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Risk of Brain Metastases in Patients with Non-metastatic Lung Cancer: Analysis of the Metropolitan Detroit Surveillance, Epidemiology, and End Results (SEER) Data

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Abstract

Background—Brain metastases (BM) remain an important cause of morbidity and mortality in lung cancer patients. Our study evaluated population-based incidence and outcomes of BM in patients with non-metastatic lung cancer.

Methods—Patients diagnosed with non-metastatic first primary lung cancer, between 1973–2011, in the Metropolitan Detroit Surveillance Epidemiology and End Results (SEER) registry were used for analysis. Age-adjusted Odds Ratios (OR) of developing BM based on various demographic characteristics and histology were calculated with 95% confidence intervals (CIs). Adjusted Cox Proportional Hazards Ratios and Log Rank Tests of Kaplan-Meier Survival Curves were calculated to evaluate survival differences for non-small cell (NSCLC) and small cell lung cancers (SCLC).

Results—The incidence of BM in non-metastatic NSCLC and SCLC was 9% and 18% respectively. There was variation in the incidence of BM according to NSCLC histology. Incidence of BM was higher in patients < 60 years old in both NSCLC and SCLC, but there were no differences by race for either histological group. Female patients with NSCLC were more likely to have BM than males. There was variation in proportion of BM in both NSCLC and SCLC patients over the three 13-year of diagnosis periods. Risk of death (hazard ratio, HR) was significantly higher for those with BM in NSCLCs, but not significantly higher in SCLC.

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Conclusions—The incidence of BM in non-metastatic lung cancer patients varies according to histology, age, and sex. BM are associated with worse survival for NSCLC but not SCLC.

Keywords

brain metastases; brain metastasis; lung cancer; SEER; non-metastatic lung cancer

INTRODUCTION

Incidence of brain metastases (BM) from any tumor varies according to the method of data collection and date reported, ranging from 8 to 14 per 100,000 people^{1-56,7}. In 2014, estimates predicted approximately 224,210 new lung cancer diagnoses in the United States and more than 157,000 related deaths⁸. Lung cancer is the most common tumor that metastasizes to the brain, and the central nervous system is the most frequent site of distant relapse in this malignancy^{6,9}. Despite being a significant problem, limited data exist on the incidence of BM in patients with non-metastatic primary lung cancer in the United States^{7,10,11}.

In recent years, the use of computed tomography (CT), fluorodeoxyglucose positron emission tomography (PET/CT) and magnetic resonance imaging (MRI) scans as part of staging for lung cancer has increased¹²⁻¹⁴. Additionally, as new treatments for lung cancer evolve, the overall survival of lung cancer patients has increased⁸. As a consequence, it is expected that the incidence of BM will increase over time. BM are a significant cause of morbidity and mortality in cancer patients, leading to neurologic symptoms, functional and emotional impairment along with significant burden to caregivers and society. The presence of BM can also limit the therapeutic options and enrollment in clinical trials. On the other hand, early diagnosis and treatment of BM may increase overall survival and independent functionality¹⁵⁻¹⁷. Therefore, a greater understanding of the clinical features of lung cancer patients associated with BM, with specific focus towards the temporal trends would be valuable.

We conducted our study to define the incidence of BM in non-metastatic lung cancer as well as to describe demographic characteristics, temporal trends and overall survival in patients with brain metastases from the Metropolitan Detroit Surveillance, Epidemiology and End Result (SEER) data from 1973 to 2011.

MATERIAL AND METHODS

Study Population

Data for this study were obtained from the Metropolitan Detroit SEER registry. Although not a required SEER data item, the Metropolitan Detroit SEER registry collected data on metastases at its area facilities where registry data collection staff abstracted charts. Up to four sites of metastasis were collected for each cancer. Non-metastatic (local and regional), adult (age ≥ 20), Caucasian and African American first primary lung cancer patients, defined as the first cancer occurring in a patient, diagnosed between 1973 and 2011 were analyzed. Carcinoids and cases diagnosed at autopsy or by death certificate only were excluded. Lung

cancer cases were categorized as to whether they did or did not have BM based on follow-up through 2011. These included patients who developed BM in the course of their disease.

Features abstracted were histology; demographic features of sex, race (categorized as African American or Caucasian) and age group at the time of diagnosis (20–39, 40–59, 60–79 or >80 years old) were available through SEER. The SEER Summary Stage of primary cancer was used rather than the American Joint Committee on Cancer (AJCC) tumor-node-metastases (TNM) system. Despite the fact that the AJCC classification is more detailed, this information was available only for those diagnosed in 2004 or later. The SEER Summary Stage categorized the lung cancer at the initial diagnosis as localized (confined entirely to the organ) or regional (disease extends either beyond the organ or includes involvement of regional nodes, i.e. involving local structures). Cases were also divided into three 13 year-of-diagnosis periods (1973–1985, 1986–1998, 1999–2011) for analysis of temporal trends.

Statistical Analysis

The proportion of cases with brain metastases was calculated for each tumor type (NSCLC, SCLC), by specific histology for NSCLC only, sex, race, stage, age, and year of diagnosis group. Chi-square analysis was used to evaluate the association of each characteristic with the incidence of BM. Age-adjusted estimates of risk (Odds Ratios, OR) of BM for each tumor type (NSCLC, SCLC) were generated by specific NSCLC histology, sex, race, stage and year of diagnosis group based on logistic regression models. Age was included as a continuous variable in the analysis and had a statistically significant impact on the regression model. Cox Proportional Hazards models were generated by histology to measure risk of dying by BM status, adjusted for covariates. Median survival and 95% confidence intervals (CI) were generated by tumor type and BM status. Kaplan-Meier curves were generated by tumor type and log rank tests were performed to compare survival for each tumor type by BM status.

RESULTS

There were 34,681 cases of non-metastatic first primary lung cancer identified with 30,446 being NSCLC and 4,235 SCLC. The incidence of BM in NSCLC was 9% for diagnoses over a 39-year period with subsequent follow-up. Among the NSCLC histologies, large cell carcinoma had the highest incidence of BM at 12% while squamous cell had the lowest at 6% (Table 1).

Within the NSCLC patient population, women (10%) had a higher incidence of BM proportionally than men ($p<0.0001$) (Table 1). The incidence of BM was similar among African-Americans (10%) and Caucasians (9%), but that difference was not statistically significant ($p=0.50$). Furthermore, within NSCLC the incidence of BM was highest in the youngest patient (20–39 years) group (19%) when compared with patients 80+ years of age (3%). Not surprisingly, the incidence of BM in patients with NSCLC was higher with later stage of disease at diagnosis, with 7% and 11% of patients with localized disease and regional disease, respectively, developing BM ($p<0.0001$).

Among the total cases of SCLC identified, 18% developed BM (Table 2). In patients with SCLC, there was no significant difference in the incidence of BM between men and women ($p=0.15$) (Table 2). African-Americans (20%) had a higher incidence of BM than Caucasians (18%), but this was also not statistically significant ($p=0.27$). Patients in all ages (20–39=25%, 40–50=23%, 60–79=17%) had greater incidence of BM than those aged 80+ (5%).

Temporal trends in the incidence of BM in both NSCLC and SCLC were analyzed in three 13-year periods, from 1973 to 2011. Though the differences were statistically significant, they were not clinically informative (Table 3). For NSCLC, there was a statistically significant decreasing trend of BM over the 13-year periods analyzed. For SCLC patients the proportion of BM fluctuated over the 3 time periods, with the highest proportion (23%) reported in the middle time period (1986–1998).

Patients with BM and NSCLC had a median survival of 16 months as compared to 21 months in patients without BM (Figure 1.) In contrast, in SCLC, survival for those with BM (14 months) was slightly better than for those without BM (11 months), but the log rank trend test was not significantly different (Figure 2).

The hazard ratio (HR) (adjusted for sex, age, treatment, stage, year of diagnosis and race) in patients with BM was increased in all histological types of NSCLC but was not statistically significantly better in SCLC (Table 4).

As expected, median survival increased consistently across the three-year of diagnosis periods (1973–1985, 1986–1998 and 1999–2011) for both NSCLC and SCLC with or without BM (Table 5). The increase was greatest for NSCLC without BM.

DISCUSSION

There have been few population-based studies describing the incidence of BM in patients with non-metastatic lung cancer at diagnosis in the United States^{3,7,11}. However, these are important data because BM are a significant cause of morbidity and mortality¹⁸. Currently, management of BM from primary lung cancer depends on the number and localization of BM within the central nervous system, the histology of the primary malignancy, symptoms from BM, the extent of the disease outside the central nervous system, patient comorbidities and life expectancy¹⁹. Detection techniques have evolved over the last few years, with greater use of MRI brain scans, as have treatment modalities for brain metastases, with increasing use of stereotactic radiosurgery^{17,20,22}. Our current study describes histological, demographic and temporal associations with the incidence of BM from lung cancer (NSCLC and SCLC). Knowledge of the characteristics associated with BM in patients with lung cancer may offer significant advantages including earlier detection and possibly more effective treatment and improved detection strategies.

Our study reports that the overall incidence of BM in patients with NSCLC diagnosed between 1973 and 2011 was 9% and, as expected, due to the natural history of SCLC, the incidence of BM in patients with SCLC was higher at 18%.

A previous study also using SEER data describes an overall incidence of BM in lung cancer diagnosed from 1973 to 2001 in the Metropolitan Detroit area as 9.2% for localized and 14.6% for regional tumors⁷. That study however did not discriminate cases of lung cancer by histology (NSCLC and SCLC). Villano, *et al.* evaluated 13,258 lung cancer patients by analyzing the Kentucky Cancer Registry (KCR) and Alberta Cancer Registry (ACR) for years 2010 and 2011. The median incidence of BM at diagnosis in patients with stage I/II and III lung cancer was 25.6% and 19.3% respectively¹¹. In another large population-based study from Sweden, Riihmaki *et al.* studied 21,169 lung cancer patients (NSCLC and SCLC diagnosed between 2002 and 2010) with metastases present at diagnosis found that brain was the most common site of metastases, presented in 39% of the cases²³.

Our study showed for NSCLC an incidence of 11% for localized stage and 7% for regional stage. Our study differed in that we did not include patients with distant metastases at diagnosis.

Our study shows that the incidence of BM in African-Americans was higher compared with Caucasians in both NSCLC and SCLC; however, these differences were not statistically significant. In contrast, differences in the incidence of BM in lung cancer between African-Americans and Caucasians have been reported earlier⁷. It is unclear if restricting the analysis to non-metastatic lung cancer in the current study can account for this difference.

We also found a higher incidence of BM in women with NSCLC than in men. The precise reasons for this difference are unclear. Other authors also observed a higher incidence of BM in women^{7,23}. Overall, women with lung cancer have better survival compared to men, and are more likely than men to be never-smokers, have adenocarcinomas, and have tumors harboring an activating mutation in the epidermal growth factor receptor (EGFR) or having an anaplastic lymphoma kinase (ALK) translocation, which have a better overall survival and may allow more time for the development of BM²⁴. No differences in the BM incidence according to sex were observed in SCLC cases.

Results of our study also show that the incidence of BM in NSCLC is the lowest in individuals 80 years of age or older (3%), with a relatively high incidence of BM in patients aged 20–39, 19%. A possible explanation may reflect a disparity in requesting brain imaging in younger patients and foregoing such imaging in elderly patients²⁵. Competing risks for death in the elderly and diagnosis at a more advanced stage in the very young (20–39), as lung cancer in this age group is a rare and an unexpected diagnosis, may also explain the differences in incidence observed.

Not surprisingly, the prevalence of BM is higher with more advanced stage of disease at diagnosis. However, the incidence of BM developing in patients with localized disease at diagnosis is not negligible. In our series, incidence of BM among NSCLC patients who had localized or regional disease at diagnosis was 7% and 11%, respectively. O'Dowd and colleagues analyzed data on 646 lung cancer patients who underwent surgical resection with curative intent and found that 6.3% of these patients developed BM, the majority within 12 months, suggesting that BM would have been present prior to surgical procedure²⁶. Gore *et al.* conducted a randomized phase III study evaluating prophylactic cranial radiation (PCI) in

stage III NSCLC patients. In this study, 18% of the patients who did not receive PCI developed brain metastases at 1 year²⁷. This is somewhat higher than the rate observed in our study but could be explained by regular brain scans conducted in study patients, a practice that is not standard of care, and the focus on more advanced stage patients. In a series of SCLC patients who underwent surgical resection the rate of development of BM was similar to the incidence observed in our study, in localized or regional SCLC patients²⁸.

It is well established that BM is associated with increased morbidity and mortality and therefore it is not surprising that the survival of NSCLC patients with BM is inferior to patients without BM. In SCLC patients, median survival was actually better in those with BM, though the log rank trend test was not statistically significant. SCLC patients with BM had a non-statistically significant slightly increased risk of death (5%) when adjusted for sex, race, treatment, stage, age and year of diagnosis. It is possible that SCLC patients undergo BM assessment more frequently and more consistently than NSCLC patients and therefore are treated before they can cause significant morbidity and mortality. Additionally, use of PCI may have contributed to this outcome, but unfortunately SEER does not provide specific information regarding the use of PCI. Furthermore, a possible explanation for patients with SCLC with BM to experience a better survival is the fact that such patients have to live long enough and to develop BM.

Our study has some limitations. The incidence of 9% for NSCLC and 18% for SCLC observed in this study may be lower than actual occurrence of BM in lung cancer patients since these results may be impacted by variability and changing patterns in assessment of brain metastases in hospital registries. Our estimates might be conservative if BM is not fully reported. Although not a required SEER data item, the Metropolitan Detroit SEER registry collected data on metastases at its area facilities where registry data collection staff abstracted charts. During the early 2000s, however, more facilities began electronically submitting their data to the Metropolitan Detroit SEER program. Neither the national SEER program nor the American College of Surgeons (ACoS) Commission on Cancer (COC) program required facilities electronically submitting their data to include the metastasis variable. Therefore, the potential for misclassification bias in the collection of brain metastasis information during the most recent period is a potential limitation of our paper. However, our results are similar to data reported in other population-based series suggesting that the reporting in our series is consistent. SEER recently mandated collection of brain metastasis for lung cancer. Future studies are needed with the newly collected BM data, which will be collected across all SEER registries. It is also worth noting that CT and MRI were not widely available for duration of this study (1970s-1980s). Therefore, patients were likely understated regarding the BM status during that period and staging during that period was suboptimal. As the use of these imaging modalities (and PET/CT) became routine in the medical field, most clinicians nowadays routinely image the brain in patients with stage III (regional SEER staging) and IV lung cancer (other metastatic sites). The decreasing trend in BM for NSCLC may reflect better upfront staging, as patients with BM at diagnosis are better detected and initially staged as having distant lung cancer (SEER staging), and not scored as developing BM. Additionally, SEER does not provide any information regarding the treatment provided to treat the patient's BM, leading to a significant limitation when analyzing survival data. Other important limitation of this data is that, while the date of

diagnosis for the primary lung cancer is known, the Metropolitan Detroit Cancer Surveillance System did not collect date when development of brain metastasis occurred. Therefore, median time from diagnosis of the lung cancer to development of the brain metastasis cannot be calculated. As mentioned above, another important limitation is that there is no information on SEER regarding the use of prophylactic cranial irradiation in patients with SCLC.

In conclusion, data on patients spanning 39 years shows that the incidence of BM in non-metastatic NSCLC patients is 9% and in SCLC patients is 18%. It also showed a higher incidence of BM among younger, female patients. The survival in NSCLC patients with BM was inferior to the survival of SCLC patients with BM. Our data provide updated estimates of the occurrence of BM in a large population-based sample. Further work is needed to develop a prediction tool that can be applied prospectively toward the prediction of BM in lung cancer patients.

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Figure 1.

legend - Survival of invasive first sequence non-small cell lung cancer by brain metastases, Metropolitan Detroit SEER, 1973–2011. Abbreviations: mets – metastases, SEER – Surveillance, Epidemiology and End Results

Figure 2.
 legend - Survival of invasive first sequence small cell lung cancer by brain metastases, Metropolitan Detroit SEER, 1973–2011. Abbreviations: mets – metastases, SEER – Surveillance, Epidemiology and End Results

Table 1

Incidence of BM and Age-Adjusted Odds Ratio (OR) for NSCLC by Variable of Interest based on Detroit SEER database, 1973–2011.

Variable of interest	Number w BM (%)	Total n	OR vs. * (95% CI)	p Value
<u>Histology</u>				
NSCLC	2712 (9)	30446		
Adeno *	1181 (11)	10543		
Squamous	722 (6)	12432	0.54 (.49 – .59)	<0.0001
Large Cell	243 (12)	1984.0	1.10 (0.95 – 1.28)	0.2
Others	566 (10)	5487.0	0.95 (0.85 – 1.06)	0.4
<u>Sex</u>				
Female *	1159 (10)	11727.0		<0.0001
Male	1553 (8)	18719.0	0.83 (0.77 – 0.90)	
<u>Race</u>				
Caucasian *	2048 (9)	23773.0		0.5
Afr-Amer	664 (10)	6673.0	1.03 (0.94 – 1.13)	
<u>Stage</u>				
Localized *	968 (7)	14416.0		<0.0001
Regional	1744 (11)	16030.0	1.55 (1.43 – 1.69)	
<u>Age Range (yrs)</u>				
20–39	54 (19)	284.0		<0.0001
40–59	1171 (14)	8130		
60–79	1407 (7)	19313		
80+	80 (3)	2719		

* **Abbreviations:** Reference Group. BM- brain metastasis, NSCLC-non-small cell lung cancer; adeno- adenocarcinoma; squamous- squamous cell carcinoma; Afr-Amer- African-American.

Table 2

Incidence of BM and Age-Adjusted Odds Ratio (OR) for SCLC by Variable of Interest based on Detroit SEER database, 1973–2011.

Variable of interest	Number w BM (%)	Total n	OR vs. * (95% CI)	p Value
<u>Histology</u>				
SCLC	760 (18)	4235		
<u>Sex</u>				
Female *	375 (19)	1984		0.15
Male	385 (17)	2251	0.89 (0.76 – 1.04)	
<u>Race</u>				
Caucasian *	612 (18)	3485		0.27
Afr-Amer	148 (20)	750	1.12 (0.92 – 1.37)	
<u>Stage</u>				
Localized *	202 (16)	1260		0.11
Regional	558 (19)	2975	1.15 (0.97 – 1.38)	
<u>Age Range (yrs)</u>				
20–39	6 (25)	24		<0.0001
40–59	297 (23)	1301		
60–79	443 (17)	2629		
80+	14 (5)	281		

* **Abbreviations:** Reference Group. BM- brain metastasis, SCLC- small cell lung cancer; Afr-Amer- African-American.

Table 3

Incidence of BM by Period of Diagnosis based on Detroit SEER database, 1973–2011

	Yes (%)	No (%)	Total n	p Value
NSCLC				
<u>Dx Group (by year)</u>				
1973–1985	990 (11)	8408 (89)	9398	<0.0001
1986–1998	1070 (10)	9994 (90)	11064	
1999–2011	652 (7)	9332 (93)	9984	
SCLC				
<u>Dx Group (by year)</u>				
1973–1985	202 (14)	1211 (86)	1413	<0.0001
1986–1998	388 (23)	1313 (77)	1701	
1999–2011	170 (15)	951 (85)	1121	

Abbreviations: NSCLC- non-small lung cancer; SCLC- small cell lung cancer; Dx- diagnosis;

Table 4

Hazard Ratio (HR) Estimate Risk of Death based on Detroit SEER database, 1973–2011 *

Primary Lung Cancer	HR BM vs. No BM	95% CI
NSCLC		
Adeno	1.53	(1.44, 1.63)
Squamous	1.39	(1.29, 1.50)
Large Cell	1.37	(1.19, 1.58)
Other	1.42	(1.30, 1.56)
SCLC	1.05	(0.97, 1.14)

* Adjusted for Sex, Race, Treatment, Stage, Age and Year of Diagnosis;

Abbreviations: NSCLC- non-small cell lung cancer; adeno- adenocarcinoma; squamous-cell carcinoma; SCLC- small cell lung cancer.

Median Survival by BM status by Period of Diagnosis based on Detroit SEER database, 1973–2011

Table 5

	Yes (%)	Median Survival (Mos.)	No (%)	Total n	Median Survival (Mos.)
NSCLC					
<u>Dx Group (by year)</u>					
1973–1985	990 (11)	13	8405 (89)	9395	14
1986–1998	1070 (10)	18	9994 (90)	11064	20
1999–2011	652 (7)	20	9332 (93)	9984	30
SCLC					
<u>Dx Group (by year)</u>					
1973–1985	202 (14)	11	1211 (86)	1413	9
1986–1998	388 (23)	14	1313 (77)	1701	11
1999–2011	170 (15)	15	951 (85)	1121	13

Abbreviations: NSCLC- non-small lung cancer; SCLC- small cell lung cancer; Dx- diagnosis; Mos- months