# Brain metastases: A Society for Neuro-Oncology (SNO) consensus review on current management and future directions

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## Abstract

Brain metastases occur commonly in patients with advanced solid malignancies. Yet, less is known about brain metastases than cancer-related entities of similar incidence. Advances in oncologic care have heightened the importance of intracranial management. Here, in this consensus review supported by the Society for Neuro-Oncology (SNO), we review the landscape of brain metastases with particular attention to management approaches and ongoing efforts with potential to shape future paradigms of care. Each coauthor carried an area of expertise within the field of brain metastases and initially composed, edited, or reviewed their specific subsection of interest. After each subsection was accordingly written, multiple drafts of the manuscript were circulated to the entire list of authors for group discussion and feedback. The hope is that the these consensus guidelines will accelerate progress in the understanding and management of patients with brain metastases, and highlight key areas in need of further exploration that will lead to dedicated trials and other research investigations designed to advance the field.

Brain metastases are common among patients with advanced solid malignancies and represent a significant source of morbidity and mortality.[1–3] Although the true incidence of brain metastases has been challenging to determine, it is estimated that approximately 10–40% of patients with solid tumors will develop brain metastases, translating to an estimated incidence of brain metastases in the United States of 70 000–400 000 cases per year.[1,4] With expanding availability and utilization of magnetic resonance imaging (MRI), as well as improving systemic therapy for extracranial control with lagging intracranial efficacy, the incidence of brain metastases has increased over time.[1,5]

Given the heterogeneous penetration of most systemic therapies into the microenvironment of brain metastases, the historical management of brain metastases has largely consisted of local, brain-directed therapy involving stereotactic radiation or large field radiation therapy and, when indicated, neurosurgical resection.[6,7] In recent years, advances in systemic therapy have led to a paradigm shift for certain patients with brain metastases, with systemic therapy as monotherapy now a first-line consideration for subgroups of asymptomatic patients.[8–10]Although the prognosis for many patients with brain metastases remains guarded, it does seem to be improving.[2,11]

Despite the high incidence of brain metastases, which rivals that of primary breast, colorectal, lung, and prostate cancer in the United States, a relative dearth of oncologic research devoted to patients with brain metastases exists (Figure 1). As a result, heterogeneity in practice exists among different centers and individuals.[12] The focus of this consensus statement is to provide a comprehensive outline regarding the epidemiology, pathogenesis, diagnosis, and treatment of brain metastases, as well as highlight future directions in investigative efforts and clinical care that may improve the outlook and management of patients with brain metastases. This work is part of a series of articles supported by SNO seeking to provide context regarding optimal oncologic treatment and highlight areas of needed research of common neurologic entities; this article complements recently published recommendations from ASCO-SNO-ASTRO.[13] Of note, leptomeningeal disease will be addressed by a separate, future effort.

## Epidemiology

### Incidence

The exact incidence of brain metastases has historically been difficult to elucidate. This has, in part, been due to a lack of mandated reporting of brain metastases to local and federal registries, such as the Central Brain Tumor
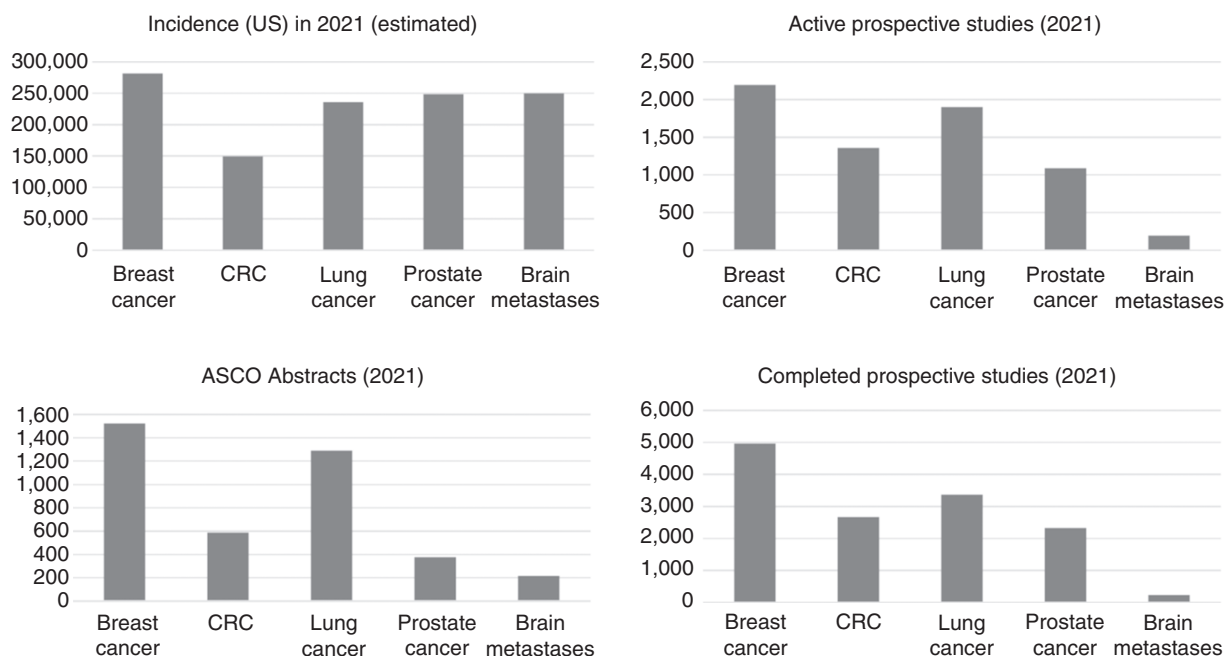


**Fig. 1** Incidence and research output as measured by ASCO abstracts (annual meeting) and active/completed prospective trials based on clinicaltrials.gov among patients with brain metastases versus other oncologic entities of similar incidence. (Abbreviations: ASCO, American Society of Clinical Oncology; CRC, colorectal cancer; US, United States).

Registry of the United States.[14,15] In 2016, the Surveillance Epidemiology and End Results (SEER) program released data regarding the presence versus absence of brain metastases among patients with extracranial primaries at the time of primary cancer diagnosis.[16] Thereafter, Cagney et al. reported the first population-based epidemiologic study of brain metastases in the United States using SEER data (Table 1).[16] However, because most consensus guidelines, such as those published by the National Comprehensive Cancer Network (NCCN), only favor screening imaging of the brain for specific malignancies/ stages of disease, including select patients with small cell

**Table 1** Incidence Proportion of Brain Metastases in the United States at Diagnosis of Malignancy by Primary Site. Reproduced with permission from Lamba et al., Neuro-Oncology, 2021[3]

| 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 |
| | Nonsmall 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 |

[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.

lung cancer (SCLC), non-small cell lung cancer (NSCLC), melanoma, testicular cancer, alveolar soft parts sarcoma, angiosarcoma, and left-sided cardiac sarcoma, but not other cancers such as breast cancer, renal cancer, gastrointestinal primaries, head/neck cancer, and most other cancers, the reported incidence for unscreened malignancies may be underestimated.[17]

A significant proportion of patients free from brain metastases at initial diagnosis will develop intracranial disease later in their clinical course.[18,19] Unfortunately, recurrence-based information after initial management is not available in SEER, although promising claims-based techniques to abstract such data now exist.[20] Data depicting the cumulative incidence of brain metastases can be obtained for select patients from other sources. For example, among patients in the adjuvant HERA trial who died, approximately 50% of patients with HER2-positive breast cancer develop intracranial metastases by the time of death.[18] These data led to the activation of prospective studies evaluating the role of screening MRI of the brain in patients with advanced, metastatic, or inflammatory breast cancer (NCT04030507, NCT03881605). Among patients with SCLC, autopsy series have indicated that approximately 80% of patients will develop brain metastases.[21] For many cancers, the role of surveillance imaging of the brain after an initially unremarkable scan has not been elucidated by prior investigations or delineated by consensus guidelines. Given the high proportion of patients at risk for development of intracranial disease after initial cancer diagnosis, characterization of the incidence/outcomes of brain metastases among this population is critical.

## Prognosis

Prior studies of prognosis in patients with brain metastases led to the development, validation, and widespread utilization of two major prognostic indices, namely the recursive partitioning analysis (RPA) and the more contemporary diagnosis-specific graded prognostic assessment (DS-GPA).[22–26] The DS-GPA is based on aggregated data from patients with brain metastases across multiple institutions and has identified significant prognostic factors, within each major primary tumor site, including Karnofsky performance status (lung, melanoma, renal cell, breast, and gastrointestinal primaries), age (lung, breast), presence of extracranial metastases (lung), and number of brain metastases (lung, melanoma, and renal cell).[22,27–30] More recent versions of these scores have also included molecular covariates, such as *EGFR* and *ALK* alterations in lung adenocarcinoma (lung-molGPA),[31] estrogen/progesterone and HER2-receptor status for breast cancer (breast-GPA),[29] and *BRAF* status in melanoma (melanoma-molGPA).[30]

Compared to GPA-based indices, population-based delineations of survival among patients with brain metastases, using validated claims-based techniques,[20] have displayed more concerning prognostic estimates (Table 2). A SEER-Medicare study of 9882 older patients with brain metastases demonstrated median survival times of <4 months across all primary sites (lung, breast, melanoma, kidney, esophageal, and colorectal) with the exception of a smaller cohort of patients with ovarian primaries.[11] In a separate SEER study

of adult patients of all ages harboring brain metastases at the time of diagnosis of the primary, a median survival of ≤12 months across nearly all primary sites was noted.[16]

Epidemiological studies of brain metastases are essential to characterize evolving trends in incidence, identify at-risk populations, inform screening paradigms, guide treatment strategies, and facilitate trial design. Efforts should be made to collect this data more routinely in national and state registries.

# Biology and Molecular Pathogenesis

## Pathogenesis

Multiple theories regarding the pathophysiology of intracranial metastatic disease have been postulated. Cancer cells spread as a result of epigenetic and proliferative changes, including growth of preexisting or development of new blood vessels,[32,33] followed by vascular invasion.[34] Cancer cells reaching the brain must traverse the blood–brain barrier (BBB) and adhere to brain endothelia potentially via upregulation of genes related to mitogenesis and extracellular matrix destruction, such as vascular endothelial growth factor and matrix metalloproteinases, activation of signaling pathways that permeabilize the BBB, and increased expression of proteins allowing for proteolysis, extravasation, and tumor cell colonization.[4,33,35–37] Once inside the brain, tumor cell interactions with brain endothelia can promote adhesion within the intracranial parenchyma, via upregulation of particular cell surface proteins and growth factors.[38,39] Finally, complex interactions between the tumor cells and brain cells, including formation of tumor-astrocyte gap junctions and subsequent secretion of inflammatory chemokines, promote tumor cell motility, invasion, and survival (Figure 2).[4] Examples of specific metastasis–brain interactions underlying the pathogenesis of brain metastases demonstrated via *in vitro* and mouse models include estradiol-induced activation of brain-derived neurotrophic factor in astrocytes interacting with TrkB receptors on breast tumor cells, synaptic formation between cancer cells and glutamergic neurons allowing for N-methyl-D-aspartate receptor (NMDAR) activation, loss of *PTEN* expression among cancer cells once in the brain microenvironment, driven by signals from resident astrocytes and leading to chemokine-mediated proliferation of the metastatic cells, and cancer cell cooption of a pro-metastatic program driven by *STAT3* in reactive astrocytes.[40–43] Targeting of these pathways offers substantial promise in inhibiting the successful proliferation of brain metastases.

Although a similar set of processes must occur regardless of primary tumor type, studies have implicated distinct genes involved with brain metastasis formation by primary site. For example, cyclooxygenase 2 (COX2), epidermal growth factor (EGFR) ligand HBEGF, and the membrane glycosyltransferase ST6GALNAC5 facilitate the development of breast cancer brain metastases, while lymphoid enhancing-binding factor 1 (LEF1), Cadherin 2, and Kinesin Family Member C1 (KIFC1) are strongly associated with lung

**Table 2** Prognosis of Brain Metastases in the United States by Primary Site as Derived from SEER, SEER-Medicare, and GPA-based Data.[a,b] Reproduced with permission from Lamba et al., Neuro-Oncology, 2021[3]

| Primary Site | Sub-Site | Median Survival (Months) Based on SEER data | 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 | | |
| | Nonsmall 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.
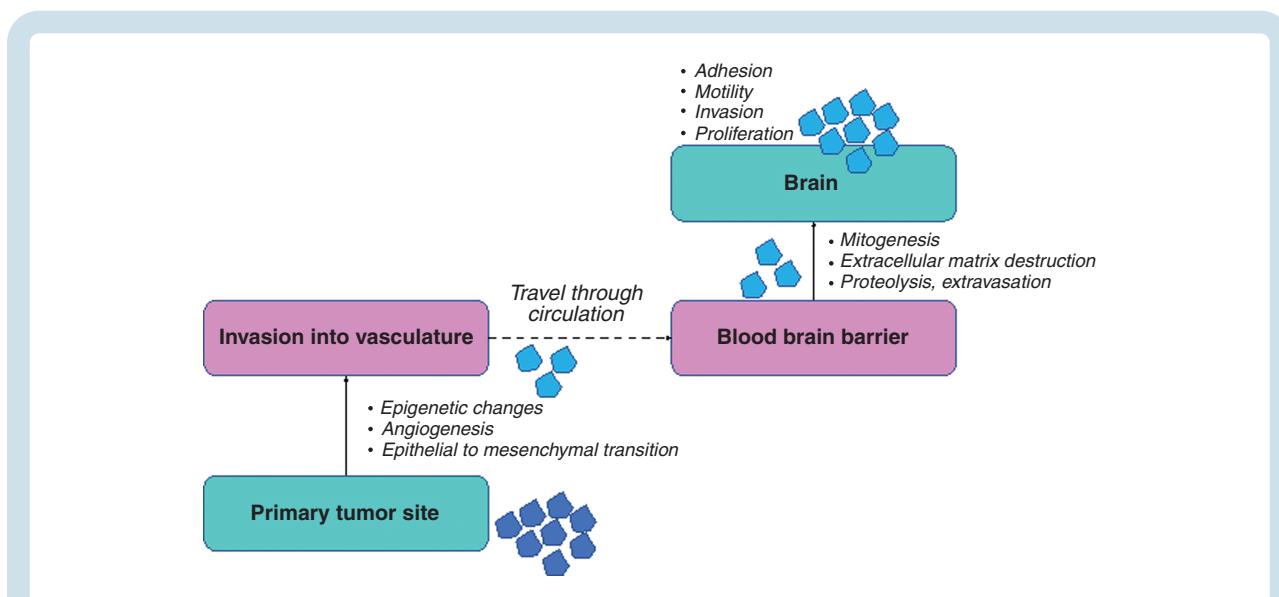
**Fig. 2** Pathogenesis of brain metastases. The development of brain metastases depends on a complex interplay of factors involving tumor cells migrating from an extracranial site into the vasculature via a series of epigenetic changes, proliferation of blood vessels, and an epithelial-to-mesenchymal transition. Once the tumor cells reach the brain, they traverse the blood brain barrier, which involves upregulation of genes and proteins involved in proteolysis, extracellular matrix destruction, and mitogenesis/growth. Once inside the brain, the cells must adhere to the brain endothelia and undergo further stimulatory processes to allow for proliferation.

cancer brain metastases.[33,38,44,45] Activation/alteration of the PI3K/AKT and cyclin-dependent kinase (CDK) pathways have also been associated with increased risk of multiple tumors to metastasize to the brain.[10,46–50] Copy number changes may also lead to the formation of brain metastases; for example, amplifications in *YAP1* and *MMP13* contribute to brain metastases in lung adenocarcinoma.[50] Characterization of the site-specific genes that must be upregulated for brain metastasis formation may allow for novel therapeutic strategies to prevent development of intracranial disease. However, further exploration is needed to determine the relationship between molecular changes, intracranial involvement/outcomes and specificity for driving brain metastases or metastatic disease in general.

## Heterogeneity

Recent data has demonstrated genomic heterogeneity between brain metastases and respective primary tumors, suggesting that specific transformations allowing cells to metastasize to the brain occur, and moreover, that genomic diversity of brain metastases may contribute to occasionally differing intracranial and extracranial responses to systemic therapy.[10,51] The significance of genetic heterogeneity between primary/extracranial and intracranial sites of disease is an area of active clinical investigation.

*Non-small cell lung cancer.*—Molecular characterization is vital to the management of patients with lung adenocarcinoma. In contrast, among patients with SCLC or squamous NSCLC, molecular studies may be less impactful due to a far lower incidence of targetable mutations.[52,53] In patients with lung adenocarcinomas, activating *EGFR* mutations are

present in approximately 15–20% and 40–50% of Caucasian and Asian patients, respectively, with most patients harboring EGFR L858R point mutations or exon 19 deletions targetable by EGFR tyrosine kinase inhibitors (TKI).[54] While some less-common mutations also are sensitive to classical EGFRTKIs, others, such as most *EGFR* exon 20 insertion mutations, are resistant.[55] Most patients receiving older (1st and 2nd generation) EGFR TKIs eventually acquire resistance through development of the exon 20 point mutation *T790M*; however, multiple other on-target and off-target resistance mechanisms exist.[56] A recent Phase III study and post hoc analyses from two Phase II studies assessing intracranial response to osimertinib, a third-generation TKI with coverage of T790M, demonstrated high intracranial response rates in patients with, at least, extracranial evidence ofT790M manifesting on prior 1st and 2nd generation TKI therapy.[57,58] Mechanisms of resistance to osimertinib include both on-target *EGFR* tertiary mutations/amplifications, such as exon 20 C797S, as well as off-target/second driver mechanisms, such as RAS-MAPK or PI3K pathway activation, *MET* amplification, *HER2* amplification, small-cell transformation, and RET or ALK gene rearrangements.[59]

Less common than *EGFR* mutations are anaplastic lymphoma kinase (*ALK*) rearrangements, which are found in 4–5% of all NSCLC patients and confer sensitivity to *ALK* TKIs.[60,61] Beyond *EGFR* and *ALK*-related changes, approximately 25–30% of patients with lung adenocarcinomas harbor a mutation/rearrangement/fusion in a potentially targetable abnormality, including *ROS1* rearrangements, *MET* mutations/amplifications, *RET* rearrangements, HER2 mutations, *BRAF* V600E mutations, *NTRK* rearrangements, and *KRAS* G12C mutations.[62] In addition to broad-based genetic testing, an assessment of PD-L1 status and potentially other markers of immunotherapy-responsiveness are essential for

optimizing treatment choice for patients with NSCLC, especially for those lacking a targetable abnormality.

*Breast cancer.*—The risk of intracranial dissemination among patients with breast cancer varies by subtype, with lower rates observed in hormone receptor-positive/HER2-negative disease and higher rates noted in HER2-positive or triple negative breast cancer.[41] Of note, receptor status can change between extracranial and intracranial sites.[63,64] In a meta-analysis of 29 studies assessing receptor conversion from primaries to paired distant sites, estrogen-receptor discordance was notably high among brain metastases at 20.8%.[65] In addition, HER2-positivity can be gained or lost, with significant associated therapeutic impact.

*Melanoma.*—Several studies have implicated activation of the PI3K-AKT pathway in melanoma brain metastases. An initial protein-based interrogation of signaling pathways identified increased expression of activation markers in the PI3K-AKT pathway in melanoma brain metastases compared to extracranial sites.[66] Subsequently, analysis of *BRAF* mutations, *NRAS* mutations, and loss of PTEN (which results in activation of the PI3K-AKT pathway) in stage III patients showed that PTEN loss predicted increased risk of brain metastasis, a finding also seen in the RCAS-TVA mouse model of melanoma.[49] Another preclinical study demonstrated that PI3K-AKT pathway activation is required for early colonization of the brain by melanoma cells.[67] Two additional studies analyzing melanoma patients with paired extracranial and intracranial tissue identified increased activation of the PI3K-AKT pathway in all brain metastases.[68,69] More recently, global analysis of gene expression in brain metastases by RNAseq demonstrated increased expression of genes in the oxidative phosphorylation (OXPHOS) metabolic pathway and decreased infiltration by multiple immune cell populations, including T cells and B cells, compared to patient-matched extracranial metastases.[70] Notably, this metabolic change in confirmatory preclinical models was observed with cells that were directly injected into brain tissue, thus precluding significant selective pressure as an explanation, and instead suggesting that induction of OXPHOS may stem from interactions of tumor cells with the tumor microenvironment of the central nervous system (CNS). Consistent with this hypothesis, analysis of brain metastases and patient-matched non-CNS tumors in breast, lung, and kidney cancer cohorts also identified increased OXPHOS, increased PI3K-AKT activation, and decreased immune infiltrates in brain metastases.[71] Another study also demonstrated unique metabolic features and dependencies of brain metastases from melanoma and breast cancer, namely upregulation of 3-phosphoglycerate dehydrogenase (PHGDH), the rate limiting enzyme for glucose-derived serine synthesis, to compensate for the very low levels of nucleotides available in the brain tumor microenvironment.[72] Importantly, inhibitors of OXPHOS and PHGDH exhibited greater anti-tumor activity against brain metastases than against metastases in extracranial sites.[70–72]

The PI3K-AKT pathway in brain metastases has also been implicated in other studies. Preclinical studies have demonstrated that chemokine receptor 4 (CCR4) is overexpressed in melanoma cells that metastasize to the brain via increased activity of the PI3K/AKT pathway.[73] Further, whole exome sequencing of brain metastases across primary sites identified new mutations in the PI3K-AKT pathway in 40–50% of patients.[10] However, such frequent differences were not seen in studies comparing brain metastases to extracranial metastases.[10,74] Both global and targeted sequencing have confirmed high concordance for *BRAF* mutations between brain metastases and non-CNS tumors. Interestingly, increased OXPHOS metabolism, increased PI3K-AKT pathway activation, and decreased immune infiltration have all been implicated in decreased responsiveness to BRAF and MEK inhibitors.[75–79] Each of these pathways/features has also been implicated in resistance to anti-PD-1-based immunotherapy.[80,81]

## Tumor Sampling and Future Directions

Although the data presented above demonstrates the promise of tailoring systemic therapies for patients with brain metastases based on molecular characterization of intracranial disease, one of the inherent challenges is obtaining tissue. However, non/less-invasive methods that allow for genomic profiling of cancers, such as the utilization of circulating tumor DNA (ctDNA), may prove promising,[82] although brain-derived, as opposed to extracranially-derived, plasma ctDNA levels can be low.[83,84] Cerebrospinal fluid (CSF) offers potential regarding detection of relevant intracranial mutations via ctDNA analyses,[83,85,86] suggesting the utility of CSF-ctDNA for identification of potential genetic targets and mechanisms of resistance, but few institutions can perform CSF-based molecular analyses in a reliable and reproducible manner; development and implementation of such assays has significant potential to advance care. In addition, imaging measures to noninvasively assess molecular status in patients with brain metastases carry promise, such as the use of HER2-targeting PET tracers in breast cancer.[87,88]

# Imaging

## Background

Imaging represents an essential component of the diagnosis and management of brain metastases, as brain tumor-directed biopsies are typically not indicated. For certain patients at high risk of developing brain metastases, such as those with SCLC, advanced NSCLC, and advanced melanoma, the initial oncologic work-up includes a screening brain MRI.[89,90] For most other primary disease sites, intracranial imaging is often reserved for the setting of neurologic symptomatology. While MRI is preferred, computed tomography (CT) may be initially performed emergently to exclude acute changes.[91,92]

For optimal evaluation of brain metastases, MRIs should incorporate IV gadolinium-based contrast. Lesion

conspicuity/detection can be enhanced using stronger magnetic fields (3T vs 1.5T), contrast agents with greater relativity, higher contrast doses, delays between injection and image acquisition, and use of T1-weighted postcontrast imaging with thin sections/volumetric imaging.[93,94] While inversion recovery gradient echo pulse sequences like MPRAGE give exquisite anatomic detail and spatial resolution, with 1 mm isotropic voxels very achievable, postgadolinium 3D T1-weighted fast spin echo pulse sequences like SPACE, CUBE, or VISTA may be superior for detection of small metastases.[95–99] Further details on consensus-recommended imaging for brain metastases, both for clinical trials and for routine clinical use, have recently been published.[95]

Brain metastases commonly appear as well-demarcated, contrast-enhancing lesions at the subcortical gray–white junction; peritumoral vasogenic edema is commonly present.[93,100] Typically, brain metastases appear iso- or hypointense on precontrast T1-weighted images; however, the presence of associated hemorrhage, common in melanoma and renal/ovarian/thyroid primaries, can yield hyperintensity on T1- and T2-weighted images, and loss of signal on T2*- or susceptibility-weighted images (Figure 3).[93,95,100] As lesions grow, they may become centrally hypointense on T1, with enhancement surrounding a nonenhancing core (ie a "cystic" metastasis); in other lesions, enhancement often remains homogeneous (ie a "solid" metastasis).[101,102] Cystic versus solid designation can affect radiosensitivity/response to oncologic treatment.[103,104] It is important to delineate cystic from necrotic brain metastases as the response-based principles above may not translate to necrotic lesions. In this regard, cystic metastases display thin/smooth ring enhancement with a uniformly spherical or elliptical T1 hypointense center, while necrotic lesions have irregular enhancing walls with non-uniform/irregular centrally T1 hypointense regions; such delineations can be challenging however. Also of note, brain metastases from SCLC, as well as occasional lesions from other underlying primaries, can restrict diffusion, with relatively low apparent diffusion coefficients (ADC), due to densely cellular histologies.[93,105]
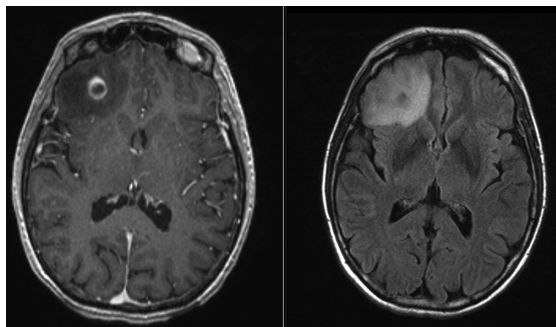


**Fig. 3** Characteristic MRI of a brain metastasis. T1-weighted postgadolinium MRI of a right frontal brain metastasis displaying characteristic rim enhancement (left) and associated T2-weighted FLAIR sequence showing extensive surrounding vasogenic edema (right). (Abbreviations: FLAIR, Fluid Attenuated Inversion Recovery; MRI, Magnetic Resonance Imaging).

## Differential Diagnosis

*Multiple intracranial lesions.*—The presence of multiple, enhancing intracranial lesions in a patient with a preceding cancer diagnosis should raise concern for brain metastases. Yet, mimickers of brain metastases exist, including primary CNS neoplasms such as multicentric glioma and CNS lymphoma, infection/abscess (eg fungal/atypical infections, septic emboli), vascular disease, and/or inflammatory processes such as multiple sclerosis, acute disseminated encephalomyelitis, or sarcoidosis.[106] Like brain metastases, abscesses can also be rim-enhancing. However, unlike most brain metastases, the central, nonenhancing, necrotic portion of abscesses tends to restrict diffusion[107,108]; cystic brain metastases may have restricted water diffusion in their relatively hypercellular walls but typically not centrally. A history/exam can also be useful in distinguishing these entities. Subacute ischemic infarcts can also mimic brain metastasis since infarcted tissues frequently begin to enhance following the acute phase.[109] Infarction with enhancement can often be distinguished from metastasis by its wedge-like (nonnodular) shape involving white matter and often overlying cortex, and the lack of surrounding vasogenic edema in the acute phase. Surveillance imaging can often differentiate infarct (enhancement regresses with time) and tumor (enhancement increases with time without effective treatment).

*Single intracranial lesion.*—Approximately 20–40% of patients with brain metastases present with a single intracranial lesion,[32] and brain metastases should remain high on the differential diagnosis for patients with a single/solitary focus of enhancement in the setting of a known extracranial primary. Other etiologies to consider, however, include primary CNS neoplasms, such as gliomas, primary CNS lymphomas, meningiomas, abscesses, and vascular malformations.

## Follow-up Imaging Regimens

Patients with brain metastases require close radiographic follow-up. Generally, it is recommended that brain MRIs be performed every 2–3 months for the first 1–2 years after initial treatment, although new/worsening symptomatology or a history of rapid disease progression should prompt earlier scans; continuing brain MRIs regularly beyond 1–2 years after initial treatment seems prudent and patients with active disease or necrosis well beyond the initial treatment period often require very close radiographic follow-up long-term.[110] In addition, the high resolution imaging provided by 3D T1-weighted postcontrast sequences allows for assessments of systemic therapy efficacy at an earlier timepoint, often within a few weeks of initiation of a new regimen, facilitating earlier implementation of salvage therapy if necessary.[111]

Imaging after stereotactic radiation therapy may show adverse radiation effects, which can be challenging to differentiate from tumor progression (Figure 4). In these situations, advanced imaging techniques, such as magnetic resonance spectroscopy (MRS), Dynamic Susceptibility Contrast (DSC) and Dynamic Contrast Enhanced (DCE)
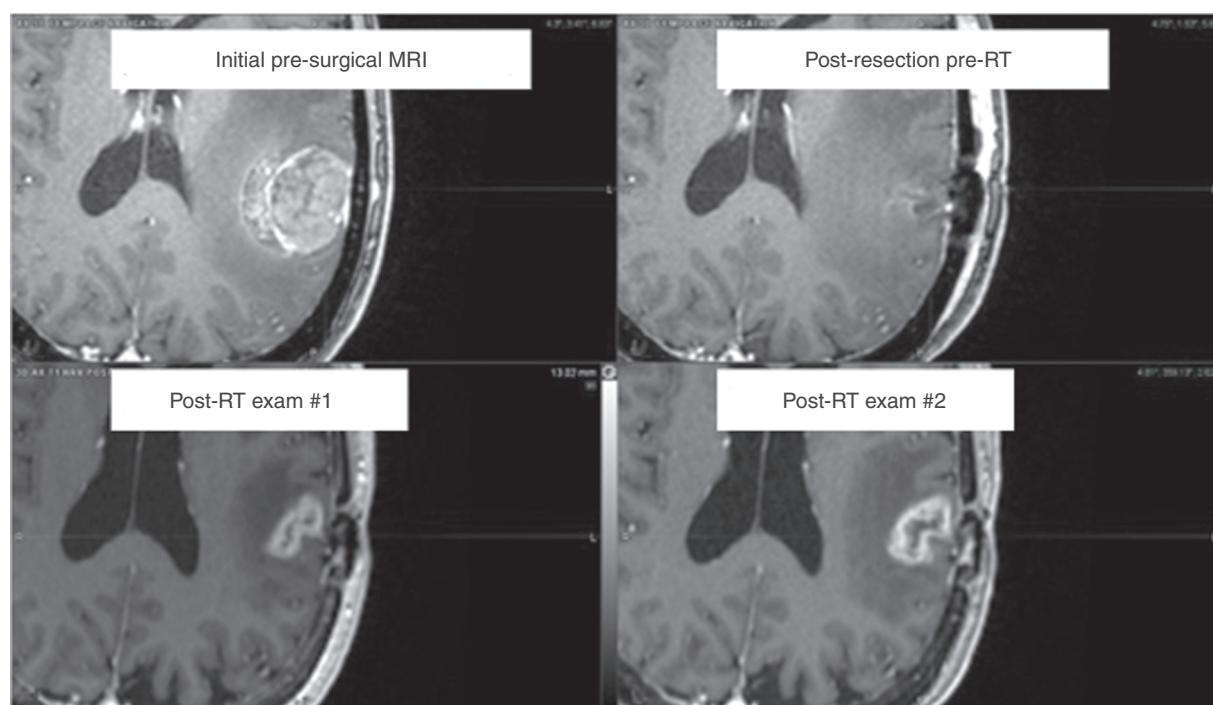
**Fig. 4** MRI-based appearance of radiation necrosis. A left parietal metastasis is shown prior to resection (top left) and postresection, preadjuvant stereotactic radiation (top right). Five years later, the patient developed enhancement at the treated site (bottom left), which enlarged with time (bottom right). The patient was taken to the operating room for resection, and the lesion proved to be radiation necrosis. (Abbreviations: MRI, Magnetic Resonance Imaging).

perfusion MRI, treatment response assessment maps/contrast clearance imaging, and FDG (Fluorodeoxyglucose) and amino acid positron-emission tomography (PET), among others, can be considered, or closer interval imaging may be warranted.[112–118] However, the Response Assessment in Neuro-Oncology Brain Metastasis group states that while advanced imaging techniques may provide value, the current medical literature is "insufficiently robust" to routinely recommend any one particular modality or approach.[119] In clinical practice, serial routine imaging, as well as correlation with a patient's clinical status, are often relied upon prior to performing such specialized imaging.

## Neuro-oncologic Management

Neuro-oncologic management of patients with brain metastases is multi-faceted.[120,121] Patients with brain metastases are often affected by significant neurologic symptomatology from both underlying intracranial disease as well as treatment-related sequelae.[122–125] In addition, metastases may differentially impact patients neurologically based on their location, with the motor strip, brainstem, and thalamus being especially sensitive to the impact of brain metastases. Such symptomatology often necessitates careful medication management, including steroids, antiepileptic drugs, analgesics, and other supportive medications (Figure 5).[126–129]

Here, we focus on common brain metastases-related neuro-oncologic issues, including symptomatic vasogenic edema, seizures, venous thromboembolism, radiation necrosis, and neurocognitive decline.[130,131]

### Vasogenic Edema

Systemic glucocorticoids play an integral role in the management of patients with symptomatic brain metastases.[132–135] Dexamethasone is typically preferred given its relative lack of mineralocorticoid activity.[136] For asymptomatic patients, prophylactic corticosteroids are usually not indicated,[137] although in patients receiving potentially edema-exacerbating local therapy, short-term preventative corticosteroids are reasonable.[138] For moderately symptomatic patients, dexamethasone in the 4–8 mg/day range given once or twice daily (eg with breakfast and lunch) seems appropriate, consistent with prior randomized studies suggesting that the therapeutic benefit of dexamethasone wanes beyond 4–8 mg/day while toxicity increases somewhat linearly.[139] For patients with marked symptomatology, mass effect, elevated intracranial pressure, and/or impending herniation, higher doses of dexamethasone (eg 16 mg/day) may be warranted.[140] Corticosteroids therapy duration should be minimized to prevent long-term sequealae[141] and generally should be tapered rather than abruptly discontinued given the gradual improvement of edema with oncologic therapy and the potential for adrenal
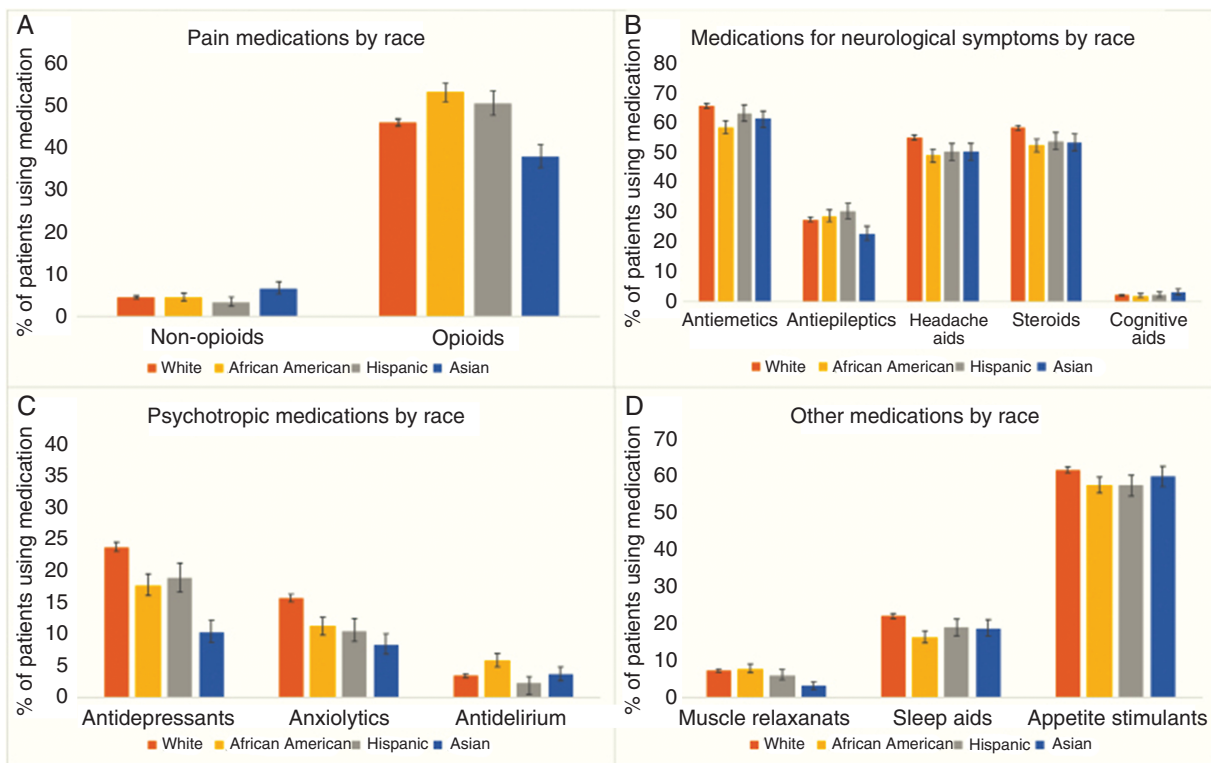
**Fig. 5** Supportive medication utilization among patients with brain metastases. Retrospective data from a population-based study of 17 957 patients with brain metastases demonstrating the high prevalence of supportive medication use in the first 30 days following a diagnosis of brain metastases (as stratified by race and medication class). Opioids, anti-emetics, headache aids, and appetite stimulants were among the most frequently utilized medications among this patient population. Reproduced with permission from Lamba et al., Neuro-Oncology, 2020.[126]

insufficiency in patients having received corticosteroids for prolonged periods.[142] For patients requiring prolonged steroid courses (typically >4 weeks), consideration of prophylaxis against pneumocystis jirovecii pneumonia with trimethoprim/sulfamethoxazole, atovaquone, or pentamidine may be prudent; prophylaxis against steroid-mediated gastritis with a proton-pump inhibitor may also be appropriate.[143] Although studies are mixed regarding steroid-mediated inhibition of immunotherapy efficacy, more recent data suggests potential for concern, particularly in patients with brain metastases.[144–147] As such, it seems prudent to restrict/minimize steroids among patients receiving immunotherapy where possible, as even doses of dexamethasone ≤4 mg/day have been associated with worse outcomes.[146,148–150]

## Seizures

Seizures reflect a complication associated with both brain metastases, local treatment, and occasionally systemic therapy.[151,152] Approximately 10–20% of patients with brain metastases present with seizures at diagnosis of intracranial involvement.[153] In addition, population-based and institutional data indicate that approximately 10–11% of patients free from seizures at diagnosis subsequently develop seizures, with greater risk noted in patients with melanoma

and/or a larger burden of untreated supratentorial disease.[152] Current guidelines suggest that anti-seizure medications should not be used as primary prophylaxis among patients with brain metastases.[154–156] These guidelines are based on a limited number of randomized studies typically involving smaller ($N \leq 100$), heterogeneous cohorts of patients with brain tumors managed with older anti-seizure medications that did not identify significant differences between patients randomized to anti-seizure medications versus not.[157,158] Whether primary prophylactic anti-seizure medications reduce seizure development among certain high-risk subgroups is not clear and should be explored in randomized studies. A potential exception to the guideline of avoiding prophylactic anti-seizure medications exists in the shorter-term among patients undergoing local therapy with epileptogenic potential, such as stereotactic radiation, neurosurgical resection, and laser interstitial thermal therapy (LITT), although data are conflicting.[138,159–163]

When anti-seizure medications are utilized, agents that do not significantly impact hepatic metabolizing enzymes, such as levetiracetam, lacosamide, or lamotrigine are generally preferred. There is no compelling evidence to select one drug over another.[164] Patients with seizures, particularly if recent or uncontrolled, should not drive; specific laws regarding seizures and driving vary by region. In addition, factors that stimulate seizure development should be minimized/managed. In this regard, sleep hygiene, avoidance of drugs/

alcohol, and minimization of stress are prudent; medically, metabolic derangements should be addressed, intracranial pressure should be controlled, and growing intracranial tumors should be definitively managed.[165–167]

## Venous Thromboembolism

Patients with advanced malignancy commonly develop venous thromboembolism (VTE) with some studies suggesting an especially high risk of VTE among patients with brain metastases, potentially due to mobility issues or overlap between the tumor types with propensity to both spread to the brain and increase the likelihood of VTE.[168,169] Anticoagulation with either low-molecular weight heparin or direct oral anticoagulants constitutes the mainstay of management for patients with cancer and VTE, although concerns regarding intracranial hemorrhage (ICH) exist in patients with brain metastases.[170–173] No dedicated trials randomizing patients with brain metastases to anticoagulation versus not have been published and few prior retrospective studies on this topic exist. In addition, published studies evaluating ICH-risk in patients with brain metastases receiving anticoagulation versus not are subject to selection bias, which may account for the general conclusion that anticoagulation is safe in such patients.[174–178] A recent study by Wood et al., however, used a propensity score-based matching algorithm, as well as multivariable modeling, and a careful pre versus postanticoagulation analysis to demonstrate an association with modestly increased ICH-risk in patients with brain metastases who receive anticoagulation, particularly among those with melanoma or prior intracranial bleeds; anticoagulation should be used cautiously in such patients.[179] Ultimately, until prospective studies are conducted, the indication for anticoagulation should be carefully weighed against the risk of ICH in patients with brain metastases when deciding whether to employ anticoagulation versus not.

## Radiation Necrosis

A subset of patients undergoing radiosurgery will develop adverse radiation effects, most commonly radiation necrosis, which involves inflammation or injury to the brain. Rates of radiation necrosis, although variable, range from 0% to 30% across studies; the range reflects variation in the definition of radiation necrosis and whether neurologic symptomatology is present versus absent.[180–185] The initial management of imaging changes related to radiation effects often entails observation given that progression of radiation-related changes typically ceases, sometimes before symptoms develop. In the setting of radiation necrosis, the first-line therapy in symptomatic patients involves glucocorticoids, although prolonged courses/tapers are often required. If corticosteroids prove unsuccessful in stabilizing radiation necrosis or yield unacceptable side effects, definitive therapy such as neurosurgical resection and/or laser interstitial thermal therapy (LITT) can be employed.[185–188] Another approach is bevacizumab, which is supported by two small randomized studies including a smaller, 14 patient crossover study randomizing patients with radiation necrosis to bevacizumab 7.5 mg/kg every 3 weeks (for two initial doses, with two additional doses administered if benefit was seen) versus placebo. All patients

in the intervention arm, as well as control patients who subsequently crossed over to the intervention arm, displayed improvement of both imaging findings and symptomatology.[189] A larger study of bevacizumab (5 mg/kg every 2 weeks for 4 doses) versus methylprednisolone (500 mg IV daily for three days followed by a prednisone taper for approximately 2 months) for radiation necrosis developing after treatment for nasopharyngeal cancer showed better radiographic/clinical control with bevacizumab than corticosteroids.[190] Practical limitations of bevacizumab include diagnostic uncertainty in delineating necrosis from tumor progression (corticosteroids may be appropriate for either scenario; bevacizumab is often only appropriate for necrosis, although this varies by underlying primary), toxicities of bevacizumab, and concerns regarding wound healing should patients require resection. Other, less-common management approaches for radiation necrosis include anticoagulation, hyperbaric oxygen, vitamin E, and pentoxifylline, but robust supporting data are lacking.[191–193] Ultimately, further prospective studies evaluating therapeutic options/sequencing for radiation necrosis are warranted.

## Neurocognitive Decline

Decline in neurocognitive function (NCF) occurs in up to 90% of patients with brain metastases,[194] affecting quality of life by interference with job function, relationships, motor vehicle operation,[195] and self-care.[196–198] Brain metastases can directly cause NCF-deficits but side effects of treatments including resection,[199] radiation,[200] chemotherapy,[201] and immunotherapy[202] also contribute significantly.[203]

Treatments for cognitive symptoms in patients with brain metastases have typically been conducted in patients with different types of brain tumors, with mixed results.[204] An acetylcholinesterase-inhibiting medication (donepezil) has been evaluated in various brain tumor populations, though only one study included a substantial proportion of brain metastases.[205] Administered after radiation, slight benefits on one metric of recognition memory compared with placebo were noted, suggesting efficacy for patients with a specific pattern of cognitive impairment (eg recent memory). Studies of agents that enhance attention (methylphenidate) or wakefulness (modafinil) in brain tumor patients also included few patients with brain metastases. Early single-arm open-label studies suggested some improvement in attention,[206] but randomized placebo-controlled trials found no improvement in fatigue.[207] Memantine is reviewed in the radiation therapy section. Cognitive rehabilitation, a nonpharmacological intervention, is well-established in patients with brain tumors[208,209] and involves development of compensatory strategies and "cognitive exercise" paradigms; such approaches have shown positive results.[210,211]

As treatments for cancer continue to improve survival, simultaneous advances in the prevention and management of neurocognitive deficits are important. Further refinements in radiation techniques (eg sparing the genu of the corpus callosum [NCT03223922] and using SRS for up to 15-20 brain metastases [NCT03075072, NCT03550391]) are being investigated, as are trials of novel neuroprotectant agents (eg porphyrin BMX-001 [NCT03608020] and

Ganglioside-Monsialic Acid [NCT04395339]) and neuroplasticity techniques.[212]

## Surgical Resection and Laser Interstitial Therapy Therapy

Surgical resection plays an important role in the management of patients with brain metastases. Standardly-accepted indications for craniotomy include: (1) diagnostic uncertainty, based on imaging, where observation is not viable, (2) brain metastases causing symptoms refractory to steroids, (3) bulky metastases (typically >3–4 cm in maximal unidimensional size), and (4) solitary brain metastases (ie one brain metastasis in the absence of extracranial disease).[213,214] Considerations regarding diagnostic uncertainty are provided in the imaging section. Among most patients with neurologic symptoms caused by brain metastases despite the use of steroids, neither radiation nor systemic therapy can reliably and quickly decompress affected areas and improve symptomatology before more permanent sequelae/decline develop. Consequently, surgery is typically indicated. However, it should be noted that for radiosensitive tumors such as SCLC, select germ cells tumors, select liquid malignancies, and Merkel cell carcinoma, radiation in lieu of surgery can be considered. Similarly, for select cancer subtypes with a known, targetable driver mutation for which effective CNS-penetrant systemic therapies exist, such as EGFR-mutant NSCLC, ALK-rearranged NSCLC, or BRAF-mutant melanoma, systemic therapy, with initial deferral of surgery and close monitoring, may prove to be viable.[215–217] For patients harboring bulky tumors, the stereotactic radiation dose that can be safely administered is limited due to constraints imposed by the surrounding brain,[181,218] often compromising control; therefore, surgery is typically indicated. Lastly, among patients with solitary brain metastases, neurosurgical resection may prove helpful, as retrospective/hypothesis-generating evidence suggests associations between combined modality local therapy (ie resection and cavity radiation) and longer-term survival relative to stereotactic radiation alone even among small foci of disease, although prospective studies are lacking.[214]

Three randomized studies have assessed the role of neurosurgical resection in addition to WBRT versus WBRT alone in patients with a single brain metastasis (Table 3).[6,219–221]

Two of the three studies showed an overall survival advantage with neurosurgical resection; subset analyses of these studies suggested that the benefit associated with neurosurgical resection may be most significant among patients with stable/controlled extracranial disease given a lower competing risk.[6,219–221] In the modern era, adjuvant WBRT has been largely replaced by adjuvant stereotactic radiosurgery for patients with a limited number of brain metastases.[222–225]

One adverse effect associated with craniotomy is pachymeningeal seeding (also called nodular leptomeningeal disease), a phenomenon in which tumor cells dispersed by surgical intervention recur along the pachymeninges beyond the adjuvant stereotactic radiation field (Figure 6).[226,227] Pachymeningeal seeding after resection was not commonly seen in the adjuvant WBRT era given the potential for WBRT to control micrometastatic disease. In the postoperative stereotactic era, however, approximately 6–12% of craniotomies are complicated by pachymeningeal seeding.[226] Multiple publications have now described this phenomenon.[226,227] Unlike classical leptomeningeal disease, hydrocephalus requiring CSF diversion is uncommon in pachymeningeal seeding and either WBRT or stereotactic radiosurgery can be employed as salvage (as pachymeningeal seeding does not involve the CSF), with little role for intrathecal chemotherapy given the penetration concerns into lesions greater than several millimeters.[228] Conversely, in classical leptomeningeal disease, imaging typically shows linear subarachnoid deposits along cranial nerves, cerebellar folia, supratentorial sulci, and/or ventricular surfaces (Figure 7).[229] In addition, hydrocephalus risk is greater, and WBRT/intrathecal chemotherapy can be considered while there is little role for stereotactic radiation. Consequently, clinical/radiographic delineation of pachymeningeal seeding from classical leptomeningeal disease is critical (Table 4).

MRI-guided laser interstitial thermal therapy (LITT) is a minimally-invasive surgical technique with efficacy in treating brain lesions (Figure 8).[230,231] LITT involves a 3–5 mm twist drill hole in the skull through which a catheter is navigated to the target; laser-derived thermal energy is used for ablation. The most established role of LITT is for radiation necrosis although LITT-based treatment for recurrent tumor after prior radiation is a consideration as well. A prospective, single-arm, multicenter study involving postradiation LITT demonstrated 12 week local progression-free survival of 100% versus 54% in patients with necrosis versus recurrent tumor.[187] Neurological

**Table 3** Randomized Studies Comparing Neurosurgical Resection + Whole Brain Radiation Relative to Whole Brain Radiation Alone in the Management of a Single Brain Metastasis

| Study | Years of Enrollment | N | Arms | Local Recurrence | Overall Survival | Functional Status |
|---|---|---|---|---|---|---|
| United States[6] | 1985–1988 | 48 | WBRT + biopsy vs WBRT + surgery | Surgery better | Surgery better | Surgery better |
| Dutch[213] | 1985–1990 | 66 | WBRT +/– surgery | N/A | Surgery better | Trend to favoring surgery |
| Canadian[215] | 1989–1993 | 84 | WBRT +/– surgery | N/A | No difference | No difference |

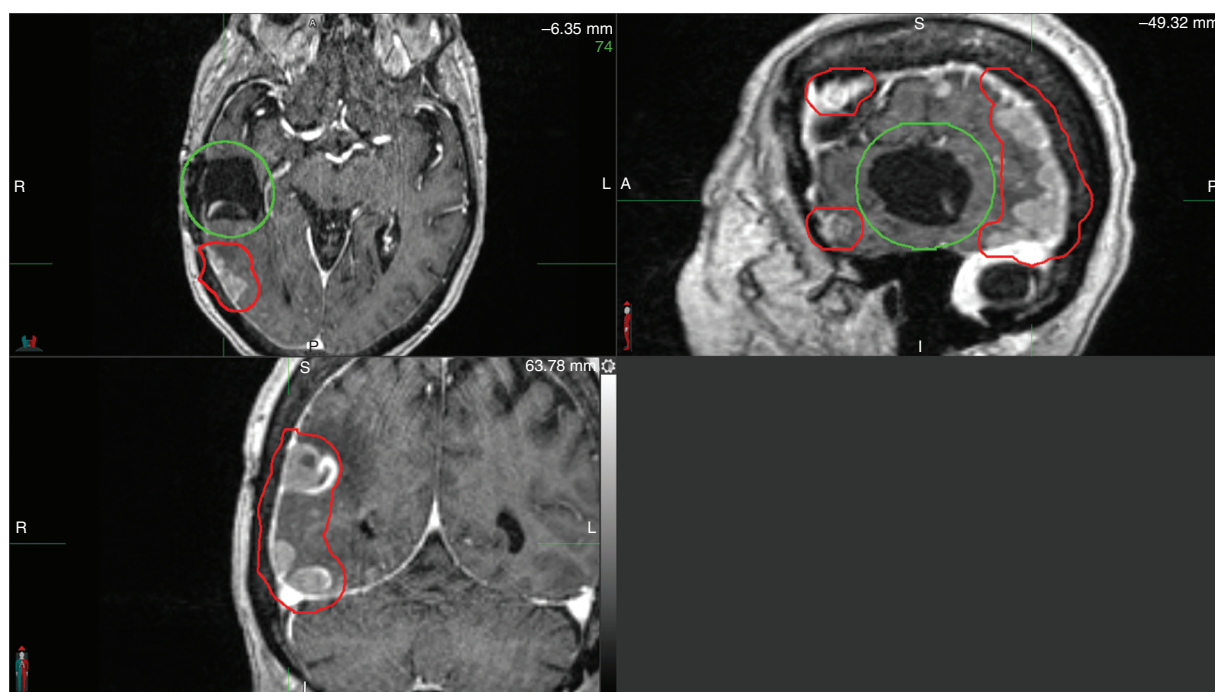**Abbreviations:** N, Number; N/A, Not Applicable; WBRT, Whole Brain Radiation Therapy.

**Fig. 6** Pachymeningeal seeding. Pachymeningeal seeding after neurosurgical resection of a brain metastasis. Note the multifocal pachymeningeal recurrences (red) occurring in the absence of a cavity recurrence (green).
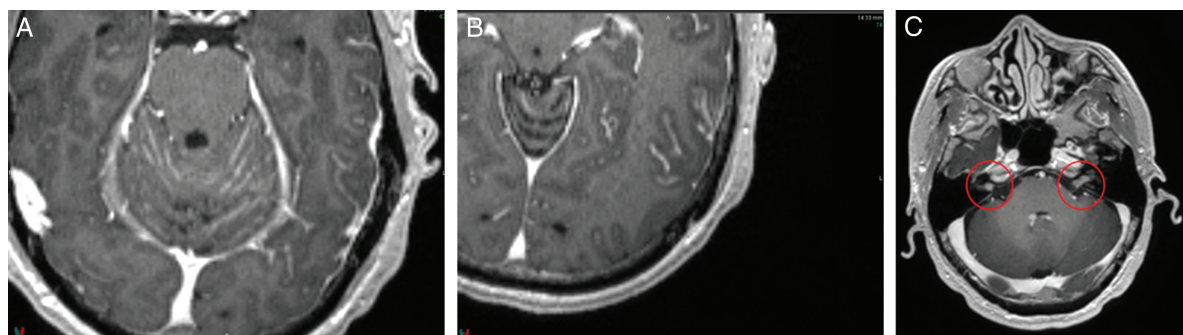


**Fig. 7** Classical leptomeningeal disease. Classical leptomeningeal disease as noted by linear enhancement along the cerebellar folia (A), supratentorial sulci (B), and cranial nerves VII/VIII bilaterally (C, red circles).

complications of LITT were seen in 7/42 patients, mainly relating to weakness/hemiparesis, neglect, headache, and hemorrhage. Consequently, among patients with radiation necrosis and perhaps recurrent tumor who are not candidates for other approaches, LITT can often achieve intracranial disease control with a reasonable toxicity profile.

Future studies relating to surgical resection and LITT should investigate surgical techniques that may decrease the likelihood of pachymeningeal seeding. In addition, ongoing clinical trials exploring preoperative, rather than postoperative, stereotactic management and the risk of pachymeningeal seeding, among other outcomes, are being pursued (NCT03741673, NCT04422639,

NCT04474925, NCT03750227). Immunogenic effects of LITT are being explored; in this regard, a study combining LITT with PD-1 inhibition is ongoing (NCT04187872). Finally, emerging techniques such as focused ultrasound may have potential applications for novel drug delivery, sonodynamic therapy, and immunomodulation (NCT04559685).[232]

## Radiation

Radiation therapy represents the historical mainstay of therapy for patients with brain metastases given concerns

**Table 4**  Etiology, Natural History, and Management of Pachymeningeal Seeding Relative to Classical Leptomeningeal Disease in Patients with Brain Metastases

|  | Pachymeningeal Seeding | Classical Leptomeningeal Disease |
|---|---|---|
| Etiology | Postsurgical | Usually not surgical |
| Natural history | Likely reflective of a one-time event | Ongoing process |
| Imaging | Pachymeningeal/dural nodular recurrences often near surgical cavity and potentially in more distant sites | Linear subarachnoid deposits along cranial nerves, cerebellar folia, supratentorial sulci, and/or ventricular surfaces |
| Hydrocephalus risk | Usually not | Sometimes |
| Whole brain radiation utilized for management | Sometimes | Often |
| Stereotactic radiation utilized for management | Sometimes | Usually not |
| Intrathecal chemotherapy utilized for management | Usually not | Sometimes |

regarding the limited intracranial efficacy of many systemic therapies. External beam radiation encompasses two primary forms of treatment: (1) WBRT with or without hippocampal avoidance and (2) stereotactic radiation. Nonstereotactic partial brain radiation is less commonly utilized and will not be reviewed.

## Whole Brain Radiation Therapy

Historically, WBRT represented the primary management modality for patients with multifocal intracranial disease. An older, small randomized study in the pre-CT/MRI era suggested a 4-week survival advantage with WBRT over steroids alone.[233] Subsequent seminal work in the 1990s established a role for adjuvant WBRT among patients with a single, resected brain metastasis, demonstrating a significant improvement in intracranial recurrence rates and neurologic death with surgical resection plus adjuvant WBRT compared to surgical resection alone.[234] Although effective against both visible and microscopic intracranial disease, WBRT carries a significant short and long-term toxicity profile, including fatigue, anorexia, xerostomia, nausea, and alopecia in the short term, and cognitive dysfunction, balance problems, and hearing loss in the longer term.[235,236] It is important to note that WBRT should be used cautiously in patients with a significant extracranial disease burden and limited systemic options given the decreased likelihood that intracranial management will impact prognosis, as seen in the QUARTZ study.[237]

Multiple strategies to mitigate the neurocognitive impact of WBRT exist. In RTOG 0614, memantine (used for 24 weeks including a 4-week uptitration period), an N-methyl-D-aspartate (NMDA) receptor antagonist, was evaluated against placebo in a randomized trial among patients receiving WBRT,[238] with a trend towards preservation in delayed recall at 24 weeks (primary endpoint) and significantly longer time to any measure of cognitive decline noted among patients receiving memantine.[238] Consequently, memantine serves as a useful adjunctive therapy for patients receiving WBRT.

The observation that a potential driver of radiation-induced cognitive toxicity from WBRT, specifically memory loss, was dose deposition to neural stem cells within the subgranular zone of the hippocampal dentate gyrus[239,240] led to development of hippocampal-avoidance WBRT (HA-WBRT), Figure 9.[241–243] NRG CC001 demonstrated lower rates of cognitive failure with HA-WBRT and memantine as opposed to traditional WBRT and memantine, establishing HA-WBRT and memantine as standard in most patients devoid of brain metastases in/near (5 mm) the hippocampi or leptomeningeal disease.[244,245] Of note, relapse rates near the hippocampus were comparable with 11 and 16 relapses in the HA region in the HA-WBRT and traditional WBRT arms, respectively, dispelling the concern that hippocampal avoidance would substantially increase the risk of peri-hippocampal recurrence.

## Stereotactic Radiation Therapy

Stereotactic radiation therapy can be delivered as either a single fraction of highly conformal, high-dose treatment (stereotactic radiosurgery [SRS], generally 18–24 Gy) or as multiple, moderately-dosed fractions (stereotactic radiotherapy [SRT], commonly 20 Gy in 2 fractions, 24–27 Gy in 3 fractions, or 25–40 Gy in 5 fractions, also known as fractionated SRS), with a planning target volume (margin for uncertainty) of 0–2 mm.[133] Of note, the nomenclature used to describe such treatment has varied in the literature; we will use the terminology/abbreviations noted above for consistency throughout the manuscript. Randomized studies of SRS alone versus SRS plus WBRT in patients with 1–4 metastases have been conducted (Table 5), collectively demonstrating higher intracranial failure (both locally and in the uninvolved brain) with SRS alone, but without an overall survival benefit with WBRT. Contemporary trials utilizing sensitive cognitive batteries have demonstrated worse neurocognition with the addition of WBRT.[222–224,247] Based on these results, stereotactic radiation alone as initial treatment, with close MRI surveillance, salvage SRS/SRT for limited distant intracranial failure, and deferral of WBRT for widespread intracranial recurrence has become widely adopted for patients with limited intracranial metastases.
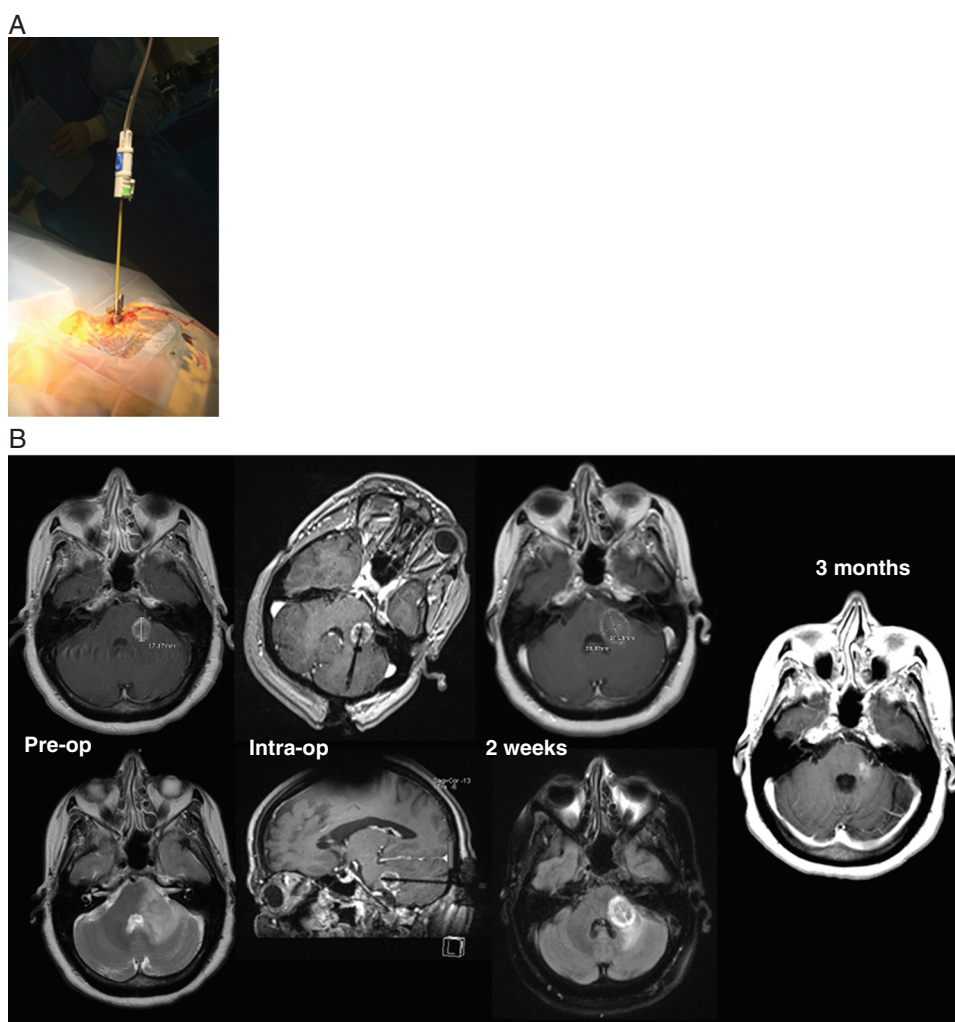
**Fig. 8** Laser interstitial therapy. LITT technique showing stereotactic laser fiber insertion to the target through a skull anchoring bolt (A) and MRI-based assessments before, during, and after LITT procedure (B). In Part (B), images reveal: (left) T1 and T2-weighted MRI showing regrowth of brain metastasis 12 months after radiosurgery; (left middle) intraoperative images displaying laser inserted into lesion; (right middle) 2-week post-LITT MRI showing postlaser ablation lesion increased in size but FLAIR signal improved; (right) MRI revealing resolution of lesion at 3 months post-LITT. (Abbreviations: FLAIR, Fluid Attenuated Inversion Recovery; LITT, Laser Interstitial Thermal Therapy; MRI, Magnetic Resonance Imaging).

## Stereotactic Radiation Among Patients with >4 Brain Metastases

The lower rate of cognitive loss associated with SRS/SRT without a decrement in survival compared to WBRT led to interest in exploring stereotactic approaches for patients with >4 brain metastases. A large, multi-institutional observational experience of SRS in patients with up to 10 brain metastases suggested relatively comparable outcomes among patients receiving SRS for 2–4 as opposed to 5–10 lesions, although fewer than expected patients with 5–10 brain metastases enrolled, as noted by the authors, raising the possibility of selection bias.[248] There are now multiple ongoing phase III studies comparing HA-WBRT to SRS among patients with >4 brain metastases (NCT03075072; NCT04277403; NCT03550391), all with potential to significantly impact care.

Recent data relating to immune checkpoint inhibitors and receptor tyrosine kinase inhibitors have demonstrated relatively high intracranial response rates in select subpopulations, often leading to an approach of deferring SRS/SRT in certain subpopulations. The broad justification for this approach stems from the contention that SRS/SRT may not improve survival in patients with >1 lesion,[7] and that it can always be employed as salvage. This may be reasonable in some subsets, but prospective randomized data supporting this practice are lacking.

## Adjuvant Stereotactic Radiation in Patients with Resected Brain Metastases

Among patients with resected brain metastases, the historical standard of care was to utilize adjuvant WBRT
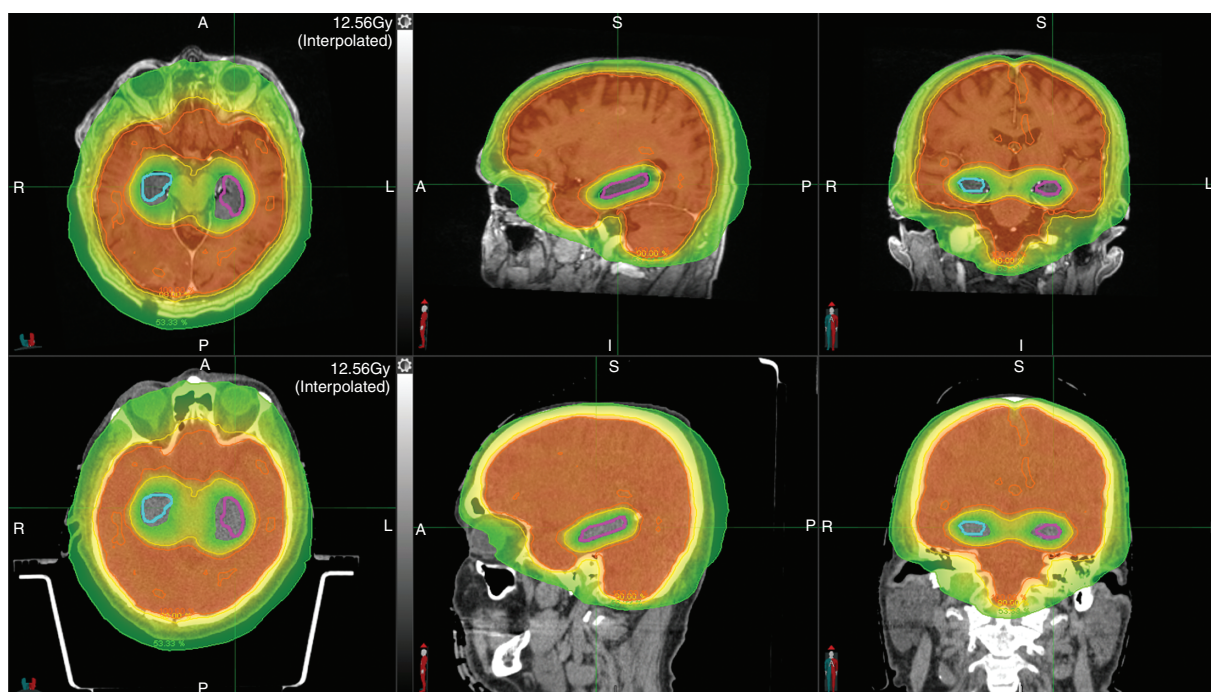
**Fig. 9** Hippocampal-sparing whole brain radiation in a patient with brain metastases. The right and left hippocampi are contoured in blue and pink, respectively. The top and bottom panel shows the planning magnetic resonance imaging and computed tomography scans, respectively. The red, orange, yellow, and green dose-based shading depict the 33 Gy, 30 Gy, 27 Gy, and 16 Gy isodose lines, respectively.

but randomized data now support the use of SRS/SRT, ideally within 4 weeks of surgery, in patients with a limited number of additional brain metastases.[223,225,249–252] However, the 1-year cavity recurrence rate in prospective/randomized studies after surgery plus stereotactic radiation remains high, ranging from 28% to 40%; in contrast, cavity recurrence rates with adjuvant WBRT are substantially lower.[223,225,234,249] This underscores the need for significant improvement in stereotactic approach/technique. In this regard, cavity SRS is being compared to cavity SRT in an ongoing randomized trial (NCT04114981). In addition, contouring guidelines may improve delineation of the target.[253] Of note, pachymeningeal relapse can occur in a significant percentage of patients managed with adjuvant SRS/SRT, with impact on patient morbidity/mortality.[226,254] Postoperative SRS/SRT is also associated with a relatively high rate of necrosis, given the typically large associated volumes, generous expansions, and interdigitation of the target with normal brain.[254] Consequently, multiple prospective trials are evaluating the role of preoperative stereotactic radiation prior to resection of a brain metastasis (NCT03741673, NCT04422639, NCT04474925, NCT03750227) with the objective of decreasing recurrence, pachymeningeal seeding, and necrosis rates.

## Stereotactic Radiation Therapy in Patients with Small Cell Lung Cancer

Historically, WBRT has been the mainstay of treatment for patients with SCLC and brain metastases given concern for widespread micrometastic intracranial disease. Patients with SCLC have been excluded from nearly all prospective evaluations of omission of WBRT.[222–225,234,247] However, SRS/SRT-based outcomes in SCLC appear encouraging.[255,256] As such, ongoing prospective trials (NCT03391362, NCT04516070, NRG CC009) are evaluating the viability of stereotactic approaches among patients with SCLC and a limited burden of intracranial disease. The treatment paradigm for brain metastases in patients with SCLC will likely continue to evolve as the results of ongoing trials become available.

## Toxicities Associated with Stereotactic Radiation Therapy

Given the limited radiation fields/volume inherently associated with SRS/SRT, relative to WBRT, acute side effects secondary to SRS/SRT tend to be more modest in nature. However, the higher biologic dose of radiation utilized can lead to posttreatment inflammatory changes among other rare effects, as well as long-term adverse radiation effects, including radiation necrosis.[163,257] Generally developing 3 months to 3 years after treatment,[183,258] radiation necrosis (when confirmed histopathologically) involves inflammation or injury to the brain approximating the SRS/SRT site. Given the variation in SRS/SRT delivery patterns across institutions and inconsistent diagnostic criteria, the reported incidence of radiation necrosis after SRS/SRT varies considerably, ranging from 5% to 35% in various retrospective series; the wide range may reflect inconsistencies in the definition of radiation necrosis and that some investigators combine radiation

**Table 5** Randomized Trials Evaluating Local Treatment with/Involving Whole Brain Radiation Therapy vs Local Treatment Alone in the Management of Brain Metastases

| Study | N | Number of BM | Arms | Years of Accrual | Intracranial Recurrence with WBRT | OS with WBRT | QoL with WBRT | Neurocognition with WBRT |
|---|---|---|---|---|---|---|---|---|
| Patchell/multi-center[246] | 95 | 1 | 1. Surgery<br>2. Surgery + WBRT | 1989–1997 | Lower | No difference | N/A | N/A |
| Japanese Radiation Oncology Study Group 99-1[236] | 132 | 1–4 | 1. SRS<br>2. SRS + WBRT | 1999–2003 | Lower | No difference | N/A | Limited data |
| MD Anderson Cancer Center[216] | 58 | 1–3 | 1. SRS<br>2. SRS + WBRT | 2001–2007 | Lower | Worse | No difference identified | Worse |
| European Organization for Research and Treatment of Cancer 22952[217] | 359 | 1–3 | 1. Local Therapy<br>2. Local Therapy + WBRT | 1996–2007 | Lower | No difference | Trend to worse | N/A |
| North Central Cancer Treatment Group N0574[218] | 213 | 1–3 | 1. SRS<br>2. SRS + WBRT | 2002–2013 | Lower | No difference | Worse | Worse |
| Japan Clinical Oncology Group 0504[240] | 271 | 1–4 | 1. Resection + Salvage SRS<br>2. Resection + WBRT | 2006–2014 | Lower | No difference | N/A | Generally worse in some domains |
| Polish[241] | 59 | 1 | 1. Resection + SRS<br>2. Resection + WBRT | 2011–2015 | No difference | Better | Mixed results | No difference |
| Alliance/North Central Cancer Treatment Group N107C[242] | 194 | 1–4 | 1. Resection + SRS<br>2. Resection + SRS + WBRT | 2011–2015 | Lower | No difference | No significant difference | Worse |
| MD Anderson Cancer Center[238] | 72 | 4–15 | 1. SRS<br>2. WBRT | 2012–2019 | – | No difference | – | Worse (possible trend) |

**Abbreviations:** N, Number; N/A, Not Applicable; OS, Overall Survival; QoL, Quality of Life; SRS, Stereotactic Radiosurgery; WBRT, Whole Brain Radiation Therapy.

necrosis with more transient, imaging-based adverse radiation effects.[182,258–260] Factors predictive of radiation necrosis include a larger volume of brain receiving doses >10–12 Gy (V10/V12), prior brain radiation, use of concurrent systemic therapies including immunotherapy, tumor histology, and inherent radiosensitivity.[181,261–263] In terms of location, the brainstem, thalamus, and optics display the greatest risk of radiographic to symptomatic conversion.[261] The diagnosis and management of radiation necrosis is reviewed in the imaging and neuro-oncology sections, respectively.

## Deciding Between Whole Brain Versus Stereotactic Radiation

Historically, the majority of patients with brain metastases received WBRT; upfront SRS/SRT has now become the predominant upfront strategy, especially for patients with limited intracranial disease.[153] This shift has been motivated by cognitive dysfunction associated with WBRT, as measured by sensitive neurocognitive test batteries in prospective clinical trials.[224,225]

Other factors may influence the decision to proceed with SRS/SRT versus HA-WBRT/WBRT as well. In patients with extensive extracranial disease with effective therapeutic options, SRS/SRT permits a more rapid transiition back to systemic therapy.[237] Geriatric patients may experience greater cognitive decline with WBRT/HA-WBRT, potentially supporting stereotactic approaches in this patient group.[264] Patients with so called "radioresistant" tumors (eg melanoma) may benefit from SRS/SRT, due to greater fractional cell kill from higher-dose radiation delivered with each treatment. Conversely, in patients with significant intracranial disease burden driven by a larger number of brain metastases (eg >4 tumors based on published randomized data but particularly >10–20 tumors), as well as those with a greater brain metastasis velocity (BMV, ie the cumulative number of new brain metastases that develop over time after SRS/SRT),[265] WBRT/HA-WBRT remains more standard, in part given the limited randomized data for SRS.[222–225] Ultimately, until further prospective trials are published, such as NCT03075072 and NCT03550391, selection of SRS/SRT versus WBRT may depend upon the above factors as well as a nuanced patient-provider discussion.

## Brachytherapy

Brachytherapy involves the intraoperative placement of radioactive isotopes within a resection bed, allowing for highly conformal delivery of high-dose radiation.[266] While

brachytherapy is uncommonly utilized in patients with brain metastases, it represents an effective salvage therapy for some patients with multiply (locally) recurrent tumors.[267] A recent review of 23 studies evaluating brachytherapy in the treatment of brain metastases demonstrated local control rates of 80–100% across most studies, although follow-up was <12 months in the majority of investigations.[268] Despite promising local control rates, the use of brachytherapy for brain metastases has been limited, primarily because it is resource intensive and more subject to specialized expertise in comparison to external beam techniques. Further, concerns regarding radiation necrosis, observed in legacy glioblastoma brachytherapy trials, have tempered enthusiasm.[268] Randomized studies to more definitively evaluate the role of brachytherapy in the management of resected brain metastases are underway (NCT04690348).

## Systemic Therapy

The evolving landscape of systemic therapy has significantly changed the management of brain metastases. Historically, the limited activity of systemic agents in the CNS effectively mandated local brain-directed therapy for nearly all patients.[269] However, increasingly effective systemic agents now exist for many extracranial malignancies.[270,271] In addition, unlike in glioma, where tumor cells infiltrate the underlying brain, brain metastases tend to form discrete tumor masses with potential breakdown of the BBB, allowing for some penetration of systemic agents into the tumor microenvironment, even if minimal penetration across an intact BBB is possible. As a result, for some patients with untreated, asymptomatic, or minimally symptomatic brain metastases, or those with progressive brain metastases despite local therapy, systemic therapy alone, with close intracranial surveillance, may prove reasonable. Here, we review systemic therapy considerations among the extracranial primaries that harbor a predisposition for intracranial dissemination, but which also have potentially viable systemic options, namely NSCLC, breast cancer, and melanoma. When relevant, the integration of systemic therapy and local, brain-directed therapy is discussed.

### Non-small Cell Lung Cancer

Increasingly, the systemic management of brain metastases in patients with NSCLC, particularly adenocarcinomas, is contingent on the presence versus absence of targetable mutations or gene rearrangements, as many current small-molecule, targeted drugs achieve some degree of intracranial penetration (Table 6). Approximately 33–45% of lung adenocarcinomas harbor such genetic changes in the United States, with even higher rates seen in nonsmokers.[9,272–280] It should be noted that, even in the absence of targetable genetic changes, anti-PD1 agents, particularly in patients who are PD-L1 positive or who harbor other biomarkers for immunogenicity, or pemetrexed (among patients with adenocarcinomas) may yield intracranial disease control in some patients, although responses

can be limited in magnitude and duration.[281–285] Of note, intervention studies stipulating local, brain-directed therapy prior to administration of novel systemic agents can make estimates of intracranial efficacy difficult to determine.[286]

Most patients with EGFR alterations harbor exon 19 deletions or exon 21 L858R substitutions, which account for approximately 90% of mutations in EGFR-mutated NSCLC; such patients are sensitive to EGFR-targeting TKIs.[287] Patients with uncommon EGFR mutations may also respond to licensed 1st–3rd generation EGFR TKIs; however, most exon 20 insertions are not sensitive to such agents.[288] Among patients with common and uncommon EGFR mutations and brain metastases, prospective studies involving erlotinib, gefitinib, or afatinib, mainly in patients with asymptomatic brain metastases, have generally indicated intracranial response rates between 70% and 88%.[28,289–291] However, the current standard of care for patients with brain metastases secondary to EGFR-mutant lung cancer is the 3rd generation inhibitor, osimertinib. In this regard, the first-line FLAURA study comparing the first-generation EGFR TKIs erlotinib and gefitinib to osimeritinib demonstrated prolonged progression-free and overall survival with osimertinib.[292] In addition, a trend to improved intracranial response rate with osimertinib was noted (68% vs 91%, respectively).[292] Osimertinib can also yield intracranial responses in patients who received other EGFR-TKI therapy and manifest a T790M resistance mutation.[57,58] Table 7 displays the intracranial efficacy of osimertinib. It is notable that most patients in these studies had stable, asymptomatic, and/or radiated brain metastases. For patients with EGFR exon 20 insertions, amivantamab, a bispecific monoclonal antibody has recently been licensed, although data relating to intracranial efficacy are lacking.[288] Of note, neratinib, a dual inhibitor of HER2 and EGFR, may have activity in select patients with EGFR mutations.[293]

Patients with ALK-rearranged NSCLC also have multiple systemic options for intracranial disease control. With the possible exception of the first-generation drug crizotinib, ALK targeting agents such as alectinib, ceritinib, brigatinib, and lorlatinib have generally displayed high rates of intracranial disease control in prospective trials (Table 8).[272,294,296–306] Lorlatinib may also be effective after progression on a second-generation ALK inhibitor, such as ceritinib, alectinib, or brigatinib.[307] The unique side effect profile of lorlatinib, which includes hyperlipidemia, central nervous system effects such as mood, cognitive, and speech changes, weight gain, edema, peripheral neuropathy, and gastrointestinal effects, and its potential for utility in later-line settings, has proven challenging with regard to first-line use among patients with ALK rearrangements.[308–310]

Whether to add radiation to the management of patients with targetable NSCLC remains an area of active controversy. Select multi-institution retrospective and hypothesis-generating data may support combined modality therapy,[311] but biases inherent to retrospective designs can impact such analyses. Randomized studies evaluating the role of local brain-directed radiation in patients receiving TKI-based therapy for targetable NSCLC are ongoing (NCT03769103, NCT04634110). However, as consolidation radiation at the point of maximal response to systemic therapy becomes more established for extracranial disease in advanced NSCLC, in order to limit

**Table 6** Incidence Proportions and Potentially Viable Systemic Options for Targetable Alterations in Non-small Cell Lung Cancer

| Alteration | Incidence Proportion Among Non-small Cell Lung Cancer (Adenocarcinoma) in United States | Potential Therapeutic Agents |
|---|---|---|
| ALK rearrangements | 4–5% | Alectinib, ceritinib, brigatinib, lorlatinib, crizotinib |
| BRAF V600E mutations | 1–3% | Dabrafenib+trametinib |
| EGFR (common and uncommon mutations) | 15–20% | Osimertinib, erlotinib, gefitinib, afatinib, dacomitinib |
| EGFR exon 20 insertion mutations | 1–2% | Amivantamab |
| HER2 Exon 20 insertion mutations | 1–3% | Trastuzumab, afatinib, ado-trastuzumab emtamsine, trastuzumab deruxtecan |
| KRAS G12C mutations | 10–12% | Sotorasib |
| MET exon 14 skip mutations/ high-level amplification | 2–3% | Capmatinib, tepotinib, crizotinib |
| NTRK rearrangements | 0–1% | Larotrectinib, entrectinib |
| RET rearrangements | 1–2% | Selpercatinib, pralsetinib |
| ROS1 rearrangements | 1–2% | Entrectinib, crizotinib, lorlatinib, ceritinib, |

**Table 7** Intracranial Response and Duration of Efficacy for Patients with EGFR-Mutant Non-small Cell Lung Cancer Managed with Osimertinib on Prospective Trials[a]

| Study | Drug | Higher Level Entry Criteria | Years of Accrual | N | Median Intracranial Response Duration | CR | PR | SD | PD | N/A |
|---|---|---|---|---|---|---|---|---|---|---|
| AURA extension/AURA2[56] | Osimertinib | Asymptomatic, stable BM with prior EGFR therapy, T790M mutant | 2014–2015 | 50 | Not reached | 12% | 42% | 38% | 6% | 2% |
| AURA3[55] | Osimertinib | Asymptomatic, stable BM with prior EGFR therapy, T790M mutant | 2014–2015 | 30 | 8.9 months | 7% | 63% | 23% | 3% | 3% |
| FLAURA[262,284] | Osimertinib | Asymptomatic, stable, or symptomatic/ unstable but radiated BM | 2014–2016 | 22 | 15.2 months | 23% | 68% | 5% | 0% | 5% |

**Abbreviations:** BM, Brain Metastases; CR, Complete Response; N, Number; N/A, Not Applicable/Available; PD, Progressive Disease; PR, Partial Response; SD, Stable Disease.
[a]Where possible table focuses on patients with measurable disease.

development of acquired resistance, the same logic in the CNS may also need to be formally explored in addition to simply studying the role of drugs in deferring CNS radiation.

## Breast Cancer

Viable systemic options vary by breast cancer subtype, with HER2+ patients having the most options for intracranial disease control. The backbone of first-line systemic management for extracranial disease involves trastuzumab, pertuzumab, and either paclitaxel or docetaxel (THP).[17] Despite excellent systemic efficacy, the intracranial penetration and disease control of THP is guarded, even when high doses of trastuzumab are used.[312] The PATRICIA trial demonstrated an intracranial response rate of 11% with high dose trastuzumab (6 mg/kg) and pertuzumab in patients who had progressed on prior trastuzumab as well as radiotherapy, although 51% achieved clinical benefit at 6 months. Trastuzumab emtansine (T-DM1) offers more

potential for intracranial disease control. In the KAMILLA study of T-DM1 in patients with advanced or metastatic HER2+ breast cancer in which patients had received prior HER2-based therapy along with chemotherapy, the best overall response (CNS and extracranial disease) was 21%; CNS objective responses were observed in 33% of patients who had most recently received CNS-directed radiation ≥30 days prior, and in 49% of radiation-naïve patients.[313] Among responders, the median duration of exposure to T-DM1 was 9.5 months. Lapatinib, a small dual tyrosine kinase inhibitor of HER1/HER2, when used with capecitabine in newly diagnosed, radiation-naïve patients, demonstrated an intracranial response rate of 66% in the LANDSCAPE study.[314] The CNS response rates were lower (~20%) in patients who had progressed after radiotherapy.[315] Neratinib, an irreversible pan-HER TKI, displayed intracranial response rates of 33–49% (based on prior lapatinib versus not) when used with capecitabine, in a population who had largely progressed after radiation.[316] More recently, regimens based on tucatinib (a

**Table 8** Intracranial Response and Duration of Efficacy for Patients with ALK-Rearranged Non-small Cell Lung Cancer Managed with Targeted Agents on Prospective Trials[a]

| Study | Drug | Higher Level Entry Criteria | Years of Accrual | N | Median Intracranial Response Duration | CR | PR | SD | PD | N/A |
|---|---|---|---|---|---|---|---|---|---|---|
| ASCEND-1[287] | Ceritinib | Asymptomatic, stable BM, mostly pretreated with ALK inhibitor | 2011–2013 | 36 | 8–11 months[b] | 0% | 42% | 19% | 17% | 22% |
| ASCEND-2[288] | Ceritinib | Asymptomatic, stable BM, prior platinum + crizotinib | 2012–2013 | 20 | N/A | 10% | 35% | 35% | 15% | 5% |
| ASCEND-4[289] | Ceritinib | Asymptomatic/stable BM, largely chemo naïve | 2013–2015 | 35 | 17 months[c] | 11% | 60% | 17% | 6% | 6% |
| AF-002JG[292] | Alectinib | Asymptomatic BM, prior crizotinib | 2012–2013 | 9 | N/A | 0% | 56% | 22% | 22% | 0% |
| Multisite global[290] | Alectinib | Stable or asymptomatic BM, prior crizotinib | 2013–2014 | 35 | 10 months | 20% | 37% | 29% | 9% | 3% |
| Multisite North American[291] | Alectinib | Stable, asymptomatic BM, prior crizotinib | 2013–2014 | 16 | 11 months | 25% | 50% | 25% | 0% | 0% |
| ALEX[292] | Alectinib | Asymptomatic BM | 2014–2017 | 15 | Not reached | 33% | 20% | 27% | 13% | 7% |
| ALUR[294] | Alectinib | Asymptomatic or symptomatic but ineligible for radiation | N/A | 24 | Not reached | 4% | 50% | 25% | 13% | 8% |
| Multisite American/ Spanish[293] | Brigatinib | Stable BM, largely pretreated with crizotinib | 2011–2014 | 15 | 19 months | 7% | 47% | 33% | 13% | 0% |
| ALTA[295] | Brigatinib | Asymptomatic, stable BM, prior crizotinib | 2014–2015 | 44 | Not reached | 5% | 48% | 32% | N/A | N/A |
| ATLA-1L[296] | Brigatinib | Asymptomatic or stable BM | 2016–2017 | 18 | Not reached | 28% | 50% | N/A | N/A | N/A |
| Multisite Global[297] | Lorlatinib | Asymptomatic BM | 2015–2016 | 81[d] | 14.5 months | 20% | 43% | 25% | 9% | 4% |
| CROWN[263] | Lorlatinib | Asymptomatic BM | 2017–2019 | 17 | Not reached | 71% | 12% | N/A | N/A | N/A |

**Abbreviations:** BM, Brain Metastases; CR, Complete Response; N, Number; N/A, Not Applicable/Available; PD, Progressive Disease; PR, Partial Response; SD, Stable Disease.

[a]Where possible, table focuses on patients with measurable disease.

[b]Variable based on receipt of ALK therapy vs not.

[c]Among patients with unirradiated brain metastases.

[d]Excludes treatment-naïve patients (N = 3).

more selective HER2-targeting TKI) have demonstrated more promise for intracranial disease control in patients with HER2+ breast cancer and brain metastases. The HER2CLIMB study, which randomized patients who previously received trastuzumab, pertuzumab, and T-DM1 to the regimen of tucatinib, capecitabine, and trastuzumab versus capecitabine and trastuzumab alone, identified an overall intracranial response rate with tucatinib, among patients with both measurable and active brain metastases, of 47% with a median duration of response of 6.8 months; respective estimates in patients only receiving capecitabine and trastuzumab were 20% and 3.0 months, respectively. Overall survival, PFS, and CNS–PFS were all significantly better with tucatinib.[317] Early data suggesting CNS efficacy of the novel antibody-drug-conjugate, trastuzumab deruxtecan, also exists. In the DESTINY-Breast01, in heavily pretreated patients (median = 6 prior regimens), 24 patients with treated/asymptomatic brain metastases were included, with an overall response rate of 58% and CNS response rate of 41%. Importantly, the median duration of response was 18.1 months.[318] An ongoing study (DESTINY-Breast12) will enroll up to 250 patients with stable or progressive HER2+ breast cancer brain metastases to further define the intracranial activity of trastuzumab deruxtecan.

The optimal sequencing of HER2-targeted agents in patients with or without brain metastases remains an area of active investigation, as does the utility of dual-agent HER2-based therapy. In this regard, ongoing clinical trials are testing novel combinations of HER2-targeting systemic agents (such as tucatinib plus T-DM1 [NCT03975647], T-DM1 plus neratinib [NCT01494662], and trastuzumab deruxtecan plus tucatinib [NCT04539938]).

Among patients with triple negative breast cancer (TNBC) and brain metastases, systemic options for intracranial disease control are limited. Few prospective trials of systemic agents exist. Sacituzumab govitecan, an antibody-drug conjugate consisting of an anti-Trop-2 antibody linked with an active metabolite of irinotecan, SN-38, was evaluated in the ASCENT study of patients with TNBC, including those with stable brain metastases. Despite systemic efficacy, the intracranial response rate and clinical benefit rate were 3% and 9%, respectively, though interpretation of these results is limited by the exclusion of patients with active brain metastases.[319] An ongoing SWOG trial is evaluating the CNS activity of sacituzumab specifically in patients with active brain metastases (NCT04647916). Immunotherapeutic agents such as atezolizumab, which is often combined with nab-paclitaxel or carboplatin/

gemcitabine in patients with PD-L1 positive TNBC, may have potential activity against brain metastases in TNBC but supporting data are lacking.[320]

Patients with hormone receptor-positive, HER2-negative breast cancer also have limited options for intracranial management. Although CDK 4/6 inhibition combined with hormonal therapy represents the first-line approach for patients with metastatic disease, intracranial responses are guarded; a phase II study of abemaciclib in patients with brain metastases secondary to hormone receptor-positive breast cancer identified a response rate of 5% (HER2-negative patients) and 0% (HER2-positive patients), although the clinical benefit rate was 11–24%.[321] In patients with PIK3CA mutations, alpelisib may have intracranial efficacy based on a smaller case series[322]; consequently molecular profiling of this population may be important.

Among patients with any subtype of breast cancer, BRCA mutations, and brain metastases, limited reports supporting the potential viability of PARP inhibitors have been published but prospective studies demonstrating significant intracranial efficacy are limited.[323] Carboplatin/bevacizumab may have some utility in patients with breast cancer and brain metastases, although regulatory approval for bevacizumab in metastatic breast cancer is lacking in the United States.[324] Other potential options in patients with HER2-negative breast cancer include eribulin,[325] capecitabine,[326] anthracyclines, and other hormonal (if hormone receptor-positive) and conventional chemotherapeutic agents, although supporting data and efficacy remain guarded. Consequently, for patients with HER2-negative breast cancer and brain metastases, utilization of local therapies for intracranial disease control remains an important consideration. Ultimately, in all subtypes of breast cancer, but particularly within triple negative or hormone receptor-positive/HER2 negative subsets, development of more promising systemic agents with potential for intracranial efficacy represents a key priority.

## Melanoma

Advances in systemic approaches, including immunotherapy and, for patients with actionable mutations (particularly BRAF), targeted therapy, have revolutionized the management and prognosis of patients with melanoma and brain metastases, with a significant percentage achieving durable disease control/cure with immunotherapeutic approaches. The optimal systemic management of patients with melanoma and brain metastases is dependent on numerous considerations including age, comorbidities, performance status, intracranial/extracranial disease burden, trajectory of disease pretreatment, prior treatment, steroid requirements, and the presence of targetable mutations in genes such as *BRAF*, *NRAS*, and *KIT*, among other factors. Among the 40–50% of melanoma patients harboring a BRAF mutation, those presenting with an intracranial or visceral oncologic crisis secondary to bulky or rapidly progressive disease may benefit from upfront BRAF/MEK inhibitors (in addition to possible local therapy) due to the possibility of a rapid and profound initial response to these agents.[327] In a prospective study of dabrafenib plus trametinib in patients with BRAF V600 mutant melanoma (COMBI-MB study), the intracranial response ranged from 44% to 59% based on subset; the intracranial disease control rate was as high as 75–88%. However, the median intracranial progression-free survival (PFS) ranged from 4.2 to 7.2 months and was reduced almost by half compared to reported PFS in patients without brain metastases (11.1 months).[327,328] Other BRAF/MEK regimens, including encorafenib plus binimetinib or vemurafenib plus cobimetinib, may be viable options for patients as well, although prospective data in this population are lacking.[329,330] Of note, for patients with melanoma, brain metastases, and NRAS mutations, limited data support the use of MEK inhibitors such as binimetinib in achieving a limited and sometimes shorter term response.[331] Toxicities of BRAF/MEK inhibition include fevers, diarrhea, asthenia, headache, nausea, diarrhea, arthralgias, myalgias, elevated liver enzymes, musculoskeletal toxicities, and dermatologic toxicities, including rashes, cardiomyopathies, and QTc prolongation.[327,332]

In patients with a targetable BRAF mutation harboring a less-pressing need to achieve rapid disease control, immunotherapeutic approaches have appeal, given concerns regarding the sustainability/durability of responses to targeted therapy and challenges in converting BRAF/MEK therapy to immunotherapy given the possibility of rapidly progressive disease after cessation of BRAF/MEK agents.[111] Immunotherapy also represents the first-line systemic treatment in patients lacking a BRAF alteration. Early data regarding the role of immunotherapy in the management of patients with melanoma and intracranial involvement stemmed from a single-arm phase 2 trial involving ipilimumab in which disease control was achieved in 24% and 10% of patients who were devoid of neurologic symptoms/steroid requirements versus not, respectively.[147] More impressively however, relatively few patients who were alive at 12 months died thereafter, indicating durability of response. Subsequent trials involving PD-1 inhibition as monotherapy also yielded promising results, with intracranial response rates of approximately 20%, which was notably lower than the extracranial response rate of 35–40%.[281,333]

The currently preferred immunotherapeutic regimen for patients with melanoma and brain metastases involves concurrent ipilimumab and nivolumab followed by maintenance nivolumab. Data supporting dual-agent immunotherapy stem from two landmark trials (Table 9): (1) CheckMate 204, a single-arm phase II study of combination ipilimumab/nivolumab in patients with melanoma and active/unirradiated brain metastases who were devoid of (Cohort A) or who harbored (Cohort B) symptoms/steroid requirements and (2) the ABC study, a randomized study of patients with asymptomatic/unirradiated brain metastases secondary to melanoma assessing ipilimumab/nivolumab (Cohort A) versus nivolumab (Cohort B), along with a single-arm cohort (Cohort C) of patients with progressive disease after local therapy, leptomeningeal disease, or neurologic symptoms managed with nivolumab monotherapy.[8,146,333,334] In patients on Cohort A from either CheckMate 204 or the ABC study, the intracranial response/clinical benefit rate was approximately 50–60%, with an encouraging duration of response noted in addition to significant correlation between

**Table 9**  Prospective Trials of Dual-agent Immunotherapy in the Management of Patients with Melanoma and Active Brain Metastases

|  | CheckMate 204 (Cohort A)[8,144] | CheckMate 204 (Cohort B)[8,144] | ABC Study (Cohort A)[324] |
|---|---|---|---|
| High-level eligibility | ≥1 unirradiated brain metastasis (0.5–3.0cm in size), asymptomatic | ≥1 unirradiated brain metastasis (0.5–3.0cm in size), symptomatic or on steroids[a] | Asymptomatic brain metastasis, naïve to local, brain-directed therapy |
| Sample size | 101 | 18 | 35 |
| Median follow-up (months) | 20.6 | 5.2 | 14 |
| Years of enrollment | 2015–2017 | 2015–2017 | 2014–2017 |
| Treatment | Ipilimumab + nivolumab | Ipilimumab + nivolumab | Ipilimumab + nivolumab |
| Intracranial response rate | 54% | 22% | 46% |
| Intracranial PFS, median (months) | Not reached | 1.2 | Not reached |
| Extracranial response rate | 49% | 22% | 63% |
| Extracranial PFS, median (months) | Not reached | 2.2 | 14 |
| Overall survival, median (months) | Not reached | 8.7 | Not reached |

**Abbreviations:** PFS, Progression-Free Survival.
[a]≤4 mg/day of dexamethasone (or equivalent).

intracranial and extracranial efficacy. As a result, ipilimumab plus nivolumab forms the backbone of management for patients with melanoma and asymptomatic brain metastases. Unfortunately, intracranial responses with dual-agent immunotherapy in patients who are either symptomatic or on significant doses of steroids are more limited; CheckMate 204 identified an intracranial response rate of only 16.7% in such patients (Cohort B) and, concerningly, patients were only permitted to receive a maximum daily dose of dexamethasone (or equivalent) of 4 mg, suggesting the potential for even lower response rates in patients with greater steroid requirements.[145,333,335] It is important to note that immunotherapy can carry a significant risk of side effects. In CheckMate 204, 55% of patients experienced a grade 3–4 adverse effect that was felt to be related to study treatment.[8] Adverse effects of dual-agent immunotherapy include immune-related pneumonitis, hepatitis, colitis, nephritis, pancreatitis, arthritis, myositits, dermatologic changes, neurologic toxicities, cardiac inflammation, decreased blood counts, fatigue, and infusion reactions.[336] It should be noted however, that the toxicity profile in patients with brain metastases was identical to that in patients without brain metastases, and there were no unique or novel side effects observed in this population.

Whether to combine local, brain-directed therapy along with dual-agent immunotherapy remains unresolved. Multi-modality therapy offers potential synergy between immunotherapeutic, surgical, and radiotherapeutic approaches.[337,338] Radiation, for example, appears to be more effective when concurrent immunotherapy is administered, although supporting evidence remains largely retrospective.[338] In addition, neurosurgical management can quickly decompress bulky or symptomatic brain metastases, potentially rendering patients less steroid-dependent and facilitating effective combination immunotherapy.[339] Consequently, in patients who are symptomatic or steroid-dependent, interdigitation of local, brain-directed therapy

along with dual-agent immunotherapy seems reasonable. Concerns about multi-modality therapy largely center around toxicity, including pachymeningeal seeding in patients undergoing a craniotomy and radiation necrosis in patients undergoing stereotactic, brain-directed radiation.[226] Consequently, the role of local, brain-directed therapy in patients with asymptomatic disease remains unclear.[185,226] A randomized study of ipilimumab plus nivolumab with or without brain-directed stereotactic radiation among patients with melanoma and asymptomatic brain metastases is underway (NCT03340129).

Future directions in the management of melanoma and brain metastases include evaluating combinations such as novel immunotherapeutic agents with or without bevacizumab or VEGF-targeting TKIs and the development of biomarkers to identify which patients are most likely to respond to immunotherapy. In addition, among patients with targetable BRAF mutations, combination studies of BRAF-targeted and immunotherapeutic approaches are being conducted (NCT04511013); such approaches may allow patients to benefit from the typically rapid responses to targeted therapy while also providing the opportunity to attain long-term disease control via immunotherapy. Furthermore, evaluation of BRAF/MEK inhibitors with improved CNS penetration are now being explored in phase I studies (NCT04543188, NCT03332589, NCT04190628).

## Advancing Clinical Trials

Compared with other oncologic entities of similar incidence, such as breast, prostate, lung and colorectal cancer, relatively few ongoing or completed brain metastases-related prospective studies exist (Figure 1). In addition, brain metastasis trials are often difficult to

execute, complete, and interpret, in part due to heterogeneous patient populations, selection bias, effect of prior treatment, dropout, and difficulties with selection of a suitable primary endpoint. With regard to patient heterogeneity, study participants often vary with regard to underlying cancer type (particularly for local therapy studies), molecular alterations, underlying disease trajectory, intracranial and extracranial disease burdens, prior therapy, viable systemic options, prognosis, and functional status.[223,340,341] Patient heterogeneity contributes to effect modification and challenges in real-world application. For trials of novel systemic therapies among patients with brain metastases, patients with neurologic symptomatology or bulky intracranial disease have often been excluded, leading to estimates of response and recurrence that may only apply to patients with stable/treated brain metastases, asymptomatic disease, and a modest intracranial disease burden.[9,299] For example, in CheckMate 204, the intracranial response rate to dual-agent immunotherapy in nonsteroid dependent patients with asymptomatic brain metastases secondary to melanoma was 54%; the respective rate in an expansion cohort consisting of symptomatic or steroid-dependent patients was only 22%.[146] In addition, prior treatment, notably radiation, can confound interpretation of systemic response given the potential for radiation to durably control intracranial disease, and due to complexities in ascertaining which intracranial lesions have been radiated versus not. Moreover, obtaining Food and Drug Administration (FDA) approval for novel systemic therapies can ultimately be challenging given the historical need to show both intracranial and extracranial efficacy. Conversely, in local, brain-directed therapy studies, patient dropout can be significant,[238] leading to decreased power, difficulty obtaining study assessments, and a potentially compromised opportunity to identify a statistically significant benefit related to a novel intervention.

Regarding primary endpoint generation, the competing risk of systemic death and salvage options available for intracranial progression can compromise the viability of selecting overall survival as a primary endpoint, particularly for local therapy studies. Progression-free survival may also be of limited utility; for example, in studies examining omission of WBRT in lieu of stereotactic approaches among patients with a limited number of brain metastases, progression-free survival was nearly always better with WBRT even though stereotactic approaches now constitute the preferred approach.[223–225,247] The use of alternative survival-based outcome measures, such as neurologic survival, can be difficult to apply and interpret, in part due to a lack of a validated/accepted definition of this endpoint. In addition, local response and local recurrence can be challenging to delineate in the context of immunotherapy-related pseudoprogression,[342] bevacizumab/TKI-mediated blunting of contrast enhancement,[343] or necrosis related to stereotactic radiation,[187,262] each of which can cloud such delineations. Investigations centered on quality of life or neurocognitive function offer promise in characterizing key functional endpoints relevant to patients with brain metastases; although such outcomes may be especially relevant given that many patients cannot be cured and that a primary goal of treatment relates to maintaining/sustaining function and quality of life, such assessments can be especially challenging to obtain in patients who are impacted most by neurologic symptomatology, oncologic disease, and/or treatment leading to bias with regard to missing data. As a result, for some studies related to brain metastases, there may not be a "best" primary outcome measure.

Efforts to improve clinical trials relating to brain metastases are underway. The Response Assessment in Neuro-Oncology-Brain Metastasis (RANO-BM) working group has advanced the assessment of intracranial tumor response and delineation of study-related end points, including among patients managed with immunotherapy and local, brain-directed therapy (Table 10).[119,344,345] RANO-BM criteria is distinguished from RECIST by establishing the brain as a separate compartment and accounting for steroid use and clinical deterioration[346]; in addition to use within the domain of clinical trials, RANO-BM criteria have applicability for routine clinical care.[347] With regard to imaging, consensus guidelines outlining standardization of imaging protocols for patients in brain tumor-related trials have been published.[95] Moreover, the Food and Drug Administration has recently released recommendations regarding clinical trial eligibility for patients with brain metastases, emphasizing the importance of including patients with brain metastases on trials where feasible, defining enrollment parameters based on extent of CNS disease (treated/stable vs active vs leptomeningeal disease), and proposing specific situations

**Table 10**    RANO-BM Criteria for Response Assessment

| Parameter | Complete Response | Partial Response | Stable Disease | Progressive Disease |
|---|---|---|---|---|
| Target lesions | No evidence of disease | ≥30% decrease in sum of longest diameter of target lesions | Response between <30% decrease to <20% increase in sum of longest diameter of target lesions | ≥20% in sum of longest diameter of target lesions |
| Nontarget lesions | No evidence of disease | Stable/improved | Stable/improved | Unequivocal radiographic progression |
| Steroids | None | Stable/reduced | Stable/reduced | Not applicable |
| Clinical status | Stable/improved | Stable/improved | Stable/improved | Deterioration |

**Abbreviations:** RANO-BM, Response Assessment in Neuro-Oncology - Brain Metastases.

where exclusion may be justified.[348,349] In addition, systemic therapy-based trials are enrolling patients with active/unirradiated brain metastases.[8,317,334,350–352] Lastly, quality measures to monitor and improve the care of patients with brain metastases have been proposed.[353]

Multiple ongoing or recently completed prospective studies are pushing the historical boundaries of brain metastasis-related investigations. For example, increasingly, brain metastases-related trials are being focused on select subsets of patients, often linked by a histology or even specific molecular alterations. In this regard, NCT03994796 is a cooperative group study in which patients with specific mutations (CDK, PI3K/mTOR, NTRK/ROS1) are stratified and then receive alteration-specific targeted agents. A recently published randomized trial of tucatinib, capecitabine, and trastuzumab compared to capecitabine, trastuzumab, and placebo among patients with HER2+ breast cancer demonstrated an overall survival benefit to the tucatinib arm; this study enrolled patients with active intracranial disease, representing a shift from many prior studies.[317] The use of neurologic death as a primary endpoint is being explored via a tribunal approach in NCT03391362 (a phase II study of stereotactic radiation for SCLC) with neurologic death defined as marked, progressive radiographic progression in the brain accompanied by corresponding neurologic symptomatology in the absence of systemic disease progression/systemic symptoms of a life-threatening nature; this study will determine whether a consistent definition of neurologic death can be reproducibly applied among independent reviewers. In addition, all MRIs for the clinical course of a given patient are registered to minimize error related to patient positioning and generate greater inference regarding necrosis versus progression-based delineations (Supplemental Figure 1).

Although significant progress has been made with regard to the design and implementation of brain metastases-related prospective trials, numerous hurdles persist, as noted above. However, increasing recognition of the impact of brain metastases on a patient- and systems-level has reinvigorated efforts to advance the care of this population in need. Minimization of patient heterogeneity, refinement of eligibility criteria, improvements in primary endpoint generation, and advances in study conduct have potential to transform the management of patients with brain metastases.

## Summary

Brain metastases have garnered increasing attention among patients, providers, investigators, and health care systems, resulting in significant progress in management over recent years. Yet, significant challenges remain. Ongoing efforts have potential to further improve outcomes for this increasingly relevant population of patients.

## Supplementary Material

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

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