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Emergency department visits and inpatient hospitalizations among older patients with brain metastases: a dual population- and institution-level analysis

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Abstract

Background. Older patients with brain metastases (BrM) commonly experience symptoms that prompt acute medical evaluation. We characterized emergency department (ED) visits and inpatient hospitalizations in this population.

Methods. We identified 17 789 and 361 Medicare enrollees diagnosed with BrM using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database (2010-2016) and an institutional database (2007-2016), respectively. Predictors of ED visits and hospitalizations were assessed using Poisson regression.

Results. The institutional cohort averaged 3.3 ED visits/1.9 hospitalizations per person-year, with intracranial disease being the most common reason for presentation/admission. SEER-Medicare patients averaged 2.8 ED visits/2.0 hospitalizations per person-year. For patients with synchronous BrM (N = 7834), adjusted risk factors for ED utilization and hospitalization, respectively, included: male sex (rate ratio [RR] = 1.15 [95% CI = 1.09-1.22], $P < .001$; RR = 1.21 [95% CI = 1.13-1.29], $P < .001$); African American vs white race (RR = 1.30 [95% CI = 1.18-1.42], $P < .001$; RR = 1.25 [95% CI = 1.13-1.39], $P < .001$); unmarried status (RR = 1.07 [95% CI = 1.01-1.14], $P = .02$; RR = 1.09 [95% CI = 1.02-1.17], $P = .01$); Charlson comorbidity score >2 (RR = 1.27 [95% CI = 1.17-1.37], $P < .001$; RR = 1.36 [95% CI = 1.24-1.49], $P < .001$); and receipt of non-stereotactic vs stereotactic radiation (RR = 1.44 [95% CI = 1.34-1.55, $P < .001$; RR = 1.49 [95% CI = 1.37-1.62, $P < .001$). For patients with metachronous BrM (N = 9955), ED visits and hospitalizations were more common after vs before BrM diagnosis (2.6 vs 1.2 ED visits per person-year; 1.8 vs 0.9 hospitalizations per person-year, respectively; RR = 2.24 [95% CI = 2.15-2.33], $P < .001$; RR = 2.06 [95% CI = 1.98-2.15], $P < .001$, respectively).

Conclusions. Older patients with BrM commonly receive hospital-level care secondary to intracranial disease, especially in select subpopulations. Enhanced care coordination, closer outpatient follow-up, and patient navigator programs seem warranted for this population.

Keywords

brain metastases | emergency department | hospitalization | population

Brain metastases (BrM) affect 20%-40% of patients with solid malignancies and are associated with significant disease- and treatment-related sequelae.[1,2] Common symptoms among patients with BrM include fatigue, nausea, anorexia, seizures, headache, confusion, dizziness, generalized weakness, and focal neurologic deficits, many of which can be challenging to manage in the outpatient setting and therefore prompt emergency department (ED) visits and/or inpatient hospitalizations.[3] The guarded intracranial efficacy of systemic therapy often necessitates local, brain-directed treatment, such as radiation or surgery, which can cause additional toxicities that prompt escalation of care.[4,5] In addition, BrM tend to develop in patients with advanced systemic disease,[6] progression of which can also lead to ED visits and inpatient hospitalizations. Given their reduced ability to tolerate treatment and treatment-related complications older patients with BrM may be especially likely to require intensification of supportive care.[7]

Effective ED-based management of patients with metastatic cancer is challenging.[8] Patients with BrM are generally managed by multiple specialists and tend to have complex treatment histories, the details of which are not readily digestible in the fast-paced, high-acuity environment of the ED.[9] In addition, patients often visit a local ED, rather than the institution providing oncologic care, compromising the ability of ED clinicians to access prior clinical records and leading to additional testing, imaging, and/or hospitalizations.[10,11] Moreover, patients consistently report higher quality of life when symptoms are managed at home,[12,13] and hence, an improved understanding of the reasons for potentially avoidable hospitalizations seems warranted.

While prior studies characterizing ED utilization and hospitalizations among patients with cancer have described relative incidences compared to non-oncologic patients and/or focused on patients with a particular primary site,[14,15] studies examining ED utilization and hospitalizations among patients with BrM are lacking. In addition, the potential etiologies for escalations of care to the ED/hospital setting among patients with BrM remain unclear, and consequently, the relative contribution of intracranial vs extracranial-related disease/symptomatology to such care transitions is unknown. Here, we aimed to characterize the utilization, indications, and risk factors for ED visits and inpatient hospitalizations among older patients with BrM at both a population- and institutional level, as well as compare rates of ED visits and hospitalizations before and after a diagnosis of intracranial disease to better understand if the development of BrM drives the need for hospital-level care among such patients. Such studies may allow oncologists and health care systems to more readily identify those patients with BrM who may benefit from more intensive outpatient follow-up and decrease their need for hospital-level care.

Materials and Methods

Patient Population and Study Design

Surveillance, Epidemiology, and End Results (SEER)-Medicare cohort.—The SEER registry contains demographic and clinical information for approximately 35% of patients with cancer in the United States.[16] The SEER-Medicare program has linked Medicare claims data to SEER data for approximately 93% of Medicare patients in the SEER database.[17] We utilized the SEER-Medicare database to identify patients >65 years old diagnosed with BrM between 2010 (first year with information on the presence vs absence of BrM at diagnosis of primary malignancy present in SEER) through 2016 (the most recent year with available data). To identify patients with BrM, we mandated ≥3 claims associated with an ICD-9-CM (198.3) or ICD-10-CM (C79.31, 79.32) diagnosis code for secondary neoplasm of the brain, cerebral meninges, and spinal cord, a methodology associated with a 97% sensitivity and 99% specificity for identifying patients with intraparenchymal BrM via claims.[18] SEER provides information on which patients harbored BrM at primary tumor diagnosis, facilitating delineation of synchronous BrM (present at diagnosis of primary cancer) vs metachronous BrM (developed after diagnosis of primary cancer). We ascribed the date of the first BrM-associated claim as the BrM diagnosis date, an approach associated with 92% sensitivity for predicting the actual date of BrM diagnosis to ≤30 days relative to chart review.[19]

To reliably identify ED visits and inpatient hospitalizations, we mandated that patients have continuous part A and B coverage, with no HMO enrollment from the year before primary cancer diagnosis through the date of censoring/death (N = 19 497). To avoid incomplete capture of ED visits or hospitalizations, patients who entered hospice were censored at hospice enrollment. Patients who entered hospice on or before the date of primary tumor or BrM diagnosis (N = 843), those diagnosed with cancer at autopsy/death (n = 131), and those for whom intracranial disease status at primary tumor diagnosis was unknown (n = 734) were excluded. The final cohort consisted of 7834 patients with synchronous and 9955 patients with metachronous BrM.

To identify ED visits, we searched for relevant HCPCS (99281, 99282, 99283, 99284, 99285, 99291) and Revenue Center Codes (0450, 0451, 0452, 0453, 0454, 0455, 0456, 0457, 0458, 0459, 0981) or an emergency room visit charge >$0, an approach previously utilized to identify ED visits via claims.[20] To account for duplicate entries and billing-related data inaccuracies, ED claims on the same date or separated by 1 day for a given patient were considered as the same ED visit. The principal diagnosis code associated with each ED claim was tabulated. For patients with multiple claims per ED visit, diagnosis codes for each claim were considered, although claims with the same date and diagnosis code were not counted twice.

Patients were considered to have an inpatient hospitalization if a record in the MEDPAR file indicating a short- or long stay with a hospital charge >$0 was present. The admitting diagnosis code associated with each hospitalization claim was captured.

For patients with synchronous BrM, we mandated that ED and inpatient claims be dated ≥15 days after the date of BrM diagnosis and be on/before the date of death or censoring; for patients with metachronous metastases, follow-up time was divided into 2 periods: (1) 15 days after the date of primary cancer diagnosis to 15 days before the date of BrM diagnosis (period before the diagnosis of BrM) and (2) 15 days after the date of BrM diagnosis to the date

of death or censoring (period after diagnosis of BrM). This approach was chosen to avoid counting ED visits that were related to the diagnosis of primary malignancy or intracranial disease.

To identify intracranial treatment strategies among the SEER-Medicare cohort, brain-directed stereotactic radiation could be readily identified via claims. For patients receiving non-stereotactic brain-directed radiation, the vast majority of patients likely received whole-brain radiotherapy (WBRT). However, in a small percentage of patients, some centers in the United States administer partial brain radiation in a non-stereotactic manner, and both WBRT and non-stereotactic partial brain radiation would be captured among claims as brain-directed non-stereotactic radiation.

Institutional cohort.—For the institutionally based analysis, we retrospectively identified Medicare beneficiaries with newly diagnosed BrM managed at Brigham and Women's Hospital/Dana-Farber Cancer Institute (BWH/DFCI, Boston, MA) between 2007 and 2016 for whom Medicare claims data were available through the BWH/DFCI Medicare claims database (N = 361). Similar methodology as above was employed with respect to counting only unique ED visits (>1 day apart for the same patient) and mandating claims be >15 days after BrM diagnosis. Given that Massachusetts is not a SEER state, we expected minimal overlap between the SEER-Medicare and institutional cohorts.

Statistical Methodology

Among patients in the SEER-Medicare cohort, we sought to quantify the utilization of, describe reasons for, and determine risk factors associated with ED visits and inpatient hospitalizations among patients with BrM. Normally distributed, non-normally distributed, and categorical baseline characteristics among patients with synchronous and metachronous BrM were compared using the *t* test, Wilcoxon rank sum test, and chi-square test, respectively. To determine risk factors for ED visits and inpatient hospitalizations, we performed univariable and multivariable Poisson regression for the respective cohorts with synchronous and metachronous BrM, where the primary outcome was the number of ED visits or inpatient hospitalizations summed over the at-risk period (ie, the period after BrM diagnosis to death/censoring) for each patient. Separate models were created for ED visits and inpatient hospitalizations. Models were adjusted for age, sex, race, Charlson comorbidity index (CCI, according to Deyo et al),[21] primary tumor site, marital status, high school completion rate (zipcode level), median household income (zipcode level), residence type (non-urban/unknown vs urban), type of managing hospital (medical school-associated vs not), and initial BrM treatment strategy. High school completion rates and median household income were based on the rates and income for the specific zipcode that the patient lived in, respectively. The designations of "urban" vs "non-urban" residence were based on grouping patients whose residence type was listed in the SEER dataset as "Big Metro," "Metro," or "Urban" into the former category and as "Less Urban" or "Rural" into the latter category. We performed a separate Poisson regression among patients with metachronous BrM comparing the total number of ED visits or hospitalizations before vs after BrM diagnosis after accounting for intra-patient correlations. An offset term was included in all Poisson models to account for the duration of at-risk time. Models were scaled to account for overdispersion; model validation was verified with a goodness-of-fit chi-square test. A 2-sided *P* value <.05 was considered statistically significant. Among patients in the institutional cohort, given the fewer number of total events, we did not perform multivariable modeling for this cohort but focused on characterizing reasons for ED visits and inpatient hospitalizations. Analyses were performed using SAS v9.4. This study was approved by our institutional review board.

Results

SEER-Medicare Cohort

Baseline characteristics.—Baseline characteristics for patients stratified by synchronous vs metachronous BrM diagnoses are presented in Table 1. The median age in both cohorts was 74 years. Non–small cell lung cancer (NSCLC) represented the most common primary tumor in both cohorts.

ED visits.—Among the entire cohort, in the period following BrM diagnosis, we identified 26 767 unique ED visits over 9502 person-years (2.8 visits/person-year). The most common reasons for presenting to the ED included: acute respiratory failure (5.4%), pneumonia (4.5%), lung cancer (4.1%), sepsis (3.8%), malaise and fatigue (3.4%), and intracranial disease (3.3%) (Table 2). Among patients with a primary cancer other than NSCLC/small cell lung cancer, intracranial disease was the second most common reason for presenting to the ED (4.1% of all visits). When examining the first ED visit for each patient, we found that 58.2% of initial ED visits led to an inpatient hospitalization (hospitalization date within 1 day of ED visit).

To assess the risk of ED visits over time for a given patient, we examined the rate of ED visits shortly after a diagnosis of BrM (15-45 days after BrM diagnosis, once again intentionally excluding the first 15 days to avoid overestimating ED visits related to the actual diagnosis of BrM), as well as in the 30 days prior to death/date of censoring. We found that rates were higher at both of these time points (4.4 visits/person-year and 10.3 visits/person-year in the later phase, respectively, relative to the overall rate of 2.8 visits per person-year).

On multivariable regression of patients with synchronous BrM, older age (rate ratio [RR] = 1.01 per year increase [95% CI = 1.00-1.01], *P* = .04), male sex (RR = 1.15 [95% CI = 1.09-1.22], *P* < .001), African American vs white race (RR = 1.30 [95% CI = 1.18-1.42], *P* < .001), unmarried vs married social status (RR = 1.07 [95% CI = 1.01-1.14], *P* = .02), CCI > 2 vs 0-2 (RR = 1.27 [95% CI = 1.17-1.37], *P* < .001), and

Table 1. Baseline Characteristics of SEER-Medicare Patients Diagnosed With Brain Metastases Identified at vs After Primary Cancer Diagnosis

	Brain Metastases Present at Time of Primary Cancer Diagnosis (N = 7834)	Brain Metastases Diagnosed After Primary Cancer Diagnosis (N = 9955)	*P*
Age at diagnosis of primary cancer, years, mean (SD)	74 (6)	74 (6)	.01
Sex, N (%)			.005
Male	3864 (49)	4698 (47)	
Female	3970 (51)	5257 (53)	
Race/ethnicity, N (%)			<.001
White	6369 (81)	8328 (84)	
African American	689 (9)	741 (7)	
Hispanic	361 (5)	432 (4)	
Asian/Pacific Islander	383 (5)	407 (4)	
Other/unknown	32 (<1)	47 (<1)	
Marital status, N (%)			<.001
Married/domestic partnership	3921 (50)	5415 (54)	
Unmarried/single	3623 (46)	4005 (40)	
Unknown	290 (4)	535 (5)	
Type of residence, N (%)			.05
Urban	6878 (88)	8857 (89)	
Non-urban	945 (12)	1087 (11)	
Unknown	11 (<1)	11 (<1)	
Graduated from high school, median (IQR)[a]	87 (78-92)	87 (79-92)	<.001
Household income (per 10K USD), median (IQR)[a]	4.89 (3.59-6.69)	5.05 (3.73-6.93)	<.001
Charlson comorbidity index, N (%)[b]			<.001
0-2	6155 (79)	8136 (82)	
>2	1144 (15)	1339 (13)	
Unknown	535 (7)	480 (5)	
Primary tumor site, N (%)			<.001
NSCLC[c]	5777 (74)	4715 (47)	
SCLC	1230 (16)	1562 (16)	
Breast	182 (2)	1141 (11)	
Melanoma	283 (4)	812 (8)	
Renal	186 (2)	462 (5)	
Colorectal	100 (1)	505 (5)	
Esophagus	58 (1)	222 (2)	
Ovarian	18 (<1)	107 (1)	
Other[d]		429 (4)	
Medical school-associated hospital, N (%)			<.001
No	2585 (33)	2983 (30)	
Yes	4644 (59)	6541 (66)	
Unknown	605 (8)	431 (4)	
Initial brain-directed treatment strategy, N (%)			<.001
Non-stereotactic brain radiation, without SRS/SRT or resection[e]	3480 (44)	3855 (39)	

Table 1. Continued

	Brain Metastases Present at Time of Primary Cancer Diagnosis (N = 7834)	Brain Metastases Diagnosed After Primary Cancer Diagnosis (N = 9955)	*P*
SRS/SRT, without resection	1132 (14)	1281 (13)	
Any resection	911 (12)	703 (7)	
No local therapy	2311 (30)	4116 (41)	

Abbreviations: IQR, interquartile range; N, number; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation; SRS/SRT, stereotactic radiosurgery/radiation therapy; USD, United States Dollars.
(1) Categories for certain variables were grouped together so as to comply with NCI data policy of not displaying any cells with values <11. (2) Percentages may not add up to 100 due to rounding. (3) The *P* value refers to the comparison per *t* test, Wilcoxon rank sum test, or chi-square test between patients with brain metastases at the time of vs after primary cancer diagnosis.
[a]Zipcode level.
[b]Diagnosis of metastatic cancer excluded so as not to inflate all scores by 6 points.
[c]Includes lung primaries that are not specifically listed as adenocarcinoma, squamous cell, adenosquamous, large cell, or bronchoalveolar (a histology still designated by SEER).
[d]Such patients had multiple primary cancers, with the first cancer in time corresponding to a primary other than lung, breast, melanoma, kidney, ovarian, esophageal, or colorectal cancer.
[e]Includes whole brain radiation and non-stereotactic partial brain radiation, which cannot be readily delineated using claims data.

Table 2. Most Common Reasons for Emergency Department Visits and Inpatient Hospitalizations After a Diagnosis of Brain Metastases[a]

Emergency Department Visits			Inpatient Hospitalizations		
Diagnoses (Codes)	Number of ED Claims	Percentage of ED Claims	Diagnoses (Codes)	Number of Hospital Visits	Percentage of Hospital Visits
Acute respiratory failure (51881)	2134	5.4	Shortness of breath (78605)	941	6.2
Pneumonia (486)	1782	4.5	Malaise and fatigue (78079)	891	5.9
Malignant neoplasm of bronchus and lung (1629)	1609	4.1	Pneumonia (486)	825	5.4
Unspecified septicemia (0389)	1498	3.8	Altered mental status (78097)	720	4.8
Malaise and fatigue (78079)	1340	3.4	Malignant neoplasm of bronchus and lung (1629)	516	3.4
Secondary malignant neoplasm of the brain and cerebral meninges (1983)	1315	3.3	Secondary malignant neoplasm of the brain and cerebral meninges (1983)	488	3.2
Dehydration (27651)	1086	2.8	Unspecified septicemia (0389)	465	3.1
Altered mental status (78097)	829	2.1	Dehydration (27651)	425	2.8
Shortness of breath (78605)	668	1.7	Fever, unspecified (78060)	338	2.2
Urinary tract infection (5990)	659	1.7	Acute respiratory failure (51881)	246	1.6
Atrial fibrillation (42731)	527	1.3	Syncope and collapse (7802)	245	1.6
Chest pain, unspecified (78650)	508	1.3	Other respiratory abnormalities (78609)	242	1.6
Other respiratory abnormalities (78609)	475	1.2	Unspecified convulsions (78039)	231	1.5
Syncope and collapse (7802)	457	1.2	Nausea with vomiting (78701)	216	1.4
Unspecified convulsions (78039)	450	1.1	Urinary tract infection (5990)	215	1.4

Abbreviation: ED, emergency department.
Total number of unique ED claims = 39 476, where a claim was considered unique for any non-identical combination of patient ID, date of visit, and diagnosis code. Total number of hospitalizations = 15 138.
[a]Only emergency department visits and hospitalizations >15 days after the BrM diagnosis date were counted in the table above to avoid inflating the incidence and capture only those visits subsequent to a known BrM diagnosis rather than symptoms that led to a diagnosis of brain metastases. In addition, given that the majority of claims during our study period were coded per the ICD-9 system and due to the challenges in correlating ICD-9 and ICD-10 diagnosis codes, only visits coded under the ICD-9 system were utilized when tabulating the most common reasons for presentation.

Table 3. Poisson Regression for Predictors of Emergency Department Visits Among Patients With Brain Metastases Present at Time of Primary Cancer Diagnosis

	Univariable RR (95% CI)	*P*Value	Multivariable RR (95% CI)	*P*Value
Age at primary cancer diagnosis, per year increase	1.01 (1.00-1.01)	.06	1.01 (1.00-1.01)	.04
Sex		<.001		<.001
Female	Ref		Ref	
Male	1.18 (1.11-1.25)		1.15 (1.09-1.22)	
Race/ethnicity				
White	Ref		Ref	
African American	1.44 (1.31-1.57)	<.001	1.30 (1.18-1.42)	<.001
Hispanic	1.13 (1.00-1.28)	.06	1.04 (0.92-1.19)	.50
Asian/Pacific Islander	0.82 (0.73-0.92)	<.001	0.80 (0.71-0.90)	<.001
Other/unknown	1.13 (0.74-1.73)	.57	0.98 (0.64-1.48)	.91
Marital status at diagnosis				
Married/partnered	Ref		Ref	
Unmarried/single	1.08 (1.02-1.14)	.009	1.07 (1.01-1.14)	.02
Unknown	1.14 (0.98-1.32)	.09	1.12 (0.96-1.29)	.14
Graduated from high school (per % increase)	0.99 (0.99-0.99)	<.001	1.00 (0.99-1.00)	.002
Household income (per 10K USD increase)	0.97 (0.96-0.98)	<.001	0.99 (0.98-1.01)	.31
Residence				
Non-urban	Ref		Ref	
Urban	0.95 (0.86-1.04)	.23	1.03 (0.94-1.14)	.48
Unknown	0.78 (0.36-1.71)	.53	0.97 (0.45-2.09)	.95
Charlson comorbidity index[a]				
0-2	Ref		Ref	
>2	1.35 (1.25-1.47)	<.001	1.27 (1.17-1.37)	<.001
Unknown	0.95 (0.84-1.08)	.43	0.93 (0.82-1.05)	.23
Primary tumor site				
NSCLC	Ref		Ref	
SCLC	1.12 (1.04-1.21)	.003	1.00 (0.93-1.08)	.96
Breast	0.61 (0.50-0.74)	<.001	0.63 (0.52-0.76)	<.001
Melanoma	0.90 (0.78-1.05)	.17	1.01 (0.87-1.16)	.94
Renal	0.97 (0.82-1.16)	.74	1.06 (0.89-1.26)	.51
Colorectal	0.93 (0.70-1.22)	.59	0.93 (0.71-1.22)	.58
Esophagus	0.85 (0.62-1.16)	.30	0.97 (0.72-1.32)	.85
Ovarian	0.63 (0.26-1.51)	.30	0.66 (0.28-1.53)	.33
Other	1.05 (0.42-2.60)	.92	1.26 (0.52-3.03)	.61
Medical school-associated hospital				
No	Ref		Ref	
Yes	0.94 (0.88-1.00)	.05	0.97 (0.91-1.03)	.34
Unknown	0.90 (0.76-1.07)	.24	0.91 (0.77-1.08)	.29
Initial BrM treatment strategy				
SRS/SRT, without resection	Ref		Ref	
Non-stereotactic brain radiation, without SRS/SRT or resection	1.48 (1.38-1.59)	<.001	1.44 (1.34-1.55)	<.001
Any resection	0.95 (0.87-1.04)	.25	0.92 (0.84-1.01)	.07
No local therapy	1.14 (1.04-1.24)	.003	1.10 (1.01-1.20)	.04

Abbreviations: BrM, brain metastases; CI, confidence interval; N, number; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; RR, rate ratio; SRS/SRT, stereotactic radiosurgery/radiation therapy; USD, United States Dollars.
[a]Diagnosis of metastatic cancer excluded so as not to inflate all scores by 6 points.

receipt of non-stereotactic vs stereotactic brain-directed radiation therapy (RR = 1.44 [95% CI = 1.34-1.55, $P < .001$) were risk factors for ED utilization. Asian race (RR = 0.79 [95% CI = 0.70-0.88], $P < .001$), higher zipcode level high school graduation rate (RR = 1.00 [95% CI = 0.99-1.00], $P < .001$), and breast cancer as primary tumor vs the reference of NSCLC (RR = 0.63 [95% CI = 0.52-0.73], $P < .001$) were associated with decreased ED utilization (Table 3).

To examine whether age at time of BrM diagnosis affected risk factors for ED visits, we divided patients based on age (<74 years vs ≥74 years) and found that among patients diagnosed at an age less than 74, male sex, unmarried social status, African American race, greater Charlson comorbidity score, (>2), and receipt of non-stereotactic brain-directed radiation therapy were all significant risk factors for ED visits. Unlike the larger cohort of patients with all age groups, age at time of diagnosis was no longer a significant risk factor for ED visits. Similarly, when limiting to patients diagnosed at an age greater than or equal to 74, we found that male sex, African American race, greater Charlson comorbidity score (>2), and receipt of non-stereotactic brain-directed radiation therapy were all significant risk factors for ED visits. Unlike the larger cohort of patients that included patients of all age groups, age at time of diagnosis and unmarried social status were no longer associated with an increased risk for ED visits.

Because the majority of patients with BrM are secondary to NSCLC or breast cancer, we also looked at risk factors associated with ED visits among just patients with NSCLC or breast cancer. When we limited to just patients with NSCLC, we found similar risk factors to those identified in the larger cohort. However, when we limited to patients with breast cancer, there no significant covariates that were predictive of ED visits.

Among patients with metachronous BrM, similar risk factors for ED visits, including male sex, African American race, unmarried social status, CCI > 2, and receipt of non-stereotactic, brain-directed radiation therapy, were observed (all RR > 1 and $P < .05$; Supplementary Table A3).

When dividing patients who were diagnosed with BrM into earlier (year of BrM diagnosis <2013) vs more recent (year of BrM diagnosis ≥2013) cohorts, similar rates of ED visits were observed among both groups (2.8 visits/person-year vs 2.9 visits/person-year, respectively).

Inpatient hospitalizations.—Among the entire cohort, we identified 18 585 inpatient hospitalizations over 9052 person-years (2.0 hospitalizations/person-year). The most common reasons for admission included: shortness of breath (6.2%), malaise and fatigue (5.9%), pneumonia (5.4%), altered mental status (4.8%), lung cancer (3.4%), and intracranial disease (3.2%) (Table 2). Among patients with a primary cancer other than NSCLC/small cell lung cancer, intracranial disease was the fourth most common indication for hospitalization (3.9%) and altered mental status, a symptom likely secondary to intracranial disease, was the second most common reason (5.5%).

Multivariable modeling among patients with synchronous BrM indicated that male sex (RR = 1.21 [95% CI = 1.13-1.29], $P < .001$), African American vs white race (RR = 1.25 [95% CI = 1.13-1.39], $P < .001$), unmarried vs married social status (RR = 1.09 [95% CI = 1.02-1.17], $P = .01$), CCI > 2 vs 0-2 (RR = 1.36 [95% CI = 1.24-1.49], $P < .001$), and receipt of non-stereotactic vs stereotactic brain-directed radiation therapy (RR = 1.49 [95% CI = 1.37-1.62, $P < .001$) were risk factors for inpatient hospitalization; in contrast, Asian race (RR = 0.72 [95% CI = 0.62-0.82], $P < .001$), Hispanic ethnicity (RR = 0.82 [95% CI = 0.72-0.98], $P = .02$), higher zipcode level high school graduation rate (RR = 0.99 [95% CI = 0.99-1.00], $P < .001$), and breast cancer vs NSCLC (RR = 0.63 [95% CI = 0.50-0.79], $P < .001$) were associated with lower risk for inpatient hospitalization (Table 4).

To examine whether age at time of BrM diagnosis affected risk factors for hospitalizations, we divided patients based on age (<74 years vs ≥74 years) and found that among patients diagnosed at an age less than 74, male sex, unmarried social status, African American race, greater Charlson comorbidity score (>2), receipt of non-stereotactic brain-directed radiation therapy, and receipt of oncologic treatments other than local brain-directed therapy were all significant risk factors for hospitalizations. Unlike the larger cohort of patients with all age groups, age at time of diagnosis was no longer a significant risk factor for hospitalizations. Similarly, when limiting to patients diagnosed at an age greater than or equal to 74, we found that male sex, African American race, other race, greater Charlson comorbidity score (>2), and receipt of non-stereotactic brain-directed radiation therapy were all significant risk factors for hospitalizations. Unlike the larger cohort of patients that included patients of all age groups, age at time of diagnosis and unmarried social status were no longer associated with an increased risk for hospitalizations.

When we limited to just patients with NSCLC, we also found similar risk factors to those identified in the larger cohort. However, when we limited to patients with breast cancer, only unknown marital status was predictive of requiring inpatient hospitalization.

Multivariable regression of patients with metachronous BrM demonstrated similar risk factors for hospitalization, including male sex, African American race, unmarried social status, CCI > 2, and receipt of non-stereotactic, brain-directed radiation therapy (all RR > 1 and $P < .05$; Supplementary Table A4).

When dividing patients who were diagnosed with BrM into earlier (year of BrM diagnosis <2013) vs more recent (year of BrM diagnosis ≥2013) cohorts, similar rates of inpatient hospitalizations were observed among both groups (2.0 hospitalizations/person-year vs 1.9 hospitalizations/person-year, respectively).

Association between development of BrM and ED visits/inpatient hospitalizations.—For patients with metachronous BrM, the risk for ED visits and inpatient hospitalizations was compared between the period before vs after BrM diagnosis. The development of BrM was associated with a greater subsequent risk of ED visits (RR = 2.24 [95% CI = 2.15-2.33], $P < .001$), with rates increasing from 1.2 to 2.6 visits/person-year before vs after BrM diagnosis. Similarly, the diagnosis of BrM was associated with an increased subsequent risk for hospitalizations (RR = 2.06 [95% CI = 1.98-2.15], $P < .001$), with rates increasing from 0.9 to 1.8 hospitalizations/person-year before vs after BrM diagnosis.

Table 4. Poisson Regression for Predictors of Inpatient Hospitalizations Among Patients With Brain Metastases at Time of Primary Cancer Diagnosis

	Univariable RR (95% CI)	*P*Value	Multivariable RR (95% CI)	*P*Value
Age at primary cancer diagnosis, per year increase	1.00 (1.00-1.01)	.27	1.00 (1.00-1.01)	.16
Sex		<.001		<.001
Female	Ref		Ref	
Male	1.25 (1.17-1.33)		1.21 (1.13-1.29)	
Race/ethnicity				
White	Ref		Ref	
African American	1.40 (1.26-1.55)	<.001	1.25 (1.13-1.39)	<.001
Hispanic	0.95 (0.82-1.11)	.54	0.84 (0.72-0.98)	.02
Asian/Pacific Islander	0.73 (0.64-0.84)	<.001	0.72 (0.62-0.82)	<.001
Other/unknown	1.08 (0.66-1.76)	.77	0.89 (0.55-1.44)	.64
Marital status at diagnosis				
Married/partnered	Ref		Ref	
Unmarried/single	1.08 (1.01-1.16)	.02	1.09 (1.02-1.17)	.01
Unknown	1.20 (1.01-1.41)	.04	1.16 (0.99-1.37)	.06
Graduated from high school (per % increase)	0.99 (0.99-1.00)	<.001	0.99 (0.99-1.00)	<.001
Household income (per 10K USD increase)	0.98 (0.97-0.99)	<.001	1.00 (0.99-1.02)	.63
Residence				
Non-urban	Ref		Ref	
Urban	0.99 (0.89-1.09)	.78	1.08 (0.97-1.21)	.14
Unknown	0.61 (0.22-1.70)	.35	0.90 (0.34-2.41)	.83
Charlson comorbidity index[a]				
0-2	Ref		Ref	
>2	1.45 (1.32-1.59)	<.001	1.36 (1.24-1.49)	<.001
Unknown	1.05 (0.92-1.21)	.44	1.01 (0.89-1.16)	.85
Primary tumor site				
NSCLC	Ref		Ref	
SCLC	1.13 (1.04-1.23)	.01	1.00 (0.92-1.09)	.97
Breast	0.59 (0.47-0.75)	<.001	0.63 (0.50-0.79)	<.001
Melanoma	0.99 (0.84-1.16)	.86	1.08 (0.92-1.26)	.37
Renal	1.13 (0.94-1.36)	.19	1.22 (1.02-1.46)	.03
Colorectal	1.01 (0.74-1.37)	.96	0.99 (0.74-1.33)	.96
Esophagus	0.91 (0.64-1.28)	.58	1.00 (0.72-1.40)	.99
Ovarian	0.68 (0.26-1.77)	.43	0.73 (0.29-1.83)	.50
Other	1.23 (0.47-3.21)	.67	1.39 (0.56-3.50)	.48
Medical school-associated hospital				
No	Ref		Ref	
Yes	0.96 (0.89-1.03)	.25	0.99 (0.92-1.06)	.78
Unknown	1.08 (0.90-1.30)	.41	1.06 (0.88-1.26)	.55
Initial BrM treatment strategy				
SRS/SRT, without resection	Ref		Ref	
Non-stereotactic brain radiation, without SRS/SRT or resection	1.52 (1.39-1.65)	<.001	1.49 (1.37-1.62)	<.001
Any resection	1.05 (0.94-1.16)	.39	1.00 (0.90-1.10)	.94
No local therapy	1.16 (1.05-1.29)	.003	1.11 (1.01-1.23)	.04

Abbreviations: BrM, brain metastases; CI, confidence interval; N, number; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; RR, rate ratio; SRS/SRT, stereotactic radiosurgery/radiation therapy; USD, United States Dollars.
[a]Diagnosis of metastatic cancer excluded so as not to inflate all scores by 6 points.

Institutional Cohort

Baseline patient characteristics are depicted in Supplementary Table A5. In the period following BrM diagnosis, we identified 1257 unique ED visits corresponding to 377 person-years, or 3.3 visits per person-year. When considering diagnosis codes directly related to intracranial disease (ie, "secondary malignant neoplasm of the brain," and "malignant neoplasm of brain, unspecified"), BrM were the most common reason for presenting to the ED (6.8%) (Table 5). In the period following BrM diagnosis, we identified 719 inpatient hospitalizations over 377 person-years, or 1.9 hospitalizations per person-year. The most common reasons for admission included: intracranial disease (17.9%), pneumonia (4.8%), and sepsis (3.6%) (Table 5).

Discussion

In this dual-sample study, we examined reasons and risk factors for ED utilization and inpatient hospitalization among older patients with BrM. In both cohorts, intracranial disease and/or its sequelae were major reasons prompting hospital-level care. In patients with a known cancer diagnosis, the development of intracranial disease

Table 5. Most Common Reasons for Emergency Department Visits and Inpatient Hospitalizations Among Single-Institution Patients With Brain Metastases[a]

Emergency Department Visits			Inpatient Hospitalizations		
Diagnoses (Codes)	Number of ED Claims	Percentage of ED Claims	Diagnoses (Codes)	Number of Hospital Visits	Percentage of Hospital Visits
Malignant neoplasm of bronchus and lung (1629)	282	5.2	Secondary malignant neoplasm of the brain and cerebral meninges (1983)	105	17.9
Secondary malignant neoplasm of the brain and cerebral meninges (1983)	244	4.5	Pneumonia (486)	28	4.8
Malaise and fatigue (78079)	182	3.3	Unspecified septicemia (0389)	21	3.6
Shortness of breath (78605)	129	2.4	Care involving other specified rehabilitation procedure (V5789)[b]	18	3.1
Malignant neoplasm of brain, unspecified (1919)	128	2.3	Urinary tract infection (5990)	17	2.9
Unspecified essential hypertension (4019)	112	2.1	Malignant neoplasm of bronchus and lung (1629)	16	2.7
Chest pain, unspecified (78650)	97	1.8	Secondary malignant neoplasm of bone and bone marrow (1985)	14	2.4
Altered mental status (78097)	96	1.8	Other pulmonary embolism and infarction (41519)	14	2.4
Unspecified convulsions (78039)	75	1.4	Secondary malignant neoplasm of other parts of nervous system (1984)	10	1.7
Vascular headache (7840)	69	1.3	Secondary malignant neoplasm lung (1970)	9	1.5
Malignant melanoma (1729)	68	1.2	Secondary malignant neoplasm of other digestive organs and spleen (1978)	9	1.5
Other malignant neoplasm without specification of site (1991)	68	1.2	Malignant neoplasm of upper lobe, bronchus, or lung (1623)	8	1.4
Cough (7862)	66	1.2	Atrial fibrillation (42731)	8	1.4
Other nonspecific abnormal finding of lung field (79319)	64	1.2	Malignant neoplasm of lower lobe, bronchus, or lung (1625)	7	1.2
Fever, unspecified (78060)	60	1.1	Hypoosmolality/hyponatremia (2761)	7	1.2
Unspecified pleural effusion (5119)	59	1.1	Dehydration (27651)	7	1.2

Abbreviation: ED, emergency department.
Total number of unique ED claims = 5461 representing 1257 unique ED encounters; total number of hospitalizations = 586.
[a]Only emergency department visits and hospitalizations >15 days after the BrM diagnosis date were counted in the table above to avoid inflating the incidence and capture only those visits subsequent to a known BrM diagnosis rather than symptoms that led to a diagnosis of brain metastases. In addition, given that the majority of claims during our study period were coded per the ICD-9 system and due to the challenges in correlating ICD-9 and ICD-10 diagnosis codes, only visits coded under the ICD-9 system were utilized when tabulating the most common reasons for presentation.
[b]Rehabilitation stays could not be reliability separated from inpatient hospitalizations through institutional claims.

was associated with increased risk for both ED and inpatient utilization. Moreover, the fact that over 50% of initial ED visits led to an inpatient hospitalization suggests that patients were presenting to the ED with complex medical issues that required higher-level care. In addition, we found that among patients with BrM, those with greater comorbidity, of African American race, and those previously managed with non-stereotactic radiation therapy (inclusive of WBRT) were at highest risk for requiring hospital-level care

Multiple prior studies have demonstrated that ED use among patients with cancer is common,[22,23] but dedicated studies of patients with BrM, a particularly susceptible population, have been lacking. Upon examining the principal diagnosis codes associated with ED and hospital stays among patients with BrM, intracranial disease was the most common reason for such visits at a large cancer center and a major contributor at a population level. Moreover, factors that likely represented intracranial disease/local treatment-related sequelae (e.g., altered mental status, syncope/collapse, convulsions) were common precipitants, as well. Furthermore, among patients with metachronous BrM, hospital-based care was more common after as opposed to before BrM diagnosis. Collectively, these findings suggest that the development of BrM is associated with escalations of care.

Older patients with BrM who harbored greater comorbidity had higher rates of ED visits and hospitalizations compared to their healthier counterparts, a finding consistent with prior work in the general cancer population and one with important sequelae.[24] First, the needs of older, less-healthy patients may not be well suited for the fast pace of the ED, leading to reflexive admissions.[15] In addition, the close quarters and high volume in the ED places patients at risk for acquiring communicable diseases,[25] with potentially profound consequences given the immunosuppression present in many patients from systemic therapy or steroids.[26] Optimizing outpatient care and decreasing exposure to the hospital environment when possible is especially critical among this vulnerable subgroup.

We also found that African American patients were at significantly higher risk of requiring hospital-based care. Prior studies have demonstrated that, compared to white patients, African American patients have limited access to specialty providers and suboptimal oncologic follow-up care.[27] In the absence of close patient-provider communication, symptoms may be more likely to progress to the point of necessitating acute attention. A recent study on patients with BrM also demonstrated notable racial disparities in the prescription of supportive medications targeting symptoms that commonly afflict this population; poorly controlled neurologic symptoms among African American patients could also explain the higher rates of ED visits observed here.[28] In addition, African American patients are more likely to report poorer communication with health care providers[29,30] and decline treatments[31] compared to their white counterparts. For all these reasons, African American patients with BrM represent a particularly high-risk group that would benefit from improved patient-provider engagement and closer outpatient follow-up.

Finally, we found that patients managed with non-stereotactic, brain-directed radiation therapy (primarily WBRT), were more likely to present to the ED and be hospitalized compared to those managed with stereotactic radiation therapy. Given that patients managed with WBRT tend to have more extensive intracranial disease than those managed stereotactically,[32] it seems plausible that both the intracranial disease burden and treatment-related toxicity could be playing a role in this association. In addition, WBRT mandates a longer cessation of systemic therapy than stereotactic radiotherapeutic approaches, potentially leading to extracranial disease progression that may collectively increase patients' need for hospital-based care.

The importance of our findings relates to the deleterious consequences associated with ED and/or hospital exposure for patients with advanced malignancies. Firstly, prior work has demonstrated that many patients with advanced disease favor less aggressive end-of-life care, prefer management at home whenever possible, and report lower quality of life when hospitalized.[12,33] Secondly, ED visits place cancer patients at risk for acquiring infections that could have serious consequences given their immunosuppression.[34] Finally, the ED's fast-paced and high-acuity environment, as well as the fact that the managing ED may be different than the institution providing oncologic care, often precludes providers from accessing patients' records in a timely manner, resulting in potentially superfluous testing and admissions.[9,11] The undue burden on patients and inefficient utilization of health care resources warrants the identification of strategies to prevent ED visits and inpatient hospitalizations whenever possible, especially among patients with BrM.

One evidence-based intervention that could be investigated among patients with BrM involves the incorporation of Clinician Navigators. Clinician Navigation is a patient-centered delivery intervention that supports patients with chronic conditions via increased patient-provider contact, allowing for symptoms and concerns to be addressed in a timely manner and thereby facilitating earlier and direct access to treatment.[35] The efficacy of Clinician Navigators in oncologic settings has previously been demonstrated in prior randomized work.[36,37] In one, phase 3 trial that randomized patients with a new diagnosis of breast, colorectal, or lung cancer to "enhanced usual care" or a nurse navigator for a period of 4 months, patients on the navigator arm reported significantly higher perceptions of quality of care and improved coordination of management, receipt of health information, and access to psychosocial care.[36] In another study that randomized patients with newly diagnosed breast cancer to usual care vs a nurse case manager for 12 months, patients on the case manager arm were more likely to receive appropriate care, including adjuvant radiation therapy and chemotherapy when indicated, to report a lower burden of treatment-related symptoms, and to report active participation in their treatment decision making.[37] Large retrospective studies of active Clinician Navigator programs at several academic centers have reported increased multi-modality treatment rates as evidenced by more frequent use of infusion and radiation oncology services and decreased hospital readmission rates among patients who were part of a navigator program compared to those receiving usual care.[35,38] Moreover, it has been shown that navigation programs for cancer patients reduce ED visits, hospitalizations, and intensive care unit admissions compared to patients not part

of navigation programs.[35,38] Despite demonstrated efficacy in the oncologic setting, a Clinician Navigator-based intervention has not specifically been evaluated in the BrM population, a group with a high burden of symptoms, risk of neurologic decline, and particular susceptibility to the deleterious consequences of unaddressed symptomatology, in part due to the poor penetration and lack of efficacy of many systemic therapies in the brain. Our work here suggests that older patients with BrM, especially those with significant comorbidities, of African American race, and/or receiving WBRT, may be particularly suitable candidates for such programs. Moreover, given the substantially higher rates of ED visits we identified among patients in the period shortly after BrM diagnosis, as well as near the end-of-life, our data suggest that patients with BrM may especially benefit from navigation programs during these particularly vulnerable time periods.

Limitations of our work include our utilization of claims to identify patients who develop metastatic disease to distant sites of the body, a practice the National Cancer Institute cautions against.[39] However, in contrast to other metastatic sites, a high sensitivity (>97%) and specificity (99%) for identifying BrM using claims data have been identified and validated.[18,19] Secondly, although we were able to comment on the frequency with which ED visits and inpatient hospitalizations were attributed to intracranial disease (based on the presence of diagnosis codes), the claims-based dataset was not granular enough for us to identify particular reasons for BrM-related admissions (eg, whether an admission was secondary to a seizure, cranial nerve deficit, etc.). Thirdly, although we demonstrated that the rates of ED visits and inpatient hospitalizations among patients with metachronous BrM were greater in the period following intracranial disease diagnosis as compared to before, we could not comment on whether this increase was due entirely to the development of intracranial disease or to more progressive extracranial disease that coincided with the development BrM. Given that SEER-Medicare does not provide data on metachronous, extracranial metastases, we could not further explore this question, and this should be acknowledged as a limitation of the current paper. In addition, given that our data only go to the year 2016, we cannot comment on how the rates of ED visits and inpatient hospitalizations identified in this study may have been affected by the recent increase in utilization of systemic treatments, such as immune checkpoint inhibitors, among patients with BrM. This will be an important variable to incorporate into future studies that contain more current datasets. Finally, although we could not readily identify those patients who were being followed by palliative care at the time of ED visit or inpatient hospitalization, future studies should aim to assess whether being seen by a palliative care service influences the frequency with which hospital-level care is required. Such studies will help inform the potential role of Clinician Navigators for this patient population, as well.

Conclusions

In this dual-sample study, we found that older patients with BrM display high rates of ED visits and hospitalizations, often secondary to the presence or sequelae of intracranial disease. Given the significant burden on patients and the health care system from management in the ED or inpatient setting, our findings call for systems-based interventions that improve communication between patients with BrM and their providers, identify symptoms at earlier stages, and optimize outpatient follow-up and care coordination in order to prevent ED and hospital visits when feasible, particularly among high-risk subsets.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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