small absolute differences for these factors. The sociodemographic measures of income and education within the county of residence were not significant factors for risk of brain metastases at initial diagnosis, nor was the year of NSCLC diagnosis (albeit within a narrow range of 2010–2016). While differences between these two groups in radiotherapy and chemotherapy use were highly significant (and readily apparent in Tables 2 & 3), we opted to not include these factors in Table 4, as any potential association of these factors is directly related to the treatment choice for patients with versus without brain metastases (as opposed to these factors impacting risk of brain metastases). While this may also be true for regional lymph node sampling (i.e., those initially diagnosed with brain metastases would be less likely to benefit from, and therefore undergo, regional node sampling), we opted to include this information in Table 4 (showing significant differences between groups) as it correlates with the completeness of NSCLC staging.

Table 5 shows a multivariable logistic regression adjusting for age, race, histology, tumor stage, grade and regional node assessment, grouped by whether or not the patients underwent resection of NSCLC. For both groups, greater tumor stage (T2–3 vs T1) and higher (or unknown) pathologic grade were associated with a >twofold greater likelihood of having brain metastases (in the absence of other metastases); no or unknown evaluation of regional nodes and age <70-year old were associated with >threefold risk, and adenocarcinoma histology was associated with 3.8-fold and sixfold risk for patients who underwent versus did not undergo resection of NSCLC.

Omitting race (which was not a significant factor) and/or regional lymph node evaluation (which is not an *a priori* risk factor) from the logistic models did not appreciably change the ORs (<10% change in all ORs in the group who underwent resection of NSCLC, and <3% in the group who did not undergo resection) with the ORs falling within the 95% CIs of those shown in Table 5, and with the p-values remaining <0.0001 for all of the significant variables (data not shown in Table 5). Omitting those patients with race, grade and/or regional lymph node assessment registered to SEER as "unknown" did not appreciably change the results (see footnotes in Table 5 for numbers). Because of the large numbers of patients with unknown grade (particularly in the group that did not

Table 5. Multivariate logistic regression of patient and tumor characteristics and strength of association with brain metastases in patients with no other known sites of metastases.

Factors	Group 1		Group 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (<70 vs ≥70 years)	3.66 (2.50–5.40)	<0.0001	3.21 (2.85–3.63)	<0.0001
Race (others/unknown vs white)	1.38 (0.91–2.10)	0.13	1.10 (0.95–1.27)	0.19
Histology (adenocarcinoma vs SCCa)	3.82 (2.47–5.90)	<0.0001	5.95 (5.11–6.93)	<0.0001
T stage (T2–3 vs T1)	2.10 (1.53–2.88)	<0.0001	2.68 (2.35–3.06)	<0.0001
Grade (grade 3–4/unknown vs grade 1–2)	2.87 (2.10–3.91)	<0.0001	2.29 (1.95–2.68)	<0.0001
Regional nodes examined (no/unknown vs yes)	3.29 (2.29–4.72)	<0.0001	3.10 (2.31–4.17)	<0.0001

Group 1: Patients who underwent resection of NSCLC.
Group 2: Patients who did not undergo resection of NSCLC.
Among patients with no known metastases (n = 38,317) or metastases to the brain with no other known sites (n = 1516): in Group 1, there were 106, 1,369 and 32 patients with unknown race, histologic grade and regional node assessment, respectively, and 1483 of 24,897 (6%) patients had one or more of these unknown factors; in Group 2, there were 28, 6,850 and 48 patients with unknown race, histologic grade and regional node assessment, respectively, and 6884 of 14,936 (46%) patients had one or more of these unknown factors. Small (<10%) changes in the ORs, and no changes in the $p < 0.0001$, resulted from omitting patients with unknown variables of race, grade (accounting for most of the patients with unknown factors) and/or regional lymph node assessment, except for the OR for T stage among those patients who did not undergo resection of NSCLC, which increased 20% from 2.68 (95% CI: 2.35–3.06) to 3.23 (95% CI: 2.61–4.00; data not shown above).
OR: Odds ratio; SCCa: Squamous cell carcinoma.

undergo resection of NSCLC), and the small impact on the logistic models with ignoring these patients, a model with multiple imputations was not pursued (nor was it in a similar, recently published analysis [11]).

From a logistic regression including selection to undergo resection of NSCLC as a factor, along with age, histology, grade, tumor stage and lymph node sampling, the OR for no resection was 8.1 (95% CI: 6.4–10.2), on the same order as the estimated tenfold crude difference described above.

T1N0 adenocarcinoma

For patients with T1N0 adenocarcinoma and no nonbrain metastases (for whom the NCCN or STS do not recommend brain imaging in the absence of neurologic symptoms), 268 of 6837 (3.9%) patients <70-year old and 123 of 6273 (2.0%) patients ≥70-year old presented with brain metastases at initial diagnosis (although data on possible neurologic symptoms are not available in the SEER program). Among those who did not undergo resection of NSCLC, these rates were 219 of 1377 (6.9%) and 114 of 2476 (4.6%) for those <70- and ≥70-year old, respectively.

Discussion

We have shown, in a modern series of patients, that >5% of patients with T1-3N0 NSCLC present with brain metastases at the time of initial diagnosis; a majority of those patients with brain metastases have no other sites of known metastases at the time of initial NSCLC staging. A greater than threefold risk of presenting with brain metastases was associated with the factors of age younger than 70-year old, adenocarcinoma histology, T2–3 (versus T1) stage and higher histologic grade. Patients selected to not undergo resection of NSCLC were >tenfold more likely to have had brain metastases (10.5 vs 0.9%) and >eightfold more likely to have had brain metastases with no other known sites of metastases (5.7 vs 0.7%); these findings likely reflect a general opting against lung resection in patients with known brain metastases (as discussed below). It is also notable that patients <70-years in age, with T1N0 adenocarcinoma, had a ~4% risk of having brain metastases; this risk warrants consideration of routine brain imaging for patients who fall within this group, contrary to NCCN and NICE guidelines, and the STS Choosing Wisely statement.

Other studies have analyzed risks of brain metastases in patients with lymph node-negative NSCLC. In a study of 131,456 patients diagnosed from 1988 to 1997 and registered to the SEER program, the use of brain radiotherapy was used as a surrogate for the presence of brain metastases [12]; of 34,835 patients with N0 disease, 4.4% had undergone brain radiotherapy, similar in magnitude to what is reported in this study. Notably, the patients in this study were more recently diagnosed, and were explicitly coded for the presence of absence of brain metastases. In a relatively small retrospective study from Japan, 6 of 46 (13%) patients diagnosed with T1–2aN0 NSCLC (from

2012 to 2016) had brain metastases, with only 1 of 6 being symptomatic [24]. In contrast, a study from Australia in which 718 patients (from 2011 to 2015) underwent body positron emission tomography/computed tomography and brain imaging [25], only 2 of 302 (<1%) patients with N0 disease had brain metastases detected compared with 16 of 413 (4%) with N1–3 disease, p = 0.019. In a hospital-based National Cancer Data Base registry study [11], 10.4% of 457,481 patients diagnosed with NSCLC (from 2010 to 2012) presented with brain metastases, as did 5.1% of 204,203 patients with N0 disease (similar in magnitude to what is shown here in this study, albeit including patients with T4 disease). In the NCBD study, compared with squamous cell carcinoma histology, adenocarcinoma was associated with a threefold greater risk of brain metastases; younger age, greater tumor size, node positivity (hazard ratio of ~2) and higher tumor grade were all also significantly ($p < 0.001$) associated with greater risk of presenting with brain metastases. This study did not specifically analyze risk factors among those with N0 disease.

We chose to specifically exclude patients with lymph node positive disease, due to their higher risk of brain metastases. In a retrospective study of 193 patients [26], greater lymph node stage, multilymph node involvement and lymph node size >2 cm were significantly adverse risk factors for harboring asymptomatic brain metastases; lymph node size remained significant on multivariate analysis (p = 0.009). Node positivity also impacts the risk of developing brain metastases in those patients who initially present with nonmetastatic NSCLC. A retrospective study of 975 patients with T1-2N0-1M0 NSCLC (using the 6th edition of AJCC staging), showed that the 5-year risk of developing brain metastases is 10%, and that the absence of hilar nodal involvement was associated with approximately 1.2-fold ($p < 0.04$) decreased risk [8]. In a SEER-based study, confined to the Metropolitan Detroit region (for which follow-up data on cancer control was available), 9% of 34,681 patients with initial nonmetastatic NSCLC developed brain metastases over a 39-year follow-up [27]. Localized disease (i.e., without nodal involvement or extension to regional sites) was associated with a >1.5-fold ($p < 0.0001$) decreased risk of developing brain metastases.

Strengths of this study include the large number of patients from recent years, obtained from population-based data. These numbers should reflect 'real-world' estimates of rates of brain metastases, and factors affecting those rates.

There are several limitations inherent in any retrospective study from a population-based registry. In the SEER program, there are no data on: comorbidities; oncogene receptor or mutation status; programmed death-ligand 1 expression; presenting symptoms (if any) of the primary NSCLC or brain metastases; the type or extent of lymph node sampling performed (if done); the use of positron emission tomography for staging; the use, and type of brain imaging; the extent of brain metastases; the extent of extracranial metastases; or whether or not patients without neurologic symptoms underwent brain imaging and/or intracranial resection. While EGFR positive, anaplastic-lymphoma-kinase rearranged and *ROS1*-mutated NSCLC (predominantly adenocarcinomas) represent a minority of NSCLC, these oncogene mutations (particularly ALK) are associated with a high incidence of brain metastases, and therefore may impact decision-making for staging with brain imaging [28–32]. Another limitation is the potential under-reporting of metastatic sites in the SEER program.

Some patients registered as having M0 disease may have harbored asymptomatic brain metastases and not undergone brain imaging. Thus, the true incidence of brain metastases at diagnosis may be underestimated in this analysis. Among those with brain metastases who did not undergo resection of NSCLC, some may have been considered for resection had they not had brain metastases. However, the much greater difference in rates of brain metastases in patients who did versus did not undergo resection is most likely attributable to patients with diagnosed brain metastases not being offered resection of their NSCLC, given the potential morbidity of thoracic surgery and poor survival associated with brain metastases from NSCLC [14]. Among those patients who underwent resection of NSCLC, some may have been diagnosed with brain metastases shortly after surgery (and perhaps not been recommended to undergo resection had that information been known); others may have been diagnosed prior to surgery and opted to be treated aggressively. In a retrospective study of 585 patients with resected NSCLC, among the 25 (5.3%) of patients diagnosed with brain metastases, 20 (80%) were diagnosed after surgery, with the authors concluding (from a small group of patients) that preoperative staging of the CNS may change management in some patients [33]. Because of these and many other confounding factors, we opted against analyzing survival outcomes.

Conclusion

In conclusion, patients with lymph node-negative NSCLC are at risk of harboring brain metastases at diagnosis, with younger age, greater tumor stage, adenocarcinoma histology and higher grade associated with greater risk. Not undergoing resection of NSCLC and lack of pathologic sampling of lymph nodes were also associated with

greater likelihood of brain metastases, probably largely due to patient selection (i.e., presence of brain metastases reducing the need for nodal sampling and/or resection). Given the morbidity and mortality of brain metastases [34], consideration for routine brain imaging in patients with node-negative NSCLC seems warranted, particularly in younger patients with more advanced tumor stage and adenocarcinoma histology. More refined risks accounting for the burden of disease, costs of imaging and costs of potentially untreated brain metastases (i.e., in undiagnosed asymptomatic patients) warrant further study [34]. Large, population-based analyses, restricted to patients with T1-3N0 NSCLC and without new-onset neurologic symptoms, are also needed.

Future perspective

To best ascertain the incidence of brain metastases from NSCLC, prospective MRI would be optimal. In addition to the aforementioned clinical-pathologic correlates of risks of brain metastases, the study of genomic correlates to risk is an opportunity for future study and eventual adoption into clinical practice. As described in the discussion, oncogene receptor or mutation status (i.e., *EGFR, ALK, ROS, PDL*), which are performed routinely in many practices, can provide insight into risk of brain metastases (which are generally higher). Additional genomic correlates (yet uncharacterized) of greater propensity to develop brain metastases warrant further study. While brain metastases may be characterized by different genomic signatures than primary cancers [35], it is conceivable that certain genomic patterns (single nucleotide polymorphisms or genome-wide association) of the primary cancer can signal a greater risk of brain metastases. The financial costs of such testing would certainly need to be weighed against the costs of imaging though.

Summary points

- Several studies have examined the risk of brain metastases if patients with NSCLC, though population-based data specific for patients with node-negative NSCLC are lacking.
- Consensus guidelines for brain imaging in newly diagnosed NSCLC differ, with some guidelines based on outdated data.
- We show that, particularly for adenocarcinoma, risks of brain metastases are appreciable and may warrant consideration of brain imaging.
- Other factors associated with risks of brain metastases include younger age, higher grade and higher tumor stage.
- Patients with node-negative NSCLC (particularly adenocarcinoma) can be considered for staging with brain imaging.
- However, more refined cost-benefit analyses are warranted.

Author contributions

Contributions to conception or design of the work was conducted by MT Milano, JE Bates, J Budnik and KY Usuki. Acquisition and analysis of the data were conducted by MT Milano. All authors contributed to the interpretation of data for the work. All authors contributed to drafting the work or revising it critically for important intellectual content; final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial & competing interests disclosure

This research did not receive any specific grant funding from agencies in the public, commercial or not-for-profit sectors. MT Milano reports royalties from Wolters Kluwer (UpToDate) and honorarium from Galera Therapeutics. KY Usuki reports travel expenses from BrainLAB. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

Authors who accessed the SEER database adhered to SEER Research Data Agreement (https://seer.cancer.gov/data/sample-dua.html) and have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

References

Papers of special note have been highlighted as: •• of considerable interest

1. Stelzer KJ. Epidemiology and prognosis of brain metastases. *Surg. Neurol. Int.* 4(Suppl. 4), S192–S202 (2013).
2. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 94(10), 2698–2705 (2002).
3. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J. Clin. Oncol.* 22(14), 2865–2872 (2004).
4. Villano JL, Durbin EB, Normandeau C, Thakkar JP, Moirangthem V, Davis FG. Incidence of brain metastasis at initial presentation of lung cancer. *Neuro. Oncol.* 17(1), 122–128 (2015).
5. Cagney DN, Martin AM, Catalano PJ *et al.* Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro. Oncol.* 19(11), 1511–1521 (2017).

•• **US population-based study, 26.8% of patients with lung adenocarcinoma and 15.9% of patients with lung squamous cell carcinoma (all stages) were diagnosed with brain metastases at the time of initial presentation.**

6. Kromer C, Xu J, Ostrom QT *et al.* Estimating the annual frequency of synchronous brain metastasis in the United States 2010–2013: a population-based study. *J. Neurooncol.* 134(1), 55–64 (2017).
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J. Clin.* 69(1), 7–34 (2019).
8. Hubbs JL, Boyd JA, Hollis D, Chino JP, Saynak M, Kelsey CR. Factors associated with the development of brain metastases: analysis of 975 patients with early stage nonsmall cell lung cancer. *Cancer* 116(21), 5038–5046 (2010).

•• **A single institution retrospective study of patients with T1-2N0 NSCLC showed that the absence of hilar nodal involvement was associated with ~1.2-fold ($p < 0.04$) decreased risk of developing brain metastases.**

9. Mujoomdar A, Austin JH, Malhotra R *et al.* Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. *Radiology* 242(3), 882–888 (2007).
10. An N, Jing W, Wang H *et al.* Risk factors for brain metastases in patients with non-small-cell lung cancer. *Cancer Med.* 7(12), 6357–6364 (2018).
11. Waqar SN, Samson PP, Robinson CG *et al.* Non-small-cell lung cancer with brain metastasis at presentation. *Clin. Lung Cancer* 19(4), e373–e379 (2018).

•• **In this hospital-based registry study, 5.1% of 204,203 patients with T1-T4N0 NSCLC presented with brain metastases. Adenocarcinoma was associated with a threefold greater risk of brain metastases**

12. Waqar SN, Waqar SH, Trinkaus K *et al.* Brain metastases at presentation in patients with non-small cell lung cancer. *Am. J. Clin. Oncol.* 41(1), 36–40 (2018).

•• **In this US population-based study, a total of 4.4% of patients with node-negative NSCLC underwent brain radiotherapy for brain metastases.**

13. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. *J. Neurooncol.* 75(1), 5–14 (2005).
14. Sperduto PW, Yang TJ, Beal K *et al.* Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol.* 3(6), 827–831 (2017).
15. National Comprehensive Cancer Network. Non-small cell lung cancer version 4.2019 (2019). www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf
16. Lim E, Baldwin D, Beckles M *et al.* Guidelines on the radical management of patients with lung cancer. *Thorax* 65(Suppl. 3), 1–27 (2010).
17. Postmus PE, Kerr KM, Oudkerk M *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 28(Suppl. 4), iv1–iv21 (2017).
18. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management (2019). www.nice.org.uk/guidance/ng122
19. The Society of Thoracic Surgeons. Five things physicians and patients should question. Choosing Wisely (2013). www.choosingwisely.org/societies/the-society-of-thoracic-surgeons/
20. The American Thoracic Society and The European Respiratory Society. Pretreatment evaluation of non-small-cell lung cancer. *Am. J. Respir. Crit. Care Med.* 156(1), 320–332 (1997).
21. Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. *J. Neurooncol.* 44(3), 275–281 (1999).
22. Tanaka K, Kubota K, Kodama T, Nagai K, Nishiwaki Y. Extrathoracic staging is not necessary for non-small-cell lung cancer with clinical stage T1–2 N0. *Ann. Thorac. Surg.* 68(3), 1039–1042 (1999).

23. Silvestri GA, Gonzalez AV, Jantz MA *et al.* Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 143(Suppl. 5), e211S–e250S (2013).
24. Ando T, Kage H, Saito M *et al.* Early stage non-small cell lung cancer patients need brain imaging regardless of symptoms. *Int. J. Clin. Oncol.* 23(4), 641–646 (2018).
25. Diaz ME, Debowski M, Hukins C, Fielding D, Fong KM, Bettington CS. Non-small cell lung cancer brain metastasis screening in the era of positron emission tomography-CT staging: current practice and outcomes. *J. Med. Imaging Radiat. Oncol.* 62(3), 383–388 (2018).
26. Rice SR, Molitoris JK, Vyfhuis MaL *et al.* Lymph node size predicts for asymptomatic brain metastases in patients with non-small-cell lung cancer at diagnosis. *Clin. Lung Cancer* 20(1), e107–e114 (2019).
27. Goncalves PH, Peterson SL, Vigneau FD *et al.* Risk of brain metastases in patients with nonmetastatic lung cancer: analysis of the Metropolitan Detroit Surveillance, Epidemiology, and End Results (SEER) data. *Cancer* 122(12), 1921–1927 (2016).

•• **In this regional population-based study, localized disease (i.e., without nodal involvement or extension to regional sites) was associated with a >1.5-fold decreased risk of developing brain metastases.**

28. Griesinger F, Roeper J, Pottgen C, Willborn KC, Eberhardt WEE. Brain metastases in ALK-positive NSCLC – time to adjust current treatment algorithms. *Oncotarget* 9(80), 35181–35194 (2018).
29. Iuchi T, Shingyoji M, Itakura M *et al.* Frequency of brain metastases in non-small-cell lung cancer, and their association with epidermal growth factor receptor mutations. *Int. J. Clin. Oncol.* 20(4), 674–679 (2015).
30. Patil T, Smith DE, Bunn PA *et al.* The incidence of brain metastases in stage IV *ROS1*-rearranged non-small cell lung cancer and rate of central nervous system progression on crizotinib. *J. Thorac. Oncol.* 13(11), 1717–1726 (2018).
31. Rangachari D, Yamaguchi N, Vanderlaan PA *et al.* Brain metastases in patients with *EGFR*-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer* 88(1), 108–111 (2015).
32. Remon J, Besse B. Brain metastases in oncogene-addicted non-small cell lung cancer patients: incidence and treatment. *Front. Oncol.* 8, 88 (2018).
33. Hudson Z, Internullo E, Edey A, Laurence I, Bianchi D, Addeo A. Brain imaging before primary lung cancer resection: a controversial topic. *Ecancermedicalscience* 11, 749 (2017).
34. Peters S, Bexelius C, Munk V, Leighl N. The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer. *Cancer Treat. Rev.* 45, 139–162 (2016).
35. Brastianos PK, Carter SL, Santagata S *et al.* Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov.* 5(11), 1164–1177 (2015).