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Epidemiology of brain metastases and leptomeningeal disease

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Abstract

Brain metastases affect a significant percentage of patients with advanced extracranial malignancies. Yet, the incidence of brain metastases remains poorly described, largely due to limitations of population-based registries, a lack of mandated reporting of brain metastases to federal agencies, and historical difficulties with delineation of metastatic involvement of individual organs using claims data. However, in 2016, the Surveillance Epidemiology and End Results (SEER) program released data relating to the presence vs absence of brain metastases at diagnosis of oncologic disease. In 2020, studies demonstrating the viability of utilizing claims data for identifying the presence of brain metastases, date of diagnosis of intracranial involvement, and initial treatment approach for brain metastases were published, facilitating epidemiologic investigations of brain metastases on a population-based level. Accordingly, in this review, we discuss the incidence, clinical presentation, prognosis, and management patterns of patients with brain metastases. Leptomeningeal disease is also discussed. Considerations regarding individual tumor types that commonly metastasize to the brain are provided.

Brain metastases are common among patients with advanced solid tumors.[1–3] Estimates of the incidence of brain metastases in the United States have varied, but it is likely that 70 000-400 000 new cases of brain metastases are diagnosed in the United States per annum and that 10%-40% of patients with solid tumors will develop brain metastases over their clinical course.[4–6] Brain metastases appear to be 10-fold more common than primary malignant brain tumors.[7] The development of brain metastases can markedly alter the clinical course of a patient given the associated neurologic symptomatology, psychological impact, alterations in oncologic treatment plan, and restrictions on clinical trial eligibility.[8] Systemic therapy often achieves unreliable penetration through the blood-brain barrier, and as a result, local, brain-directed therapy, such as radiation or neurosurgical resection, are commonly employed.[9] Moreover, while advances in systemic therapy have led to improvements in extracranial disease control and prolonged overall survival, the lagging intracranial efficacy of most systemic therapies has been associated with a concomitant increase in the incidence of brain metastases over time.[10] However, among certain tumor types, advances in the intracranial efficacy of systemic therapy have facilitated the utilization of drug-based therapy as monotherapy for select patients with intracranial disease. An understanding of the epidemiology of brain metastases is of great importance and serves as the objective of this review. The epidemiology of leptomeningeal disease is also described. Metastases to the calvarium, pachymeninges, pituitary gland, pineal gland, choroid plexus, and orbit are not specifically addressed.

Incidence

Limitations in Assessing the Incidence of Brain Metastases

The exact incidence of brain metastases is difficult to determine. Unlike primary brain tumors, reporting of brain metastases to local and federal registries such as the Central Brain Tumor Registry of the United States is not mandated.[11] A significant step forward in delineating the incidence of

brain metastases occurred in 2016 when the Surveillance Epidemiology and End Results (SEER) program released data relating to the presence vs absence of brain metastases at diagnosis of extracranial disease.[12] However, the SEER program does not report information relating to disease recurrence after initial diagnosis/management; given that brain metastases frequently develop after initial diagnosis of oncologic disease,[13] many patients with brain metastases remain uncaptured by SEER.

The National Cancer Institute advises caution when utilizing claims to identify metastases to any site after primary cancer diagnosis.[14] However, in contrast to other metastatic sites, brain metastases are commonly treated with local therapies for which diagnostic/billing codes exist; recently published studies have demonstrated that claims data can reliably be used to identify brain metastases with a high sensitivity (>97%) and specificity (99%) relative to manual chart review.[15,16] In addition, the date of diagnosis of brain metastases can now be ascertained via claims to within 15 days of the true diagnosis date in 87% of cases.[16] As a result, claims-based registries can now be used for epidemiologic investigations relating to brain metastases, including those that develop after the time of primary cancer diagnosis.

The utility of screening imaging of the brain can also impact the observed incidence of brain metastases; the role of brain-directed imaging in asymptomatic patients varies by primary site. The National Comprehensive Cancer Network (NCCN) recommends screening imaging of the brain, typically in the form of magnetic resonance imaging (MRI) at the time of diagnosis of oncologic disease, for select malignancies/stages of disease, including small cell lung cancer, non–small cell lung cancer, melanoma, testicular cancer, alveolar soft parts sarcoma, angiosarcoma, and left-sided cardiac sarcoma, as shown in Table 1.[17] Lastly, the nature of the imaging used to assess the brain can impact the likelihood of identification of intracranial disease, with MRI being superior to computed tomography (CT).[18,19] When MRIs are obtained, imaging regimens that incorporate thin slice (thickness 1.5 mm or less) T1 post-contrast sequences have greater sensitivity to identify intracranial disease than regimens lacking this sequence.[20,21]

Incidence/Incidence Proportion of Brain Metastases

The incidence proportion of brain metastases by primary site at the time of diagnosis of oncologic disease was first described on a population-based level in 2016-2017, after the initial release of such data by the SEER program in 2016.[12,22] Given that SEER data stem from approximately 35% of the US population, such estimates provide generalizable data relating to the percentage of patients with intracranial disease at presentation with malignancy. SEER-based incidence proportions of brain metastases by primary cancer type are summarized in Table 2 and indicate that the malignancies with the greatest potential for intracranial involvement appear to be small cell lung cancer, non–small cell lung cancer (particularly adenocarcinomas), and melanoma; rates of brain metastases appear to be significantly higher among patients with extracranial metastases secondary to these primaries (with 23%-28% of such patients harboring brain metastases).

In addition, patients with extracranial metastases secondary to renal cancer, HER2-positive breast cancer, and triple-negative breast cancer also display a significant incidence of brain metastases (with incidence proportions of 8%-11% among such patients, even without widespread utilization of screening imaging of the brain). Among metastatic gastroenterologic primaries, esophageal primaries seemed to harbor the greatest risk of intracranial involvement, with a rate of identified brain metastases of approximately 5%, similar to the risk seen in metastatic head/neck primaries, including thyroid cancer.[12] Prostate cancer almost never directly metastasizes to the brain but can involve the brain secondarily via breakthrough beyond the calvarium and pachymeninges.[12]

The incidence proportion of brain metastases after diagnosis of the primary malignancy is difficult to determine, but patients with primaries that commonly spread to the brain may be at risk for development of brain metastases even if intracranial involvement is not present at cancer diagnosis.[23] In patients with small cell lung cancer, prospective data indicate the cumulative risk of development of brain metastases increases with time, with over 50% of patients with small cell lung cancer developing brain metastases after screening negative for intracranial disease initially.[24] In a prospective study of patients with HER2+ breast cancer, over 50% of patients who died

Table 1 Primary Sites/Histologies for Which Screening Imaging of the Brain Is Recommended vs Not per the National Comprehensive Cancer Network

Screening Recommended[a]	No Routine Screening Recommended
Lung (non–small cell lung cancer)	Breast
Lung (small cell lung cancer)[b]	Bladder
Melanoma (non-uveal)	Gastrointestinal
Sarcoma (alveolar soft parts sarcoma/angiosarcoma/left-sided cardiac sarcoma)	Gynecologic
Testicular[c]	Head/neck
	Hepatobiliary
	Melanoma (uveal)
	Pancreatic
	Prostate
	Renal
	Sarcoma (other than alveolar soft parts sarcoma/angiosarcoa/left-sided cardiac sarcoma)
	Thymic
	Thyroid

[a]Recommendation varies by stage.
[b]Includes small cell/neuroendocrine histologies of other primary sites.
[c]If indicated based on histology, extent of disease, tumor markers, and/or symptoms.

Table 2 Incidence Proportion of Brain Metastases in the United States at Diagnosis of Malignancy by Primary Site

Primary Site	Sub-Site	Incidence Proportion Among Entire Cohort[a]	Incidence Proportion Among Subset With Metastatic Disease[b]
Breast			
	HR+/HER2–	0.22	5.46
	HR+/HER2+	0.61	7.98
	HR–/HER2+	1.09	11.45
	Triple-negative	0.68	11.37
Head and Neck	All	0.20	5.06
Gastrointestinal			
	Esophagus	1.66	5.31
	Gastric	0.64	1.96
	Hepatobiliary	0.36	1.77
	Pancreatic	0.41	0.82
	Colorectal	0.27	1.36
	Anal	0.11	1.58
	Other gastrointestinal	0.68	2.08
Genitourinary			
	Renal	1.48	10.84
	Bladder	0.25	3.45
	Prostate	0.07	1.47
	Testicular	0.88	7.61
	Other genitourinary	0.23	2.88
Gynecologic			
	Ovarian	0.24	0.94
	Endometrial	0.22	3.40
	Cervical	0.38	2.94
	Other gynecologic	0.21	2.19
Lung			
	Small cell	15.83	23.46
	Squamous cell	5.29	15.86
	Adenocarcinoma	14.44	26.82
	Bronchioloalveolar	2.31	15.47
	Non-small cell not otherwise specified	12.81	25.56
Melanoma	Any	0.65	28.16
Sarcoma	Any	0.74	4.44
Thyroid	Thyroid	0.12	5.86
All others	All others	1.73	9.94

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor.
[a]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.
[b]Incidence proportion was defined as the number of patients diagnosed with brain metastases and a specific primary cancer divided by patients with de novo metastatic disease to any distant site.

developed relapse in the central nervous system by the time of death.[13] These data suggest that as patients develop an increasing burden of extracranial disease and progress through additional lines of systemic therapy, the risk of brain metastases can increase significantly, likely due to molecular changes that can predispose patients to developing brain metastases as well as the lagging intracranial efficacy of many systemic therapies.[25] As a result,

surveillance of the brain using MRI is recommended per NCCN guidelines for patients with small cell lung cancer; the role of further screening imaging of the brain after an initially unremarkable imaging study among patients with other cancers largely remains undefined.[26]

Clinical Presentation

The clinical presentation of patients with brain metastases varies based on a number of factors including primary tumor type and whether intracranial involvement was detected via screening vs neurologic symptomatology; in total, 60%-75% of patients present with neurologic symptoms.[27] Approximately 10%-20% of patients present with seizures and an additional 10%-12% of seizure-naïve patients at initial presentation will later develop seizures.[28] Other common presenting symptoms include: focal neurologic deficits (20%-75%), altered mental status (5%-60%), headaches (25%-57%), gait abnormalities/ataxia (15%-20%), speech changes (5%-20%), visual changes (5%-8%), nausea/vomiting (5%), and somnolence (5%).[29] The mode for the number of brain metastases present at initial presentation is 1; approximately 20%-40% of patients will present with >4 metastases.[30] Brainstem disease is typically present in <10% of cases.[27]

Prognosis

The prognosis of patients with brain metastases remains guarded. Historically, the brain metastasis recursive partitioning analysis (RPA) was used to prognosticate patients with brain metastases into 3 subsets based on age, performance status, and status of the primary/extracranial disease.[31] More contemporary and population-based estimates of prognosis among patients with brain metastases at presentation of systemic malignancy (synchronous brain metastases) from the SEER program have indicated a median survival of 12 months or less across nearly all primary sites (Table 3).[12] Among older patients (age ≥65 years) with brain metastases that are diagnosed at or after primary malignancy (metachronous brain metastases) the prognosis is even poorer, with median survival of 4 months or less for nearly all evaluable primary sites (Table 3).[32] Data largely stemming from clinical trials or academic medical centers comprising the graded prognostic assessment (GPA) have indicated more favorable prognoses among patients with brain metastases (Table 3), with median survivals ranging from 8 to 16 months by primary site.[33] The better prognosis seen in the GPA studies relative to population-based data (eg, SEER) may be reflective of screening or selection processes linked to enrollment in clinical trials or incorporation into an institutional or departmental database; patients on clinical trials are typically younger, healthier, less symptomatic, and more functional than non-trial patients.[34,35] In addition, data from individual departments or institutions may favor the academic interests of researchers compiling a given database; for example, many central nervous system radiation oncology databases have incorporated patients who predominantly receive stereotactic radiosurgery given the academic interest in this treatment.[32,36,37]

Management Patterns

The blood-brain barrier has limited the effective penetration of many systemic therapies into the brain.[9] While, for some patients, novel targeted or immunotherapeutic-based systemic therapies have demonstrated potential for intracranial disease control,[38–40] for most patients, local therapies, such as brain-directed radiation and/or neurosurgical resection, are employed.[41,42] It has recently been shown that intracranial management strategies are obtainable from claims data, allowing for patterns of care studies in patients with brain metastases, although it is notable that non-stereotactic partial brain radiation cannot be readily delineated from whole-brain radiation via claims; the latter approach is less commonly utilized, however.[43] SEER-Medicare data have suggested that, between 2014 and 2016, approximately 52%-64%, 17%-20%, 10%-13%, 6%-11%, and 25%-32% of patients received non-stereotactic brain-directed radiation (inclusive of whole-brain radiation), stereotactic brain-directed radiation, neurosurgical resection, systemic therapy without local brain-directed therapy, and other therapy/no therapy, respectively (percentages do not add up to 100% given that patients can receive multiple concurrent approaches).[32]

Leptomeningeal Disease

Leptomeningeal disease/carcinomatosis, also known as neoplastic meningitis or carcinomatous meningitis, occurs when tumor cells infiltrate the leptomeninges of the brain and spinal cord, as well as the cerebrospinal fluid.[44] Leptomeningeal disease is present at the time of initial intracranial involvement in 2%-12% of cases but, based on prospective studies, can also develop later in the clinical course in 1%-37% of patients.[27,34,35,45–48] Variable methods of diagnosis (radiographic changes vs positive cytology on spinal tap) can confound estimates of incidence. It is important to distinguish leptomeningeal disease from postsurgical pachymeningeal seeding, in which tumor cells displaced at the time of neurosurgical resection recur along the regional pachymeninges/dura, a phenomenon which complicates approximately 8% of resections for brain metastases and is generally associated with a significantly better prognosis than true leptomeningeal disease.[49] Patients with leptomeningeal disease often present with headache, nausea, cranial nerves deficits, seizures, sensory loss, weakness, gait abnormalities, incontinence, and symptoms associated with hydrocephalus.[44] Management options include non-stereotactic radiation-based approaches, systemic therapy with potential to penetrate the blood-brain barrier, intrathecal chemotherapy and, for patients with increased intracranial pressure, consideration

Table 3 Prognosis of Brain Metastases in the United States by Primary Site as Derived From SEER, SEER-Medicare, and GPA-Based Data[a]

Primary Site	Sub-Site	Median Survival (Months) Based on SEER Data[b]	Median Survival (Months) in Older Patients Based on SEER-Medicare Data[c]	Median Survival (Months) Based on GPA Data
Breast			2.1-4.5	16
	HR+/HER2–	14.0	2.0-4.9	
	HR+/HER2+	21.0	2.5-6.4	
	HR–/HER2+	10.0		
	Triple-negative	6.0	2.3-3.4	
Head and Neck	All	5.0		
Gastrointestinal				8
	Esophagus	4.0	2.3-4.0	
	Gastric	4.0		
	Hepatobiliary	3.0		
	Pancreatic	2.0		
	Colorectal	6.0	2.5-3.0	
	Anal	7.0		
	Other gastrointestinal	4.0		
Genitourinary				
	Renal	5.0	1.8-3.5	12
	Bladder	4.0		
	Prostate	12.0		
	Testicular	Not reached		
	Other genitourinary	7.0		
Gynecologic				
	Ovarian	5.0	7.5-7.7	
	Endometrial	4.0		
	Cervical	4.0		
	Other gynecologic	Not reached		
Lung			2.9-3.3	
	Small cell	6.0	3.0-3.6	
	Squamous cell	4.0	2.2-2.8	
	Adenocarcinoma	6.0	3.7-3.8	15
	Bronchioloalveolar	10.0		
	Non-small cell not otherwise specified	4.0	1.9-2.7	
Melanoma	Any	6.0	2.8-3.0	10
Sarcoma	Any	4.0		
Thyroid	Thyroid	5.0		
All others	All others	3.0		

Abbreviations: GPA, graded prognostic assessment; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SEER, Surveillance Epidemiology and End Results.

[a]Empty cells reflect missing data.

[b]For patients with brain metastases at the time of diagnosis of primary malignancy.

[c]Range reflects estimates for synchronous (present at diagnosis of systemic malignancy) and metachronous (developed after diagnosis of systemic malignancy) brain metastases; limited to patients ≥65 years of age.

of diversion of the cerebrospinal fluid.[50] The prognosis for patients with leptomeningeal disease is poor, with a typical median survival of 1-4 months although subsets with viable systemic options or radiosensitive disease may display better outcomes.[51]

Brain Metastases From Specific Primary Sites

Non–Small Cell Lung Cancer (NSCLC)

Given the prevalence of NSCLC and the propensity NSCLC to spread to the brain, NSCLC constitutes the primary site/tumor type for approximately 50% of patients with brain metastases.[12,48] In addition, patients can sometimes present with a solitary brain metastasis, in which a single brain tumor represents the only active site of disease in the body; a small but significant percentage of such patients may be curable with local, brain-directed therapy.[30] The risk of intracranial dissemination appears to be greater in patients with epidermal growth factor receptor (EGFR)-mutant or anaplastic lymphoma kinase (ALK)-rearranged tumors, although the underlying etiology for this phenomenon remains unclear.[52,53] It is possible that such tumors display an innate biological predisposition to spread to the brain although the longer survival which such patients display could explain the greater lifetime risk of brain metastases in this population. It is increasingly important to molecularly profile cases of NSCLC, particularly adenocarcinomas, with intracranial involvement given the potential for targeted systemic therapies to be utilized for both extracranial and intracranial disease control (Table 4). Such profiling should include EGFR mutations, ALK rearrangements, ROS1 rearrangements, MET mutations/amplifications, RET fusions, HER2 alterations, BRAF mutations, NTRK fusions, and KRAS G12C mutations; such alterations comprise approximately 33%-45% of NSCLC cases in the United States, with higher rates of many abnormalities seen in nonsmokers.[39,54–62] For patients with nonmutated and select mutated tumors, an assessment of PD-L1 (programmed death-ligand 1) status and other markers of responsiveness to immunotherapy may be beneficial.[63,64] NSCLC also harbors potential for leptomeningeal dissemination, with approximately 2% of patients with NSCLC displaying leptomeningeal disease at diagnosis of intracranial involvement. Thereafter, the cumulative incidence of leptomeningeal disease increases with time, particularly among patients with ALK rearrangements or EGFR mutations.[65] The prognosis for patients with leptomeningeal disease secondary to NSCLC is generally poor, with a median survival of 2-4 months on average, although patients with targetable mutations may display more favorable outcomes, with median survival times up to 19 months in some studies.[51,66,67]

Small Cell Lung Cancer

Small cell lung cancer has a greater propensity to spread to the brain than any other malignancy. Autopsy series have suggested that approximately 80% of patients with small cell lung cancer will develop brain metastases.[68] The risk of brain metastases is so great in small cell lung cancer that prophylactic cranial radiation (whole-brain radiation in the absence of identifiable intracranial disease) may have a role for some patients.[24,69] Given the studies supporting the role of prophylactic cranial irradiation, the historic standard approach to patients with small cell lung cancer who have brain metastases, regardless of the number of brain metastases present, has entailed whole-brain radiation, and patients with small cell lung cancer have been excluded from randomized studies involving omission of whole-brain radiation in lieu of focal therapy.[5,34,35,45–48] However, recent studies have questioned whether patients with small cell lung cancer and a limited number of brain metastases can be managed with stereotactic radiation in lieu of whole-brain radiation given the improved quality of life and neurocognitive function seen with stereotactic approaches in patients with other primaries.[70] This question is being explored prospectively (NCT03391362). In addition, the ongoing MAVERICK trial (SWOG S1827, NCT04155034) is assessing whether brain-based imaging surveillance with MRI alone results in similar survival compared to MRI surveillance combined with prophylactic cranial irradiation among patients with both limited and extensive-stage small cell lung cancer. The prognosis of patients with small cell lung cancer remains guarded. Although such patients respond to radiation well, the propensity of intracranial and extracranial dissemination of disease in patients with small cell lung cancer remains a significant threat.[71]

Table 4 Targetable Molecular Alterations in Non–Small Cell Lung Cancer

Alteration	Incidence Proportion Among Non–Small Cell Lung Cancer in the United States (%)	Potential Therapeutic Agents
EGFR mutation	15-20	Osimertinib, erlotinib, gefitinib, afatinib, dacomitinib
ALK rearrangement	4-5	Alectinib, ceritinib, brigatinib, lorlatinib, crizotinib
ROS1 rearrangement	1-2	Entrectinib, lorlatinib, ceritinib, crizotinib
MET mutation/amplification	2-3	Capmatinib, crizotinib
RET rearrangement	1-2	Selpercatinib, pralsetinib, cabozantinib
HER2 mutation	1-3	Trastuzumab, afatinib, ado-trastuzumab emtamsine
BRAF mutation	1-3	Dabrafenib + trametinib
NTRK fusions	0-1	Larotrectinib, entrectinib
KRAS G12C mutations	10-12	Sotorasib

Patients with small cell lung cancer are also at risk for developing leptomeningeal disease. A prospective study of 458 patients with newly diagnosed small cell lung cancer with (18%) or without (82%) brain metastases indicated a 2% incidence of leptomeningeal disease at the time of diagnosis of the primary malignancy. The 2-year cumulative incidence of leptomeningeal disease among all patients was 10%. The median survival after a diagnosis of leptomeningeal disease was 1.3 months, indicating an highly guarded prognosis among small cell lung cancer patients with leptomeningeal disease.[72]

Melanoma

Patients with locally advanced or metastatic non-uveal melanoma commonly develop brain metastases, with 10%-40% of melanoma patients ultimately developing intracranial involvement.[73,74] Patients who are male or older in age, or those who harbor elevated lactate dehydrogenase, BRAF or NRAS mutations, C-C chemokine receptor 4 expression, or activation of the phosphoinositide 3-kinase/protein kinase B pathway may be more likely to develop brain metastases.[75–77] In the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma, patients with metastases to the central nervous system carry a unique metastasis (M) stage, M1d, to both highlight the significance of central nervous system involvement in this population and to facilitate future clinical trial design and analysis.[78] Oncogenic mutations in BRAF are present in approximately 40% of patients with melanoma, leading to activation of the MAPK pathway; such mutations are less common in mucosal primaries.[79–81] NRAS mutations are present in approximately 15%-25% of patients,[82] with KIT mutations present in an additional 15%-30% of patients.[83] Historically, patients with melanoma and brain metastases have displayed a dismal prognosis, likely driven by aggressive phenotypes and a lower likelihood of responsiveness to brain-directed radiation.[84] However, immune checkpoint inhibition has revolutionized the management of patients with melanoma and brain metastases, leading in some patients to prolonged disease-free survival and cure.[38,85] In one recent population-based study, first-line treatment of patients with brain metastases secondary to melanoma with immune checkpoint inhibition was associated with an improvement in overall survival from a median of 5.2 months without to 12.4 months with immunotherapy.[86] Immunotherapy seems to be most effective among patients who are asymptomatic neurologically and not on steroids.[38] Patients with BRAF V600 mutant melanoma and brain metastases can be managed with BRAF/MEK inhibition.[87] Patients with NRAS mutations can receive MEK inhibitors, sometimes in the context of a trial, with potential for brain penetration as well.[88] Leptomeningeal disease is uncommon at the time of diagnosis of intracranial involvement in patients with melanoma but can develop subsequently with a 1-year cumulative incidence of approximately 12% and an associated median survival of 2 months.[89]

Breast Cancer

Breast cancer, particularly when HER2-positive or triple-negative, and metastatic to distant extracranial sites, may harbor greater potential to metastasize to the brain than other primary sites for which screening imaging of the brain is not recommended by consensus guidelines; 8%-11% of such patients will harbor brain metastases at diagnosis of the primary malignancy.[22] In addition, approximately 50% or more of patients with metastatic HER2+ or triple-negative breast cancer will develop brain metastases during their clinical course.[13,90] The remaining subtype, hormone receptor-positive/HER2-negative breast cancer, is less likely to metastasize to the brain, with 5% of patients harboring brain metastases at the time of diagnosis of primary malignancy.[12] Regardless of subtype, patients with inflammatory breast cancer may be more likely to develop brain metastases than comparable patients without inflammatory disease.[91] As a result of the lack of intracranial imaging for screening, patients with breast cancer tend to present with more advanced intracranial disease, often requiring more aggressive management approaches such as whole-brain radiation.[27] Clinical trials evaluating the role of screening MRI of the brain in patients with advanced, metastatic, or inflammatory breast cancer are currently ongoing (NCT04030507, NCT03881605). Breast cancer subtype can impact systemic therapy options significantly; it is important to note that the subtype can change between extracranial and intracranial sites.[92,93] Patients with HER2-positive tumors harbor the most targeted systemic options for intracranial management, including regimens anchored by lapatinib, neratinib, T-DM1, tucatinib, or trastuzumab deruxtecan.[40,94] For patients with ER+ tumors, assessment of PIK3CA mutations may facilitate utilization of alpelisib.[95] For patients with triple-negative breast cancer, an assessment of markers of immune activity such as PD-L1 may be helpful in assessing the role and potential benefit associated with immunotherapy.[96] Leptomeningeal disease is present at the time of intracranial involvement in approximately 10%-12% of patients with breast cancer and develops in up to one-third of patients thereafter; although patients with leptomeningeal disease from breast cancer may have a better prognosis than patients with leptomeningeal disease from other primary tumors, median overall survival is still guarded for most patients, ranging from 3 to 4 months. However, outcomes may be better among patients with viable systemic/intrathecal options or indolent disease, with reports of select patients living more than 1 year.[27,97–100]

Conclusions

Brain metastases will be increasingly relevant to oncologic management as advances in systemic therapy promote extracranial disease control. In addition, the management of brain metastases is becoming more specific to the primary tumor type. An understanding of the epidemiology associated with brain metastases is important to characterize the burden of disease and patterns of management

in the United States and beyond but limitations in reporting of brain metastases to federal registries limit epidemiologic investigations. Advances in the characterization of the incidence, presentation, prognosis, and management of brain metastases using claims data carry potential to move the field forward, as do carefully conducted institutional studies and trials. Further epidemiologic studies relating to brain metastases would be important for patients, providers, and health care systems alike.

Keywords

brain metastases | breast cancer | epidemiology | leptomeningeal disease | lung cancer

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