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Brain Metastases at Presentation in Patients with Non-Small-Cell Lung Cancer

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Abstract

Objective—We used brain radiotherapy as a surrogate for the presence of brain metastases in patients with non-small cell lung cancer (NSCLC) in order to determine the prevalence of brain metastases using the Surveillance Epidemiology and End Results (SEER) database.

Methods—Patients with NSCLC diagnosed 1988-1997 were subdivided according to brain radiotherapy status at presentation into: “none” or “radiation therapy indicated”. We calculated the frequency of brain radiotherapy use in all patients. Odds ratios for the indication of brain radiotherapy were calculated for individual pre-specified covariates of interest. All statistical tests were 2-sided and p-values <0.05 were considered significant.

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CONFLICTS OF INTEREST:

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Results—At presentation, brain radiotherapy was indicated in 10963 (8.3%) of the 131,456 patients diagnosed with NSCLC between 1988 and 1997. On multivariable analysis the following were significantly associated with brain radiotherapy use: age (OR 0.653 per 10 year increase in age, 95%CI[0.642-0.665]), female gender (OR 1.05 95%CI[1.01,1.10]), adenocarcinoma histology (HR 1.67; 95%CI[1.58,1.76]) or large cell or other histology (OR 1.67, 95%CI[1.57,1.77]), tumor size > 3 cm (3.1-5 cm OR 1.22 95%CI[1.14,1.30] and > 5 cm OR 1.25 CI[1.17,1.33]), tumor grade > II (grade III OR 1.82 95%CI[1.69,1.95] and grade IV OR 1.91 95%CI[1.73,2.11]) and nodal involvement (N1 OR 1.33 95%CI[1.20,1.47]), N2 (OR 2.24 95%CI[2.10,2.40]) and N3 (OR 2.39 95%CI[2.19,2.60]).

Conclusions—Brain radiotherapy is indicated in over 8% of patients with NSCLC at presentation. We demonstrated that the risk of brain metastasis at presentation may be stratified with the use of 6 clinical factors.

Keywords

non-small cell lung cancer; lung cancer; brain metastasis; metastases; SEER

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the United States, accounting for more deaths than colon cancer, breast cancer and prostate cancer combined.¹ Brain metastases are a significant problem in patients with lung cancer, accounting for approximately half of all solid tumor metastases to the brain.^{2,3} It has been estimated that 16 to 22% of patients with lung cancer develop brain metastases from lung cancer.⁴⁻⁶ The apparent incidence of brain metastases has been increasing due to widespread availability of imaging modalities such as magnetic resonance imaging (MRI), with detection of subclinical disease. In addition, due to recent advances in systemic therapy for non-small cell lung cancer, patients tend to live longer, with more time to develop metastasis in sanctuary sites such as the brain.^{2,7} Although prophylactic cranial irradiation (PCI) has been shown to improve survival in patients with small cell lung cancer, this benefit has not been observed in patients with non-small cell lung cancer.⁸ Even with treatment, the prognosis for these patients remains poor, with a median survival of 7 months, but patients with systemic disease control, brain only metastasis, good performance status and younger age have better outcomes.⁹⁻¹¹

Although several groups have performed smaller population based studies to determine the incidence of brain metastasis, these estimates vary by trial design and are limited by small sample size and non-uniform patient populations.⁴⁻⁶ To the best of our knowledge, the frequency of brain metastasis in patients with NSCLC at initial presentation has not been described. In addition, although certain clinical factors such as age, histology, gender and molecular subtype have been linked to frequency of developing brain metastasis, the joint effect of these factors taken together in predicting brain metastasis has not been examined.^{6,12} We sought to systematically address these questions using the population-based Surveillance, Epidemiology, and End Results (SEER) database, which provides information regarding the initial treatment, including indication for brain radiotherapy.

METHODS

We searched the SEER-17 registry data for patients with non-small cell lung cancer diagnosed over a 10 year period between January 1, 1988 and December 31, 1997. The database does not record sites of metastasis or brain metastasis specifically, but does record the use of radiation therapy at the time of initial diagnosis. In this study, we used “brain radiation therapy indicated” as a surrogate for early brain metastasis. We subdivided our patient cohort according to brain radiotherapy data into “none” or “radiation therapy indicated”. The latter group included patients in whom brain radiotherapy was given, those in whom brain radiotherapy was indicated but the patient either refused or it is unknown if the patient actually received brain radiotherapy. We identified a total of 142,023 patients, 131,456 of whom had a known brain irradiation status. Patients without information regarding the indication for brain radiotherapy were listed as “unknown” (n=10,567), and were excluded from our patient cohort.

Demographic and clinical variables included age at diagnosis, gender, race, histology, tumor size, tumor grade, lymph node status (N) and American Joint Committee on Cancer (AJCC) stage. Age at diagnosis was analyzed as a continuous variable. Tumor size was subdivided into 3cm, 3.1 to 5cm, 5.1 to 7cm, and > 7cm to match the AJCC 7th edition staging for T1, T2a, T2b, and T3 respectively. The histology was coded according to the International Classification of Diseases for Oncology (ICD-O-3) into adenocarcinoma (8140–8147, 8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550, 8572), squamous cell carcinoma (8050–8052, 8070–8078), large-cell carcinoma (8012–8014), and other histologies including undifferentiated tumors (8020–8022) and carcinomas not otherwise specified (NOS) (8010). We excluded bronchioloalveolar carcinoma (8250–8254) because its natural history and clinical course differs from other subtypes of NSCLC.

Statistical analysis

Single and multivariable logistic regression analysis explored the association of age at diagnosis, gender, race, tumor histology, tumor size, tumor grade, N stage and AJCC stage in the presence of radiotherapy of the brain. Variable selection criteria included model fit criteria (deviance and deleted residual diagnostics) and Akaike Information Criteria (AIC) to assess individual and joint contribution of covariates to the probability of brain radiotherapy. To reduce the risk of overfitting and of identifying small effects or chance interactions as apparently statistically significant, given the large sample size, covariate selection also was based on literature review. Race did not contribute information to the multivariable model, suggesting that the information it provides about brain irradiation is also contained by the other predictors. AJCC stage was excluded as brain irradiation was rare outside stage IV. AJCC stage is also partly redundant with N stage, a predictor of greater clinical interest. There was a small but measurable decline in the rate of brain radiotherapy over the 10 years of the study, so the multivariable model was adjusted for year of diagnosis. All patients have data on age at diagnosis, sex, tumor histology (as a function of sample selection) and year of diagnosis. Missing data occurred in tumor grade (39.7%), tumor size (41.6%), N stage (37.8%) and AJCC stage (23.7%). Imputation of such a large amount of missing data was considered unreliable, and the missing values were included in a separate “unknown”

category. There were 41,710 patients (31.7%) with complete data for all covariates. An analysis of these patients indicated that the incidence of brain irradiation was lower than in all 131,456 patients (6.1%, as opposed to 8.3% in all 131,456 patients). Figure 2 uses a color intensity scale to summarize increases of 5% in the frequency of brain irradiation (0%-4.9%, 5%-9.9%, 10%-14.9%, 15%-19.9%, 20%-24.9% and 25%-50%, the maximum observed frequency) for patients having each combination of prognostic features. In this illustration age at diagnosis is in 4 categories. Adjusted odds ratios were calculated with 95% confidence intervals and a receiver operation curve (ROC) summarizes the information about the outcome contained in the multivariable model predictors.

RESULTS

Demographics

A total of 142,023 patients were identified, who met the inclusion criteria, of whom we excluded 10,567 patients due to unknown brain radiotherapy status. The remaining 131,456 patients comprised our cohort (**Figure 1**). Of these, 20,245 (15.4%) were stage I; 4,243 (3.2%) stage II; 31,753 (24.2%) stage III; 44,002 (33.5%) stage IV and 31,213 (23.7%) with an unknown stage. Most patients were men (59.8%) and white (82.8%). The minimum age was 16 years, the maximum 110 and the median 69. The histologic distribution included 52,636 patients (40.0%) with adenocarcinoma, 37,384 (28.4%) with squamous cell carcinoma, 12,006 (9.1%) with large-cell carcinoma, and 29,430 (22.4%) with other histologies. There were 31,969 tumors ≥ 3 cm (24.3%), 24,801 between 3.1 and 5 cm (18.9%) and 20,023 larger than 5 cm (15.2%). Most patients had a grade III primary tumor (45,178 patients; 34.4%), with smaller numbers of grade I (5,100; 3.9%), grade II (19,601; 14.9%) and grade IV (9,424; 7.2%). Most patients had no node involvement (34,835; 26.5%) or regional node involvement (N2, 29,942; 22.8%) with smaller percentages with N1 (8,288; 6.3%) or N3 (8,633; 6.6%).

Use of brain radiotherapy

Brain radiation was indicated in 10,567 (8.3%) of the 131,456 patients with NSCLC, which included patients with all disease stages. Based on univariate analysis, predictors of brain radiotherapy included younger age, black race, tumor size of over 3 cm, higher grade tumors (grade III or higher), N1, N2 or N3 lymph node involvement and AJCC stage greater than stage I (**Table 1**).

On multivariate analysis, characteristics of patients most likely to receive brain radiotherapy include younger age, non-squamous histology, tumor size > 3 cm, tumor grade III or IV and N1, N2 or N3 nodal involvement (**Table 2, figures 2 and 3**). Taken jointly and adjusted for year of diagnosis, brain irradiation is about 35% less likely with each 10 year increase in age (OR 0.65), and it is 5% more likely in female patients than in male patients (OR 1.05). Relative to squamous cell tumors, brain irradiation is 67% more likely in both adenocarcinomas and in large cell than other histologies (OR 1.67 in both cases). Brain irradiation is 80%-90% more likely to occur amongst patients with undifferentiated or poorly differentiated tumors (grades III and IV) than in moderately or well-differentiated tumors (grades I and II) (OR 1.82 and 1.91, respectively). Brain irradiation is also 22%-25%

more likely in tumors larger than 3.1-5cm or >5cm than in those < 3cm (OR 1.22 and 1.25, respectively). N stage N1 raises the odds of brain irradiation by 33% (OR 1.33), whereas N2 or N3 raises the odds by more than 2 times (OR 2.24 and 2.39, respectively). The area under the receiver operating curve (ROC) analysis was 0.70 (**figure 4**).

DISCUSSION

In our study, brain radiation was indicated in over 8% of patients with NSCLC within the first 4 months of diagnosis. This proportion is likely an underestimate of the true frequency of brain metastasis at presentation, as staging with brain MRI was not commonly used in the selected study time frame. The SEER database also captures patients in whom radiation was indicated, but not received, which may include patients with poor performance status, who are usually otherwise excluded from prospective studies following patients for eventual development of brain metastasis.¹³

This data does not include information regarding molecular abnormalities in the tumor, including presence of activating mutations of the epidermal growth factor receptor (EGFR) tyrosine kinase domain and anaplastic lymphoma kinase (ALK) gene rearrangements, which are now routinely checked at presentation. Such patients would likely be treated with molecularly targeted agents that penetrate the cerebrospinal fluid, and not receive brain radiation upfront for asymptomatic brain metastases. However, the time period of this study predates routine assessment for these molecular abnormalities.

This study corroborated findings from previous studies that link demographic and clinical characteristics to the development of brain metastasis, including female gender, non-squamous histology, younger age, tumor size and nodal station involvement.¹³⁻¹⁵ The observation that brain radiotherapy use was inversely correlated with age may not necessarily mean that the incidence of brain metastasis is lower in older adults, but may be a reflection of less utilization of brain radiotherapy in older adults, possibly due to poor performance status and expected toxicity. The 2-year estimate for brain relapse in patients with stage III adenocarcinoma treated with chemoradiation (22%) is over twice that for squamous cell carcinomas (10%).¹³ However, this is the first study, to the best of our knowledge, to factor all these variables together in determining risk of brain metastasis.

NSCLC is a molecularly heterogeneous disease, and the molecular mechanisms underlying the development of brain metastasis are not well understood. At present there are no reliable biomarkers to predict brain metastasis in patients with NSCLC. Most studies to date have utilized gene expression or immunohistochemical assays to identify patterns of altered expression of limited number of genes in primary lung tumors themselves that correlate with eventual metastasis.^{16,17} Recently the PI3 kinase aberrant primary tumors have been linked to the clinical development of brain metastasis in patients with squamous cell carcinoma, though the mechanism underlying spread to the brain in these tumors has not been elucidated.¹⁸ As we expand our understanding of molecular determinants of brain metastasis, the present study will serve as a baseline platform of clinical predictors, all of which need to be considered alongside the contribution of individual molecular changes that drive the process of NSCLC's eventual metastasis to the brain.

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Figure 1.
Consort diagram showing patients included in our study

Figure 2.
Color intensity scale showing the frequency of use of brain radiotherapy according to combination of clinical risk factors

Figure 3.
Forest plot showing odds of brain radiotherapy in relation to clinical variables

Figure 4.
ROC curve illustrating performance of the multivariable model to predict brain radiotherapy use

Table 1

Clinical risk factors for the use of brain radiotherapy in patients with NSCLC based on univariate analysis

Parameter		N	RT (%)	Odds Ratio	95% CI	p-Value
Age at Diagnosis	Per 10 Yr Increase	131456	10963 (8.34)	0.641	0.630, 0.652	<.0001
Gender	Male	78636	6397 (8.14)	Reference		
	Female	52820	4566 (8.64)	1.07	1.03, 1.11	0.0011
Race	White	108802	8889 (8.17)	Reference		
	Black	14633	1432 (9.79)	1.22	(1.15, 1.29)	<.0001
	Other / Unknown	8021	642 (8.00)	0.978	(0.900, 1.06)	.60
Histology	Squamous	37384	1943 (5.20)	Reference		
	Adenocarcinoma	52636	4868 (9.25)	1.86	1.76, 1.96	<.0001
	Other	41436	4152 (10.02)	2.03	1.92, 2.15	<.0001
Tumor Size	0-3cm	31969	2237 (7.00)	Reference		
	3.1-5cm	24801	2180 (8.79)	1.28	1.20, 1.36	<.0001
	>5cm	20023	1927 (9.62)	1.42	1.33, 1.51	<.0001
	Unknown	54663	4619 (8.45)	1.23	1.16, 1.29	<.0001
Tumor Grade	I/II	24701	1060 (4.29)	Reference		
	III	45178	4307 (9.53)	2.35	2.19, 2.52	<.0001
	IV	9424	1076 (11.42)	2.87	2.63, 3.14	<.0001
	Unknown	52153	4520 (8.67)	2.12	1.98, 2.27	<.0001
N Stage	N0	34835	1517 (4.36)	Reference		
	N1	8288	530 (6.40)	1.50	1.36, 1.66	<.0001
	N2	29942	3067 (10.24)	2.51	2.35, 2.67	<.0001
	N3	8633	1073 (12.43)	3.12	2.87, 3.38	<.0001
	Unknown	49758	4776 (9.60)	2.33	2.20, 2.48	<.0001
AJCC Stage	I	20245	131 (0.65)	Reference		
	II	4243	80 (1.89)	2.95	2.23, 3.90	<.0001
	III	31753	606 (1.91)	2.99	2.47, 3.61	<.0001
	IV	44002	9586 (21.8)	42.8	35.95, 50.84	<.0001
	Unknown	31213	560 (1.79)	2.80	2.32, 3.39	<.0001

Table 2

Clinical risk factors for the use of brain radiotherapy in patients with NSCLC based on multivariate analysis

Parameter		Odds Ratio	95% Confidence Interval	p-Value
Age at Diagnosis	Per 10 year increase	0.653	0.642, 0.665	<.0001
Gender	Female vs. Male	1.05	1.01, 1.10	0.0146
Tumor Histology	Adeno vs. Squamous	1.67	1.58, 1.76	<.0001
	Large Cell/Other vs. Squamous	1.67	1.57, 1.77	<.0001
Tumor Grade	III vs. I/II	1.82	1.69, 1.95	<.0001
	IV vs. I/II	1.91	1.73, 2.11	<.0001
	Unknown vs. I/II	1.68	1.56, 1.80	<.0001
Tumor Size	3.1-5cm	1.22	1.14, 1.30	<.0001
	>5cm	1.25	1.17, 1.33	<.0001
	Unknown	0.875	0.826, 0.926	<.0001
N Stage	N1 vs. N0	1.33	1.20, 1.47	<.0001
	N2 vs. N0	2.24	2.10, 2.40	<.0001
	N3 vs. N0	2.39	2.19, 2.60	<.0001
	Unknown vs. N0	2.48	2.33, 2.65	<.0001