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Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study

Daniel N. Cagney,* Allison M. Martin,* Paul J. Catalano, Amanda J. Redig, Nancy U. Lin, Eudocia Q. Lee, Patrick Y. Wen, Ian F. Dunn, Wenya Linda Bi, Stephanie E. Weiss, Daphne A. Haas-Kogan, Brian M. Alexander, and Ayal A. Aizer

Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, Massachusetts (D.N.C., A.M.M., D.A.H.K., B.M.A., A.A.A.); Department of Biostatistics, Harvard T. H. Chan School of Public Health, and Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts (P.J.C.); Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts (A.J.R., N.U.L.); Department of Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, Massachusetts (E.Q.L., P.Y.W.); Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (I.F.D., W.L.B.); Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania (S.E.W.)

Corresponding Author: Ayal Aizer MD, MHS, Department of Radiation Oncology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115 (aaaizer@partners.org).

*These authors contributed equally.

Abstract

Background. Brain metastases are associated with significant morbidity and mortality. Population-level data describing the incidence and prognosis of patients with brain metastases are lacking. The aim of this study was to characterize the incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy using recently released data from the Surveillance, Epidemiology, and End Results (SEER) program.

Methods. We identified 1 302 166 patients with diagnoses of nonhematologic malignancies originating outside of the CNS between 2010 and 2013 and described the incidence proportion and survival of patients with brain metastases.

Results. We identified 26 430 patients with brain metastases at diagnosis of cancer. Patients with small cell and non–small cell lung cancer displayed the highest rates of identified brain metastases at diagnosis; among patients presenting with metastatic disease, patients with melanoma (28.2%), lung adenocarcinoma (26.8%), non–small cell lung cancer not otherwise specified/other lung cancer (25.6%), small cell lung cancer (23.5%), squamous cell carcinoma of the lung (15.9%), bronchioloalveolar carcinoma (15.5%), and renal cancer (10.8%) had an incidence proportion of identified brain metastases of >10%. Patients with brain metastases secondary to prostate cancer, bronchioloalveolar carcinoma, and breast cancer displayed the longest median survival (12.0, 10.0, and 10.0 months, respectively).

Conclusions. In this study we provide generalizable estimates of the incidence and prognosis for patients with brain metastases at diagnosis of a systemic malignancy. These data may allow for appropriate utilization of brain-directed imaging as screening for subpopulations with cancer and have implications for clinical trial design and counseling of patients regarding prognosis.

Key words

brain metastases | incidence | prognosis | SEER | survival

Importance of the study

In this study, we described the incidence and prognosis of identified brain metastases among patients with newly diagnosed solid malignancies originating outside of the central nervous system. Given that SEER data on the presence or absence of brain metastases were released in 2016, our study represents the first epidemiologic study of brain metastases in the United States using the entirety of the SEER database. The highly generalizable results presented in this study have broad applications and may influence screening paradigms for brain metastases, clinical trial design, and counseling of specific subsets of patients with cancer.

Brain metastases significantly impact the clinical course of patients with systemic malignancy. Many patients present with neurologic symptoms, often causing profound impairment in cognition, quality of life, and performance status.[1–4] Although some targeted therapies display intracranial efficacy,[5] relatively few chemotherapy agents effectively penetrate the blood–brain barrier,[6] and therefore the diagnosis of brain metastases often necessitates neurosurgical or radiotherapeutic treatment.[7] Such therapies can often significantly impact quality of life, as can supportive medications such as steroids and anti-epileptic drugs.[8]

Despite the profound impact that brain metastases can have on patients with cancer, large-scale studies examining the incidence and prognosis of patients with brain metastases are lacking. The incidence of brain metastases in the United States remains unknown, in part because of historical coding systems that could not specifically capture spread of a primary cancer to the brain; as a result, estimates have varied from 21 000 to 400 000 per annum.[9,10] Reported percentages of patients with diagnosed brain metastases have similarly varied, ranging from 9% to 50%.[1,4,11,12] Large-scale and generalizable estimates of prognosis among patients with brain metastases secondary to specific cancers are also lacking.

As part of the annual update of the Surveillance, Epidemiology, and End Results (SEER) database, released in 2016, the presence or absence of brain metastases at diagnosis was made available to investigators. Accordingly, the objective of this study was to use the SEER database to make current generalizable estimates of the incidence and prognosis of patients with brain metastases in both screened and unscreened populations. This may lead to consideration/further evaluation of early screening of the brain among patients with newly diagnosed malignancies who are at an especially high risk of harboring brain metastases in the setting of newly diagnosed cancer, which in turn may influence clinical trial design and counseling of specific subsets of patients with cancer.

Materials and Methods

Patient Population and Study Design

We used the SEER database to identify 1 484 939 patients age ≥18 years who were diagnosed with an invasive solid malignancy originating outside of the CNS between January 1, 2010 and December 31, 2013. Patients with non-invasive/in situ neoplasms were not included in the study cohort. Sponsored by the National Cancer Institute, the SEER program collects and publishes cancer incidence, treatment, and survival data from population-based cancer registries. SEER tumor registries now cover ~28% of the United States population, capturing ~97% of incident cancers in those regions.[13] The year 2010 was the first that information relating to the presence or absence of brain metastases at diagnosis was made available; data are currently available through 2013. Presence or absence of brain metastasis was clarified prior to undergoing treatment. Patients were excluded if data relating to the presence or absence of brain metastases were unknown (12.3%), leaving 1 302 166 patients (87.7% of the initial cohort) in the final cohort analyzed for incidence. Patients were classified as having an unknown status if the presence or absence of brain metastasis was not documented in the patient record. For the survival analysis, patients who were diagnosed at autopsy or death certificate as well as patients with an unknown follow-up were removed, leaving 1 215 922 patients (81.9% of the initial cohort) remaining for analysis.

Statistical Analysis

Patients were stratified by cancer type. Patients with lung cancer were substratified by tumor histology using designations ascribed by SEER; classification by mutation/rearrangement status[14] was not possible given the limitations of SEER data. Patients with sarcoma and melanoma were identified by histology rather than primary site. Absolute numbers and incidence proportions of patients diagnosed with brain metastases were computed, as stratified by cancer type, age at diagnosis, gender, race, tumor stage, and nodal stage. Incidence proportion was defined as the number of patients diagnosed with brain metastases and a specific primary cancer divided by the total number of individuals diagnosed with that primary cancer[11]; we also defined a second incidence proportion in which the denominator was restricted to patients with de novo metastatic disease to any distant site. Tumor and nodal staging were conducted in accordance with the seventh edition of the American Joint Committee on Cancer staging manual.[15] Race was classified as white, African American, Hispanic, Asian American, other, or unknown, as determined by SEER. Multivariable logistic regression among the whole cohort was employed to determine whether age, race, and gender were associated with the presence of brain metastases at diagnosis; other variables in the model included primary cancer type, marital status, insurance status, tumor stage, nodal stage, residence type (urban vs rural),

education, and median household income.[16,17] Residence type, education level (ie, percentage of adults ≥25 years of age with a high school education), and median household income were determined at the county level by linkage to the 2003 United States Department of Agriculture rural-urban continuum codes,[18] 2000 United States Census,[19] and 2004 small area income and poverty estimates from the United States Census, respectively.[20] Survival estimates were obtained using the Kaplan–Meier method. Statistical analyses were performed using SAS version 9.4. This study was approved by our institutional review board; informed consent was waived.

Results

Cancer Incidence

In the 2010–2013 period, 1 302 166 patients were diagnosed with a malignancy and 217 687 had metastatic disease to any distant site. A total of 26 430 patients, 2.0% of all patients with cancer and 12.1% of those patients with metastatic disease, were found to have brain metastases at diagnosis. Given that SEER represents 28% of the United States population, we can estimate that the annual incidence of identified brain metastases in the United States among patients with newly diagnosed cancer is 23 598 per annum (95% CI: 23 297–23 899).

The proportion of patients with identified brain metastases at diagnosis varied widely by primary cancer type (Table 1 and Fig. 1A). Only small cell lung cancer, adenocarcinoma of the lung, and non–small cell lung cancer not otherwise specified/other lung cancer had an incidence proportion of brain metastases at diagnosis of >10% when cancers of any stage were considered (15.8%, 14.4%, and 12.8%, respectively). Among patients with breast cancer, renal cancer, and melanoma, only 0.4%, 1.5%, and 0.7% of patients were found to have brain metastases at diagnosis. When the denominator of the incidence proportion was restricted to patients with de novo metastatic disease (Table 1, Fig. 1B), a higher incidence proportion of patients with brain metastases was identified. In descending order, patients with metastatic melanoma (28.2%), adenocarcinoma of the lung (26.8%), non–small cell lung cancer not otherwise specified/other lung cancer (25.6%), small cell lung cancer (23.5%), squamous cell carcinoma of the lung (15.9%), bronchioloalveolar carcinoma (15.5%), and renal cancer (10.8%) were found to have an incidence proportion of identified brain metastases of >10%.

Incidence proportions of patients diagnosed with brain metastases, as stratified by primary cancer, age, race, and gender are presented in Supplementary Table S1; stratification by primary tumor and nodal stage is provided in Supplementary Table S2. On multivariable logistic regression (Supplementary Table S3) among all patients with cancer, associated with significantly greater odds of having brain metastases at diagnosis were age 41–60 years (vs age 18–40 y, odds ratio [OR] 1.55, 95% CI: 1.39–1.71), Hispanic and Asian race (vs white race, OR 1.06, 95% CI: 1.01–1.11 and OR 1.16, 95% CI: 1.10–1.23, respectively), unmarried status (vs married status, OR 1.04, 95% CI: 1.01–1.07), lower county level income (OR per $10 000 annual decrease 1.04, 95% CI: 1.01–1.07), higher county education level (OR per 10% increase in high school completion 1.04, 95% CI: 1.02–1.07), uninsured status (vs insured status, OR 1.39, 95% CI: 1.31–1.48), tumor stages 2, 3, and 4 (vs tumor stage 1, OR 1.95, 95% CI: 1.86–2.05, OR 2.22, 95% CI: 2.11–2.93, and OR 2.79, 95% CI: 2.66–2.93, respectively), and nodal stages 1, 2, and 3 (vs nodal stage 0, OR 2.13, 95% CI: 2.04–2.24, OR 2.36, 95% CI: 2.28–2.45, and OR 2.61, 95% CI: 2.49–2.73, respectively).

Survival Estimates

Median survivals of patients with brain metastases at diagnosis, as stratified by primary cancer, are presented in Table 1 and Fig. 1C. Patients with prostate cancer (median survival 12.0 mo), bronchioloalveolar carcinoma (median survival 10.0 mo), and breast cancer (median survival 10.0 mo) displayed the longest survival. Median survival estimates, as stratified by age, race, gender, and cancer type, are displayed in Supplementary Table S4. Median survivals of patients with brain metastases at diagnosis, as stratified based on the presence or absence of bone, liver, and lung metastases, are presented in Table 2.

Discussion

In this study, we described the absolute number, incidence proportion, and prognosis of identified brain metastases among patients with newly diagnosed solid malignancies originating outside of the central nervous system. To the best of our knowledge, this is the first epidemiologic study of brain metastases in the United States using the entirety of the SEER database. We stratified our results so that estimates relating to the incidence proportion and prognosis of patients diagnosed with brain metastases can be used by other investigators to study specific cancers, age groups, genders, and ethnicities. Because the SEER program encompasses 28% of the United States population, our results are highly generalizable. The data in this study have broad applications and may influence screening paradigms for brain metastases, clinical trial design, and counseling of specific subsets of patients with cancer.

In 2004, Barnholtz-Sloan et al used SEER data to describe the incidence proportion of patients diagnosed with brain metastases throughout their clinical course in the Detroit metropolitan area between 1973 and 2001. Their analysis was limited to 5 primary sites: lung, melanoma, renal, breast, and colorectal cancer; overall, 19.9%, 6.9%, 6.5%, 5.1%, and 1.8% of patients, respectively, developed brain metastases. The Metropolitan Detroit Cancer Surveillance System, which provided information relating to the presence versus absence of metastatic disease to the brain, was only available for 3 counties near Detroit, potentially limiting generalizability. More recently Goncalves et al also used the Metropolitan Detroit Cancer Surveillance System to examine the risk of development of brain metastases in patients with nonmetastatic lung cancer diagnosed

Table 1 Incidence proportion and median survival of patients with identified brain metastases at diagnosis by primary cancer site

Site	Subsite	Number of Patients with Cancer (any Stage)	Number of Patients with Metastatic Disease	Number of Patients with Brain Metastases at Diagnosis	Incidence Proportion of Brain Metastases among Entire Cohort	Incidence Proportion of Brain Metastases among Subset with Metastatic Disease	Median Survival in Months (inter quartile range) among Patients with Brain Metastases
Head and neck	Head and neck[a]	53 037	2136	108	0.20	5.06	5.0 (2.0–12.0)
Thyroid	Thyroid	48 502	989	58	0.12	5.86	5.0 (2.0–24.0)
Breast	Breast	239 102	12 844	973	0.41	7.58	10.0 (3.0–30.0)
Lung	Small cell	22 510	15 186	3563	15.83	23.46	6.0 (2.0–11.0)
	Squamous cell carcinoma	40 404	13 469	2136	5.29	15.86	4.0 (2.0–8.0)
	Adenocarcinoma	68 170	36 700	9842	14.44	26.82	6.0 (2.0–14.0)
	Bronchioloalveolar carcinoma	6370	950	147	2.31	15.47	10.0 (4.0–33.0)
	Non–small cell NOS and other	47 745	23 924	6116	12.81	25.56	4.0 (2.0–9.0)
GI	Esophagus	14 353	4478	238	1.66	5.31	4.0 (2.0–9.0)
	Gastric	23 995	7865	154	0.64	1.96	4.0 (2.0–8.0)
	Hepatobiliary	38 126	7808	138	0.36	1.77	3.0 (1.0–7.0)
	Pancreatic	39 693	19 847	162	0.41	0.82	2.0 (1.0–6.0)
	Colorectal	134 813	26 923	365	0.27	1.36	6.0 (2.0–15.0)
	Anal	6343	443	7	0.11	1.58	7.0 (3.0–10.0)
	Other GI	11 670	3803	79	0.68	2.08	4.0 (2.0–9.0)
GU	Renal	54 495	7463	809	1.48	10.84	5.0 (2.0–12.0)
	Bladder	33 337	2464	85	0.25	3.45	4.0 (2.0–11.0)
	Prostate	204 897	10 306	152	0.07	1.47	12.0 (6.0–39.0)
	Testicular	9079	1051	80	0.88	7.61	NR (10.0-NR)
	Other GU	4283	347	10	0.23	2.88	7.0 (1.0–21.0)
GYN	Ovarian	20 551	5340	50	0.24	0.94	5.0 (2.0–19.0)
	Endometrial	47 196	3092	105	0.22	3.40	4.0 (2.0–9.0)
	Cervical	12 577	1630	48	0.38	2.94	4.0 (2.0–9.0)
	Other GYN	7538	730	16	0.21	2.19	NR (14.0-NR)
Sarcoma	Any type of sarcoma	13 592	2273	101	0.74	4.44	4.0 (1.0–10.0)
Melanoma	Any type of melanoma	77 876	1804	508	0.65	28.16	6.0 (2.0–13.0)
All others	All others[b]	21 912	3822	380	1.73	9.94	3.0 (1.0–11.0)
Total for all cancers		1 302 166	217 687	26,430	2.03	12.14	5.0 (2.0–12.0)

Abbreviations: GI = gastrointestinal, GU = genitourinary, GYN = gynecologic, NOS = not otherwise specified, NR = not reached.
[a]Lip, tongue, gum, floor of mouth, and other mouth, salivary gland, oropharynx, nasopharynx, hypopharynx, pharynx, nasal cavity (including nasal cartilage), accessory, sinuses, middle and inner ear, larynx, trachea, orbit and lacrimal gland, retina, eyeball, eye, NOS.
[b]Ureter, other urinary organs, thymus, heart, mediastinum, pleura, bones and joints, blood, bone marrow and hematopoietic system, spleen, reticulo-endothelial, skin, connective and soft tissue, adrenal glands, parathyroid gland, other endocrine glands, lymph nodes, ill-defined, unknown.

between 1973 and 2011.[21] They found incidence proportions of 9% and 18% among patients with non–small cell and small cell lung cancer, respectively. No differences in the proportion developing brain metastases among patients of white versus African American race were noted, consistent with the results in our study. The studies by Goncalves et al and Barnholtz-Sloan et al have several notable differences from our study. Because the former studies date back to 1973, MRI, which represents the most sensitive method of diagnosing brain metastases, was not routinely used for portions of the study period.[22] However, patients in both former studies were followed for the development of brain metastases, thereby providing estimates of incidence spanning the lifetime of each patient. SEER does not provide follow-up information relating to recurrence, so we limited our study to the presence versus absence of

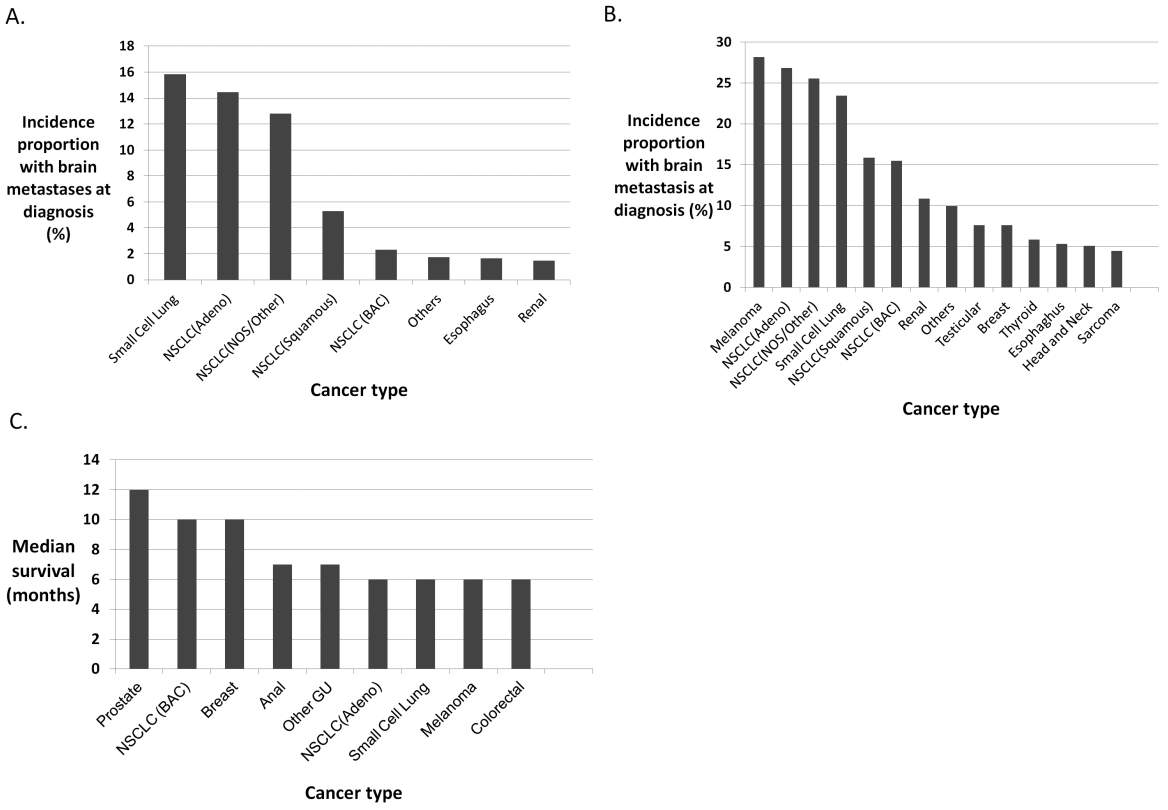

Fig. 1 Incidence proportion of patients diagnosed with brain metastases within entire cohort (A) and subset with metastatic disease (B), and median survival of patients with identified brain metastases (C), by primary cancer site. Patients not depicted in the Figure had lower incidence proportion (A, B) or median survival (C) than threshold for presentation. **Abbreviations:** BAC = bronchioloalveolar carcinoma, NSCLC = non–small cell lung cancer, NOS = not otherwise specified.

identified brain metastases at diagnosis only. Berghoff et al performed a retrospective chart review for patients treated for brain metastases of solid cancers at the University of Vienna between 1990 and 2011.[23] They noted that 26% of all brain metastases diagnosed in patients presented with a synchronous diagnosis of primary tumor. Patients with lung cancer (47%) presented most frequently with brain metastasis at diagnosis. Our study concurs with the fact that lung cancer is most likely to present with synchronous brain metastasis, likely reflecting current screening guidelines.

Brain metastases are an important cause of morbidity and mortality for patients with cancer, and patients with brain metastases can display poor quality of life.[8,24,25] Early detection of brain metastases may minimize morbidity and mortality, as well as treatment-related toxicity.[8,24,26] Screening studies of the brain are not routinely performed for patients with renal cell cancer,[27,28] breast cancer,[29] or testicular cancer.[30] However, our data revealed a 10.8%, 7.6%, and 7.6% incidence proportion, respectively, of brain metastases in patients with these 3 cancers and metastatic disease to any distant site. As screening was not mandated in these patients, brain involvement is often discovered only as a result of neurologic symptoms, often requiring neurosurgical intervention or use of more extensive radiation fields. Our data suggest that the relatively high rates of brain metastases in these populations, which are likely underestimates, may warrant consideration of MRI of the brain at diagnosis, as screening is standard among patients with a lower risk of brain involvement, such as patients with T2bN0 non–small cell lung cancer, where SEER data suggest an incidence proportion of brain involvement at diagnosis of 1.2%–8.1%.[31]

Accurate and generalizable estimates of incidence and prognosis are also important for clinical trial design. Many oncology trials restrict enrollment to newly diagnosed disease and treatment-naïve patients, the same population depicted in this study. The data in this study may help investigators quantify the number of patients excluded from trial enrollment if brain metastases are an exclusion criterion. Moreover, for studies relating to patients with brain metastases, this study may provide generalizable estimates of prognosis for use in power calculations and other elements of trial design.

We noted a number of variables which were independently associated with the presence of brain metastases. Factors such as lack of health insurance[32,33] and unmarried social status[16] have previously been shown to be associated with less favorable outcomes in patients with cancer, so it is not surprising that they are with increased

Table 2 Incidence proportion and median survival of patients with brain metastases by extent of systemic disease

Site	Subsite	Type of Systemic Metastasis	Number of Patients	Proportion with Brain Metastases	Median Survival in Months (interquartile range)
Head and Neck	Head and neck[a]	Bone	19	5.48	7.0 (4.0–18.0)
		Lung	16	2.03	4.0 (2.0–8.0)
		Liver	2	1.65	NR (2.0–NR)
		2 of 3	19	6.38	4.0 (2.0–11.0)
		All 3	7	12.50	3.5 (1.0–5.0)
		None	39	8.02	5.0 (2.0–12.0)
		Unknown	6	15.00	12.0 (10.0–14.0)
Thyroid	Thyroid	Bone	8	4.85	4.5 (3.5–14.0)
		Lung	20	4.41	3.0 (1.0–14.0)
		Liver	0	0.00	NA
		2 of 3	12	8.70	18.0 (2.0–24.0)
		All 3	2	8.33	1.0 (1.0–1.0)
		None	13	7.88	NR (4.0–NR)
		Unknown	3	15.79	2.0 (2.0–3.0)
Breast	Breast	Bone	217	4.50	14.0 (5.0–35.0)
		Lung	86	6.28	8.0 (2.0–19.0)
		Liver	38	4.01	6.0 (3.0–27.0)
		2 of 3	252	9.10	10.0 (3.0–34.0)
		All 3	140	17.99	7.0 (2.0–20.0)
		None	165	9.34	10.0 (3.0–37.0)
		Unknown	75	19.28	10.0 (2.0–22.0)
Lung	Small cell	Bone	324	18.40	6.0 (3.0–11.0)
		Lung	236	18.72	6.0 (2.0–11.0)
		Liver	420	13.21	5.0 (2.0–9.0)
		2 of 3	559	18.25	6.0 (2.0–9.0)
		All 3	165	24.63	4.0 (2.0–8.0)
		None	2900	34.66	7.0 (2.0–13.0)
		Unknown	233	33.05	5.0 (2.0–10.0)
	Squamous cell carcinoma	Bone	272	11.57	3.0 (2.0–6.0)
		Lung	203	7.17	4.0 (2.0–8.0)
		Liver	114	12.51	2.0 (1.0–5.0)
		2 of 3	256	16.24	2.0 (1.0–4.0)
		All 3	87	26.13	2.0 (1.0–4.0)
		None	1079	21.78	4.0 (2.0–9.0)
		Unknown	125	24.32	3.0 (2.0–8.0)
	Adenocarcinoma	Bone	1642	21.54	5.0 (2.0–13.0)
		Lung	1130	18.48	6.0 (2.0–15.0)
		Liver	343	20.88	4.0 (2.0–9.0)
		2 of 3	1450	26.79	4.0 (2.0–11.0)
		All 3	459	34.80	4.0 (2.0–11.0)
		None	4197	32.53	7.0 (3.0–17.0)
		Unknown	621	36.77	4.0 (2.0–11.0)
	Bronchioloalveolar adenocarcinoma	Bone	22	18.80	10.0 (3.0–21.0)
		Lung	14	4.39	10.0 (3.0–NR)
		Liver	2	12.50	19.0 (2.0–36.0)

Table 2 Continued

Site	Subsite	Type of Systemic Metastasis	Number of Patients	Proportion with Brain Metastases	Median Survival in Months (interquartile range)
		2 of 3	33	29.20	10.0 (7.0–15.0)
		All 3	5	33.33	6.0 (4.5–NR)
		None	62	18.34	13.0 (5.0–NR)
		Unknown	9	28.13	5.5 (5.0–19.0)
	Non–small cell and other	Bone	725	18.33	3.0 (2.0–8.0)
		Lung	625	16.83	3.0 (2.0–8.0)
		Liver	366	16.18	3.0 (1.0–7.0)
		2 of 3	774	21.73	3.0 (1.0–6.0)
		All 3	225	28.34	3.0 (1.0–5.0)
		None	2900	34.66	4.0 (2.0–10.0)
		Unknown	501	16.06	3.0 (1.0–7.0)
GI	Esophagus	Bone	29	5.66	4.0 (2.0–7.0)
		Lung	15	2.64	3.0 (2.0–6.0)
		Liver	27	2.27	5.0 (2.0–7.0)
		2 of 3	49	5.99	4.0 (2.0–6.0)
		All 3	16	11.27	2.0 (1.0–3.0)
		None	81	7.37	6.0 (3.0–19.0)
		Unknown	21	14.09	5.0 (1.0–14.0)
	Gastric	Bone	14	2.80	3.0 (3.0–7.0)
		Lung	12	2.73	3.5 (2.0–10.0)
		Liver	21	0.79	4.0 (1.0–7.5)
		2 of 3	26	3.39	2.0 (1.0–6.0)
		All 3	13	11.02	3.0 (3.0–9.0)
		None	54	1.72	4.0 (2.0–8.0)
		Unknown	14	5.62	13.0 (4.0–24.0)
	Hepatobiliary	Bone	18	2.02	3.0 (2.5–7.0)
		Lung	26	1.77	2.0 (1.0–4.0)
		Liver	11	0.50	2.0 (1.0–5.0)
		2 of 3	24	2.44	2.0 (1.0–5.0)
		All 3	10	7.81	3.0 (2.0–7.0)
		None	37	1.99	4.0 (2.0–9.0)
		Unknown	12	4.08	7.0 (2.0–13.0)
	Pancreatic	Bone	7	2.54	3.5 (2.0–13.0)
		Lung	14	1.08	2.0 (1.5–3.0)
		Liver	31	0.27	2.0 (1.0–5.0)
		2 of 3	49	1.77	2.0 (1.0–5.0)
		All 3	15	4.09	4.0 (2.0–10.0)
		None	29	1.02	4.0 (1.0–10.0)
		Unknown	17	2.81	2.0 (1.5–5.0)
	Colorectal	Bone	11	3.74	3.0 (1.0–9.0)
		Lung	47	2.87	6.0 (2.0–22.0)
		Liver	50	0.36	6.0 (2.0–17.0)
		2 of 3	103	2.25	6.0 (2.0–16.0)
		All 3	30	6.45	3.0 (1.0–11.0)
		None	96	1.75	5.0 (2.0–15.0)
		Unknown	28	4.85	6.0 (3.0–7.0)

Table 2 Continued

Site	Subsite	Type of Systemic Metastasis	Number of Patients	Proportion with Brain Metastases	Median Survival in Months (interquartile range)
	Anal	Bone	0	0.00	NA
		Lung	1	2.04	1.0 (1.0–1.0)
		Liver	1	0.77	3.00 (3.0–3.0)
		2 of 3	1	1.69	NR (NR–NR)
		All 3	0	0.00	NA
		None	2	1.37	8.5 (7.0–10.0)
		Unknown	2	12.50	8.5 (4.0–13.0)
	Other GI	Bone	5	4.85	2.0 (1.5–2.5)
		Lung	7	2.55	9.0 (3.0–15.0)
		Liver	11	0.65	5.0 (5.0–NR)
		2 of 3	20	4.85	3.0 (2.0–9.0)
		All 3	7	10.00	1.0 (1.0–3.5)
		None	18	1.62	4.0 (2.0–12.0)
		Unknown	11	8.73	2.5 (1.0–5.0)
GU	Renal	Bone	69	5.44	6.0 (2.0–14.0)
		Lung	238	10.23	6.0 (3.0–12.0)
		Liver	20	4.08	3.5 (2.0–6.0)
		2 of 3	211	12.54	5.0 (2.0–10.0)
		All 3	62	16.19	4.0 (2.0–9.0)
		None	168	15.50	6.0 (3.0–33.0)
		Unknown	41	17.98	4.0 (2.0–13.0)
	Bladder	Bone	10	1.82	7.5 (2.0–17.0)
		Lung	12	2.76	8.0 (3.5–13.0)
		Liver	3	1.21	6.5 (2.0–11.0)
		2 of 3	22	6.04	2.0 (1.0–4.0)
		All 3	12	12.37	2.0 (2.0–4.0)
		None	22	3.14	6.0 (3.0–11.0)
		Unknown	4	5.63	1.0 (1.0–3.0)
	Prostate	Bone	72	0.88	12.0 (6.0–27.0)
		Lung	2	1.52	7.00 (7.0–7.0)
		Liver	1	1.14	11.00 (11.0–11.0)
		2 of 3	32	4.16	11.0 (6.0–28.0)
		All 3	12	10.00	14.0 (5.0–20.0)
		None	14	1.69	NR (3.0–NR)
		Unknown	19	8.26	13.0 (7.0–17.0)
	Testicular	Bone	1	3.85	NR (NR–NR)
		Lung	41	8.76	NR (12.0–NR)
		Liver	0	0.00	NA
		2 of 3	25	17.86	14.0 (2.0–NR)
		All 3	5	38.46	NR (NR–NR)
		None	4	1.15	NR (7.0–NR)
		Unknown	4	20.00	NR (7.0–NR)
	Other GU	Bone	3	5.77	7.0 (1.0–NR)
		Lung	0	0.00	NA
		Liver	0	0.00	NA
		2 of 3	1	1.37	21.00 (21.0–21.0)

Table 2 Continued

Site	Subsite	Type of Systemic Metastasis	Number of Patients	Proportion with Brain Metastases	Median Survival in Months (interquartile range)
		All 3	0	0.00	NA
		None	6	7.23	4.0 (1.0–7.0)
		Unknown	0	0.00	NA
GYN	Ovarian	Bone	4	5.13	3.0 (3.0–3.0)
		Lung	8	1.03	4.5 (2.0–27.0)
		Liver	2	0.21	1.0 (1.0–1.0)
		2 of 3	7	2.01	5.5 (2.0–7.0)
		All 3	4	9.09	NR (17.0–NR)
		None	20	0.68	6.0 (3.0–NR)
		Unknown	5	2.72	2.5 (2.0–9.0)
	Endometrial	Bone	5	3.79	3.0 (3.0–6.0)
		Lung	29	4.77	4.0 (2.0–9.0)
		Liver	3	1.20	4.0 (2.0–13.0)
		2 of 3	18	6.55	2.0 (1.0–6.0)
		All 3	7	12.28	3.0 (2.0–6.0)
		None	38	2.22	5.0 (3.0–9.0)
		Unknown	5	8.93	6.0 (5.0–6.0)
	Cervical	Bone	7	5.65	3.0 (1.0–6.0)
		Lung	14	4.58	4.0 (3.0–8.0)
		Liver	2	1.96	9.0 (1.0–17.0)
		2 of 3	7	4.24	4.5 (2.0–7.0)
		All 3	1	2.78	NR (NR–NR)
		None	14	1.64	6.0 (2.0–12.0)
		Unknown	3	6.98	2.0 (1.0–3.0)
	Other GYN	Bone	0	0.00	NA
		Lung	6	3.08	NR (14.0–NR)
		Liver	0	0.00	NA
		2 of 3	4	5.33	13.0 (7.0–16.0)
		All 3	1	25.00	NR (NR–NR)
		None	2	0.60	NR (NR–NR)
		Unknown	3	27.27	NR (NR–NR)
Sarcoma	Any type of sarcoma	Bone	12	6.67	6.0 (2.0–13.0)
		Lung	13	1.70	4.0 (1.0–7.0)
		Liver	4	1.55	2.0 (1.0–4.5)
		2 of 3	21	6.62	2.5 (1.5–13.0)
		All 3	10	12.82	5.0 (2.0–14.0)
		None	31	5.12	4.0 (2.0–9.0)
		Unknown	10	14.08	2.0 (1.0–5.0)
Melanoma	Any type of melanoma	Bone	18	14.17	6.0 (2.0–12.0)
		Lung	132	29.20	5.0 (2.0–13.0)
		Liver	8	5.63	2.0 (1.0–31.0)
		2 of 3	89	29.47	5.0 (2.0–10.0)
		All 3	48	39.02	4.0 (2.0–9.0)
		None	173	29.47	9.0 (4.0–24.0)
		Unknown	40	56.34	5.0 (2.0–9.0)

Table 2 Continued

Site	Subsite	Type of Systemic Metastasis	Number of Patients	Proportion with Brain Metastases	Median Survival in Months (interquartile range)
All others	All others[b]	Bone	26	4.79	3.0 (2.0–7.0)
		Lung	40	4.85	6.0 (2.0–11.0)
		Liver	20	2.90	2.5 (2.0–12.0)
		2 of 3	44	5.72	3.0 (1.0–7.0)
		All 3	47	22.07	3.0 (1.0–8.0)
		None	114	21.15	4.0 (1.5–19.0)
		Unknown	89	36.48	3.0 (1.0–6.0)

Abbreviations: GI = gastrointestinal, GU = genitourinary, GYN = gynecologic, NR = not reached, NA = not applicable.
[a]Lip, tongue, gum, floor of mouth, and other mouth, salivary gland, oropharynx, nasopharynx, hypopharynx, pharynx, nasal cavity (including nasal cartilage), accessory, sinuses, middle and inner ear, larynx, trachea, orbit and lacrimal gland, retina, eyeball, eye, NOS.
[b]Ureter, other urinary organs, thymus, heart, mediastinum, pleura, bones and joints, blood, bone marrow and hematopoietic system, spleen, reticuloendothelial, skin, connective and soft tissue, adrenal glands, parathyroid gland, other endocrine glands, lymph nodes, ill-defined, unknown

risk of brain metastasis at diagnosis. Other factors such as increasing tumor and nodal stage are logical in terms of increasing risk of brain metastasis. Of note, patients who were Hispanic or Asian were at higher risk of harboring brain metastases than white patients. Whether environmental or biologic factors are responsible for these associations may be a topic of further investigation.

It is important to consider our study in the context of its limitations. First, we were only able to identify brain metastases at initial cancer diagnosis. SEER does not provide information relating to disease recurrence, so we could not identify patients who developed brain metastases after the period of initial diagnosis. For cancers which tend to present at early stages, this represents a major limitation of the database. For example, patients with metastatic disease to any site comprised only 5.4% of patients with newly diagnosed breast cancer and 13.7% of patients with newly diagnosed renal cell carcinoma in our dataset. Other studies have established that brain metastases continue to occur over time in patients with established metastatic disease.[34–39] Second, we do not have information relating to the number or size of the brain metastases that were present. Third, screening is not employed across all malignancies. Thus the incidence proportion of brain metastases in unscreened populations is likely an underestimate of the true figure. However, some patients, such as those with lung cancer and melanoma, were likely screened for the presence of brain metastases, consistent with consensus guidelines.[31,40,41] As a result, such patients may have been more likely to present with asymptomatic brain metastases, whereas patients with cancers for which routine screening of the brain is not employed may have presented more commonly with symptomatic brain metastases. SEER data do not indicate whether brain metastases were symptomatic or asymptomatic at diagnosis. Similarly, SEER does not provide treatment information for metastatic sites, so we cannot describe the brain-directed treatment patients received. This is important, as treatment chosen may influence survival rates that we are presenting. Fourth, although SEER provides information on 28% of the population based on the state/location that a patient resides in, patients seeking care at an institution outside of the SEER network may have incomplete clinical information. Finally, information relating to patient comorbidities and smoking history are not available in SEER, so we could not use those variables in our analyses.

Despite these limitations, our study provides new insights into the epidemiology of brain metastases in the United States. Data relating to the incidence of brain metastases, the specific proportion of patients with identified brain metastases among various cancer types, and the prognosis of patients with brain metastases are of broad clinical interest and will continue to help shape the development of screening and treatment guidelines.

Supplementary Material

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

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