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Chapter

Innovations in Metastatic Brain Tumor Treatment

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Abstract

Metastatic brain tumors (MBTs) are the most common intracranial tumor and occur in up to 40% of patients with certain cancer diagnoses. The most common and frequent primary locations are cancers originating from the lung, breast, kidney, gastrointestinal tract or skin, and also may arising from any part of the body. Treatment for brain metastasis management includes surgery, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and chemotherapy. Standard treatment for MBTs includes surgery and SRS which offer the best outcomes, while the WBRT is still an important treatment option for patients who cannot tolerate surgery and SRS or patients with multiple brain metastases. Newer approaches such as immunotherapy and molecularly targeted therapy (e.g., small molecules and monoclonal antibodies) are currently being evaluated for the treatment of MBTs. In this chapter, we will review current available treatments for MBTs and discuss treatments that are undergoing active investigation.

Keywords: brain metastasis, chemotherapy, radiotherapy, targeted-therapy, neuroimaging

1. Introduction: epidemiology and pathophysiology

Metastatic brain tumors (MBTs) are the most common central nervous system tumors in the United States [1, 2]. Patients are living longer with cancer with the advent of imaging modalities leading to earlier detection and improved systemic therapies. As a result, the probability of patients developing brain metastases (BM) over time has increased [2]. A number of studies support the expected trend of rising MBT incidence. A cohort study in Sweden found the incidence for brain metastases doubled from 1987 to 2006 [3]. Another study from the Swedish National Cancer Registry reported that patients diagnosed with breast cancer from 2004 to 2006 had a 44% increase in risk in brain metastasis as compared to patients in 1998 and 2000 [4]. A forecast for greater frequency of metastatic brain cancer (MBC) emphasizes the need for continued innovation in MBT treatment.

Roughly 200,000 patients are newly diagnosed with MBC annually in the United States [5, 6]. The incidence rate for primary central nervous tumors was estimated at 6.4 per 100,000, while the incidence for metastatic brain tumors has been estimated between 8.3 and 11.3 per 100,000 [2, 7]. More recent studies suggest that MBTs may occur as much as 10 times more frequently than primary tumors [2, 8, 9]. For cancer patients, an estimated 8.5–9.6% will be diagnosed with brain metastasis [2]. In adults, the most common sources of brain metastases are lung, breast, melanoma, renal and colorectal cancer [10–13]. Another study of patients in Detroit from 1973

to 2001 found the incidence for brain metastases for melanoma (6.9%) and renal carcinoma (6.5%) superseded breast cancer (5.1%) as the second and third most common sources [5]. A 2002 study examined patients from 1986 to 1995 and found renal carcinoma was the second most common MBC followed by melanoma and breast cancer [14]. In contrast, MBC in children has the lowest incidence and has previously estimated at 1.5 per 100,000 between the ages of 0 and 14 years [15]. A study following children diagnosed with cancer at MD Anderson Cancer Center found 1.4% of individuals had a BM, which most commonly originated from sarcomas and melanomas [16]. Previous studies reported incidence as high as 4 and 4.9% among children diagnosed with solid tumors [17, 18]. For adults, melanoma, testicular and renal carcinomas have the greatest tendency to metastasize to the brain, but their relative scarcity translates to lower frequencies compared to other types of metastatic brain cancers [13] Whereas metastases in children most frequently emanated from neuroblastoma, sarcomas, and germ cell tumors [18–20].

Barnholtz-Sloan et al. reported that race, gender and age impact the incidence of brain metastasis. Shifts in these demographic features of MBC can be explained by the rising incidence of lung cancer among women compared to men [5, 21]. Investigation by Barnholtz-Sloan found that men had higher incidence percentage (IP%) of BM for each type of systemic cancer with the exception of breast and lung cancers. In patients with lung cancer, the cumulative incidence for BM in women was 21.8 and 18.9% for men [5]. There is a higher cumulative incidence of BMs in African Americans as compared to Caucasians for lung, melanoma, and breast cancers [5]. Renal cancers displayed a higher IP% among Caucasian patients compared to African American patients. Lastly, the IP% for colorectal cancer was similar between the two populations [5]. The frequency of BM increases with age for most cancer types. Primary cancers presenting with BM increases proportionally with age with a peak around 60 years old [22]. A 1996 study estimated incidence rates for MBTs by age and found the highest incidence was in the age bracket of 65–74 years at 53.7 per 100,000 [15].

1.1 Clinical presentation

MBTs might present with a number of different signs and symptoms. The most common clinical sign is headache, which occurs in as many as 50% of cases [23]. Headaches that are ≤10 weeks in duration have been suggested to be more predictive of BM [24]. These headaches usually can be generalized or localized. They can persist for hours and reoccur at various intervals. Tension headaches, migraines and even cluster type headaches are not uncommon. Lateralization of the headaches to the ipsilateral side only happened in the minority of cases [25]. The headaches have been suggested to be due to increase intracranial pressure due to mass effect and a resulting hydrocephalus. An even smaller number of patients (~20%) have a resulting papilledema due to increase intracranial pressure. Another common presenting symptom is nausea and vomiting. This has been suggested to occur in as many as 54% of cases to as few as 12% of cases [26, 27].

Focal neurological deficits are a common clinical manifestation of MBTs. They occur in approximately 40% of cases [28]. The deficits that patients suffer depends on a number of factors including number of BMs, areas of the brain affected, and more tumor specific factors such as growth, associated swelling or recent hemorrhage. These deficits can progress as the tumor increases in size. These symptoms can present acutely in a stroke-like manner due to hemorrhage or as a slow ominous progression. Weakness has been the primary presenting complaint in between 20 and 40% of BMs. Sensory deficits have been reported to be slightly less common than weakness.

Other frequently encountered symptoms included altered mental status, seizures, ataxia, and dysphagia. The actual rates of occurrence are not clear. These variations are largely predicated on the fact that MBTs unpredictably seed the central nervous system. Most frequently BMs seed the frontal lobe (32%). The parietal (18%), occipital (13%), and temporal (12%) lobes each make up a significant portion. Cerebellar metastases make up approximately 18% of BM. The least common area is the brainstem [26, 29, 30]. Studies have suggested that the sites of BMs vary based on the primary site of origin and cerebral blood flow. There are data that suggest that the differences in surface characteristics make specifics sites more conducive to invasion by circulating cancer cells. The exact mechanisms or characteristics have not been elicited [31].

1.2 Genomics

Metastatic tumors may have very different rates of occurrence and different responses to treatment. There are a number of studies that suggest that these can be explained by genetic and/or epigenetic differences. Research on BM models has shown idiosyncratic expressions of genes that mediate metastasis [32, 33]. Several chromosomal translocations are associated with the development of brain metastases. Lee et al. identified that regions 5q53, 10q23, and 17q23-24 were correlated with development of BM within 3 months of primary tumor diagnosis [34]. Specific genes have also been associated with development of BM in lung cancer such as PLGF, VEGFR1, c-MET, and CXCR4 [35–37]. Other genes suggest a greater risk for brain relapse [38–42]. Metastatic pathophysiology is not limited to protein-coding regions, since non-coding RNA regions are associated with many cancer types [43]. Studies documenting unique mutations in MBTs compared to the source tumor indicate lesions evolve in character and underscore the need for genomic evaluation for best-fit therapies [44]. Although the molecular mechanisms leading to early brain metastasis are poorly understood, these insights provide potential targets for therapy.

1.3 Microenvironment

A growing focus among researchers is understanding the dynamic interactions of cancer cells with astrocytes that may provide several novel therapeutic options. Following extravasation, individual cancer cells are surrounded by reactive astrocytes [45, 46]. Astrocytes serve as the first line of protection in the central nervous system (CNS) [45, 47, 48]. With regard to brain metastasis (BM), astrocytes reduce the number of potential metastatic cells by activating plasmin [45]. Adaptive cancer cells can evade these defense systems by expressing serpins [45]. Serpins represent a target for future therapies.

Neoplastic cells surviving this phase usually seed in the perivascular niche [49, 50], adjacent to neural stem cells and nearby nutrient and oxygen supplies [51–53]. Proliferation in perivascular niches establishes micrometastases where only a fraction of sites reach detectable volumes [54]. Recent research suggests the natural selection of micrometastases is regulated by reactive astrocytes in the microenvironment [55, 56]. Astrocytic-neoplastic interactions depend upon the presence of protocadherin 7 (PCDH7) which mediates contact between the cell groups [56]. Following interaction, gap junctions form and cell-cell communication occurs that increase cancer cell growth and resistance to chemotherapeutic apoptosis [57]. Born out of the pro-metastatic astrocytes research, silibinin represents a targeted therapy attacking the microenvironment with promising results [58]. Meclofenamate and tonabersat are another promising set of medications that target carcinoma-astrocyte gap junctions that suppressed brain metastasis in mice models [56].

2. Metastatic brain tumor diagnosis

Magnetic resonance imaging (MRI) is the current gold standard for brain mass evaluation. MRI provides a wide array of benefits including lesion detection and characterization as well guiding treatment by establishing differential diagnoses, guiding invasive procedures, and monitoring patients for changes over time. Within the past decade we have witnessed imaging transition from indirect diagnosis of lesions using cerebral angiography to precise lesion diagnosis by implementing multi-planar CT and MRI. Modern tumor imaging can be categorized as anatomic, metabolic, and functional (physiological) in nature. This section reviews conventional and advanced imaging techniques provided by CT, MRI, PET, and biomarkers as it relates to the management of metastatic brain cancer.

2.1 Computer tomography

Computed tomography images are obtained by transmitting precisely collimated beams of radiation through specimens at multiple angles. Detectors opposite the radiation source record absorbed and scattering of beams whereby computer algorithms derive attenuation at each location. Currently, multislice CT scanners (MSCT) implement a multilayered matrix system of detectors to generate registration simultaneously for several helical trajectories [59]. The chief advantage of MSCT is higher resolution and faster scan times. Metastases appear as isodense lesions or lower density relative to the density of normal brain matter in native CT scans. Tumor boundaries can be distinguished adjacent to edematous regions. Nonenhanced CT is capable of detecting neurosurgical emergencies such as hydrocephalus, hemorrhage, and mass effect. In cases where patients have implants that are not compatible with MRI, we still rely heavily on CT for diagnosis and to evaluate response to treatment. Another advantage of CT is its ability to detect the extent of bony destruction from calvarial metastases [60]. Sensitivity and ionizing-radiation exposure are the two main limitations when imaging for tumors with CT. Visibility of metastases can be enhanced with contrast-based injections typically with iodine-based injections [61].

Three-dimensional (3D) imaging technology has improved the standards of neurosurgical diagnostics and planning in general [62, 63]. 3D renderings convey greater information (e.g., the scope of bony involvement and destruction) and improves localization of abnormal lesions in relation to surrounding tissues. Combining 3D technology with CT angiography (CTA) helps elucidate tumor blood supply and their orientation with cerebral arteries. Visualizing vasculature information permits better planning for surgical access and the extent of tumor resection. CTA provides higher spatial resolution than MR angiography (MRA), but poorer contrast between arteries and surrounding tissues. One of the more useful CT technological advances in the treatment of brain tumors is perfusion CT. Perfusion CT (PCT) administers an intravenous bolus of contrast agent to evaluate changes in density characteristics of tissue. Quantitative estimates of hemodynamic perfusion cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), microvascular permeability (PS) can be acquired for monitoring the effectiveness of cancer treatment. This technique opens up the possibility for measuring the hemodynamics in brain tissue, tumors, and proximate regions. Perfusion methods estimate and quantify blood flow feeding brain regions through specialized workstations calculating CBF, CBV, MTT, and PS parameters for each voxel [64, 65] Initially, CT perfusion was utilized to evaluate the extent of ischemic brain damage by visualizing brain hypoperfusion within minutes of an ischemic attack [66, 67]. More recently, PCT has been implemented for brain tumor diagnosis and differentiation from adjacent

lesions based on hemodynamic characteristics [68, 69]. Visual perfusion analysis reconstructs parametric color maps that are proportional to the selected perfusion parameter. Maps codify the quantitative data into a visual system, which allows medical specialists to examine the vasculature supplying structures of interest [70]. It also allows greater appreciation of solid components and distinguishing the regions of viable neoplastic tissue. Parametric maps for CBF and MTT have been used to generate mean values for different metastatic tumor types, which may serve to predict the sources of tumors. A comparative assessment of perfusion parameters performed on varying lesion sizes found CBF values were higher than in smaller lesions. However, MTT values were not affected significantly with regard to lesion size. Presently, CTP is implemented for primary diagnosis of MBTs and assessing post-radiation changes. Changes in the perfusion parameters proved more effective for monitoring radiation therapy at earlier stages (2 months post-treatment) when compared to CT and MRI methods [71]. Lastly, positron emission imaging hybridized with CT image data (PET-CT) can serve to localize brain abnormalities with useful anatomical landmarks while correcting photon attenuation.

2.2 Magnetic resonance imaging (MRI)

MR imaging utilizes electromagnetic waves in radiofrequency ranges to generate incident energy and contrast between tissues. Advantages of MRI compared with CT include superior contrast in soft tissues, greater selection of contrasts between tissues, versatility of advanced imaging techniques, and lack of ionizing radiation [72]. Pulse sequences are different patterns of incident radiofrequency waves that generate multiple types of contrast between tissues. After a radiofrequency wave emitted by the scanner perturbs nuclei of the body, the body transmits a signal to MRI receivers. The returning waveform varies based on the rate of relaxation of the excited nuclei towards its initial state. Two types of relaxation are measured, i.e., longitudinal and transverse. T1 sequence is the time it takes longitudinal magnetization to return to 63% of its equilibrium value after excitation. While, T2 sequence is the same percent value for transverse magnetization. Each sequence has specific functions with particular advantages and disadvantages relative to others.

Typically, tumors have greater water content than brain parenchyma and thus exhibit hypoattenuation on T1-weighted images relative to parenchyma. This pattern is regularly altered with the presence of necrosis, fat, proteinaceous fluid, hemorrhage, and calcifications. MBTs, in particular, are roughly spherical, highly vascularized and tend to hemorrhage more than primary brain tumors. The effects of hemorrhage oftentimes obscure tumors and hematomas and require follow-up imaging, imaging with contrast or perfusion-based imaging to reveal an underlying image. Metastases develop in parenchyma and wide range of nonparenchymal regions including calvarium, diploic space, meninges, choroid plexus, and pituitary gland. Typically, contrast-enhanced MRI is the preferred imaging modality for evaluating metastases in these regions for its superior contrast, resolution, and multitude of sequences [73].

MR has higher sensitivity for recognizing small metastases compared to CT and CT/PET [74, 75]. Knowledge of the size, location, and number of metastases are essential in treating patients with MBs. The ability to detect very small tumors is essential in treatment. Multiple gadolinium-based contrast agents (GBCA) are available to enhance the sensitivity of MRI scans. These agents vary in biophysical properties but generally increase T1 relaxivity resulting in greater signal-to-noise ratios [76, 77]. Increasing GBCA leads to increased sensitivity, particularly for lesions smaller than 5 mm, but at the expense of increasing false-positive results [78]. In the same vein, stronger magnets (1.5–3.0 T) increase MRI field strengths and improves metastatic detection. Theoretical predictions suggest signal-to-noise

ratios (SNR) should improve linearly as field strength increases [79]. Altering these two variables has profoundly improved sensitivity for detection of suspected metastatic lesions [80, 81]. The emergence of 7 T MRI machines may allow for better lesion detection while reducing the contrast dose and scan time [82]. In light of the association between GBCA and nephrogenic fibrosis, higher doses may be avoided without compromising scan quality. Magnets have been manufactured for 8 and 9.4 T systems are currently being used on humans [83]. We expect image quality and tumor elucidation to continue to improve into the near future. Another option for enhancing detection is to increase time delay between contrast administration and T1 acquisition [84]. The development of machine learning and automated detection of brain lesions with human interpretation could generate greater sensitivity and accuracy of lesion characterization [85, 86].

The hallmark of malignancy is uncontrolled cell proliferation and an increase in blood supply once the tumor reaches 2–4 mm^3 [87]. Tumor growth leads to focal hypoxia and hypoglycemia which stimulates angiogenesis. Tumor-derived blood vessels differ from normal brain vessels in vascular consistency, fragility, permeability, trajectory underlie the differences observed in hemodynamic parameters measured in MRI perfusion [88–90]. MRI perfusion technique administers a bolus of contrast agent and calculates the intensity of the MR signal during its transit [91–93]. CBF, CBV, and MTT maps assess tumor vascularity similar to PCT, but perfusion MRI avoids several pitfalls, e.g., radiation exposure and iodine-based contrast agents. MR perfusion has several common techniques including dynamic susceptibility contrast (DSC), arterial spin labeling (ASL), and dynamic contrast-enhanced (DCE) which have different tradeoffs. Ktrans is a DCE derived perfusion-based metric that describes leakiness of blood vessels [94]. ASL can be acquired without GBCA by labeling blood water protons to generate an endogenous tracer [95]. MRI perfusion also maintains its superior anatomical characterization of tumors along with hemodynamic measurements [96, 97]. While perfusion MRI has existed for over 20 years, it has not been used as much as other techniques and has not become standard of care for brain tumor patients [98, 99]. Reasons for under-utilization include an unclear reimbursement scheme, lack of approved GBCA for perfusion MRI, insufficient methodological standardization, and limited evidence supporting a significant advantage for patients than current practices [99]. Despite these limitations, perfusion MRI is an intriguing candidate for determining tumor grade, prognosis and therapeutic efficacy.

2.3 Metabolic imaging: PET

Positron emission tomography (PET) is an imaging technique that depicts the metabolism of brain metastases and other brain lesions [100]. A wide range of PET tracers are labeled with a positron-emitting radionuclide to promote decay by positron emission. Collisions with nearby electrons produces two gamma-rays with a fixed energy separated by 180°. Detectors absorb the photon energy and reemit the energy as visible light. Visible light is converted into electrical current, which is proportional to the incident photon energy and reconstructed into a 3D image [101–103]. Common positrons employed with tracers consist of ^{18}F (110-minute half-life) and ^{11}C (20-minute half-life). While the most common tracer is FDG, a glucose analog taken up by insulin-dependent GLUT 1 transporters. Phosphorylation of the tracer inside the cell prevents further metabolism resulting in greater uptake in cells that are metabolically active. Image registration is exceedingly important to accurately correlate PET metabolic findings with MRI abnormalities.

There are several limitations for FDG tracers within the brain. One important problem is the high background activity present in the cortex and basal ganglia as

a result of these tissues elevated glucose consumption. High background activity sizeably degrades the SNR and reduces image sensitivity, which is critical for distinguishing small lesions from cortical regions [104]. Resolution is another hindrance (5 mm compared to sub 2 mm for MRI) stemming from multiple technical factors. As a consequence, both sensitivity and specificity for FDG PET are reduced for the detection of brain metastases when compared to MRI [75, 105, 106]. Therefore, FDG uptake is not specific for solely brain tumors, but may also indicate nontumorous lesions such as inflammatory lesions, focal epilepsy, and recent ischemic infarcts.

Despite the aforementioned limitations for diagnosing lesions, PET is particularly adept at differentiating between recurrent or residual tumor and necrotic tissue post-radiation therapy [107]. One study found that sensitivity of FDG-PET for detecting recurrent tumors versus radiation-induced necrosis was 75% and the specificity was 81% [108]. However, significant variation has been observed for low-grade, high-grade tumors, inflammatory and other brain lesions [109]. Another utility of PET is discerning responders from nonresponders in its earliest stages during chemotherapy treatment. Identification of nonresponders has practical implications in avoiding essential bone marrow reserves, patient quality of life, and unnecessary expenses on ineffective treatment [110].

Constraints posed by FDG tracer has researchers focused on developing alternative tracers to capture greater metabolic information and produce favorable imaging outcomes. Tracers reflecting amino acid metabolism help to characterize metastatic brain tumors. Amino-acid tracers take advantage of the L-amino acid transporter type 1 system to avoid the inefficient process of blood-brain barrier (BBB) breakdown for uptake. Alternative uptake for amino acid tracers greatly reduces brain background activity and correlates with a variety of malignant activities, e.g., cell proliferation and angiogenesis. Amino acid tracers appear to perform better than FDG tracer in differentiating postradiation changes from recurrent tumors. Even in brain lesions without increased uptake for FDG-PET, sensitivity and specificity for tumors (89 and 100%) were obtained [111].

2.4 Proton magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive MRI technique that produces metabolic spectra rather than producing anatomic images. Several nuclei (proton, carbon, sodium, fluorine) can be used but proton is the most common because of its high sensitivity. MRS can be used to measure the metabolite concentrations or the chemical composition of tissues. Commonly measured metabolites include N-acetyl aspartate (NAA) and choline (Cho) that are markers for neuronal integrity and membrane turnover in gliomas. Lactate, lipids, amino acids, and myoinositol can also be detected by MRS [112, 113]. MRS imaging of peri-enhancing brain regions may be useful for distinguishing solitary metastases from primary brain tumors. Gliomas often show elevated Cho in surrounding tissue, whereas MBTs are generally encapsulated and do not exhibit elevated Cho signals [114, 115]. Elevated Cho and lipid signals on MRSI make glioblastomas more likely than MBC [116]. MRSI may also have a role in evaluating prognosis based upon metabolite ratios [117–119]. However, MR spectroscopy was not adept at differentiating metastatic brain tumors of disparate etiologies. For that reason, its utility in MBT diagnostics is unproven [59].

2.5 Functional imaging

A unique feature of MRI is the ability to visualize thermal or Brownian motion of water molecules in the brain tissues. Diffusion properties of water in an isotropic medium is represented by Fick's law relating molecular flow vectors to

concentration gradient [120]. Water molecules in solutions above absolute zero exhibit Brownian motion, which in pure water behaves randomly and isotropically. The higher the diffusion coefficient value, the greater the distance molecules can move within the same time period. Apparent diffusion coefficient (ADC) acts as a surrogate for this motion and can be calculated by MRI techniques. B values are parameters of DWI pulse sequence and represent the diffusion weighting. DWI acquisition with a minimum of two distinct b values enables derivation of diffusivity for each individual voxel. Multiple images with varying b values generate ADC maps. Molecular water movement occurs within individual cells (restricted diffusion) and extracellular spaces amongst structures that constrain the motion of molecules (free and hindered diffusion). Generally, the magnitude of diffusion coefficient is dependent on microstructural organization and its respective chemical composition. Abnormal areas of reduced diffusion appear bright on DWI. The first diffusion-weighted image (DWI) was procured in 1985, but DWI did not reach clinical practice until the third generation of MR scanners emerged [121, 122].

On diffusion-weighted MR imaging, MBTs are characterized by heterogeneous changes on DWI and ADC maps. Homogenous MRI signals on DWI usually originated from solid lesions. A variety of biophysical conditions of tissue can result in reduction of diffusion. For instance, edema and increased cellularity can inhibit the motion of water molecules. DWI is considered the standard imaging technique for early diagnosis of cerebral ischemia, as it visualizes impaired diffusion following cytotoxic edema and microstructural damage to cells. In addition to this clinical application, DWI is highly sensitive to cerebral abscesses, epidermoid cysts, traumatic shearing injuries, encephalitis, and postoperative brain injury. One major drawback to DWI is the sensitivity to lesions containing high concentrations of magnetic materials, e.g., blood products, calcium, metal, bone or air. This is particularly true for postoperative DWI imaging.

2.6 Diffusion tensor imaging

Within certain brain tissues, barriers restricting water diffusion are isotropically distributed meaning water diffuses in all directions. At other sites in the brain, barriers will be distributed anisotropically leading to directional diffusion perpendicular to the barriers. In white matter, diffusion runs parallel to axonal projections and myelin fibers and restricted perpendicularly by biological membranes. Diffusion tensor imaging applies diffusion gradients in three orthogonal directions. When the three directions are compared, important differences become visible. The corpus callosum exhibits these differences with the greatest intensity. When diffusion gradients are applied in the z direction, diffusion is greatly restricted and has low signal intensity. When the gradient is applied in the x direction, diffusion is unrestricted in the right-to-left orientation and parallel to the corpus callosum fibers. This region of the brain displays anisotropy with the greatest intensity. Tensor models help quantify diffusion anisotropy by measuring ADC in three perpendicular directions x, y, and z and all combinations of the selected directions. Diagonal elements are transformed to coincide with the principle axis of diffusion for each voxel. New diagonal elements correspond to three eigenvectors and three eigenvalues codifying the main directions of diffusion and associated diffusivities (radial, axial, median). Fractional anisotropy (FA) measures the mean anisotropic diffusion. Color-coded maps can then be developed corresponding to directionality of water movement along axons.

DTI-tractography is a post-processing method for selecting white matter pathways in the brain. Fiber bundles in the brain correspond to the color maps. Diffusion tensor MRI is the means for evaluating the brain with attention to the

anatomic microstructure or brain white matter. These white matter maps can then be used to infer functional pathways. This knowledge allows neurosurgeons to plan surgical resections with a better margin of safety. Before the onset of modern brain mapping, complications rates for brain tumor resections were as high as 26% [123–126]. DTI and presurgical brain mapping have made a tremendous impact on surgical risk-benefit analysis and outcomes following surgery [127]. Tractography provides the qualitative information for assessing nerve bundle status, whether there is mass effect, tumor infiltration, edema, or functional reorganization [128]. Mass effect often leads to deviation in nerve tracts. Infiltration refers to any section of the tract with lower anisotropy but preserved morphology. Degeneration of tracts can be visualized with reduced fiber size or lower anisotropic values. Finally, fibers may appear interrupted or discontinuous indicating organizational alteration lesions. Appreciation of these features by surgeons allows for preoperative planning for maximal resection, targeting specific regions for biopsy, and avoiding functional tissue. DTI is a promising imaging technique for examining microscopic differences in tumors. In combination with intraoperative localization techniques, neurosurgeons can tailor presurgical mapping data to reduce operation times by testing language and motor functions while dissecting along tumor borders. Electrical stimulation is one method implemented for testing the white matter function [129, 130]. Transient speech or language deficit during dissection means imminent white matter injury is within millimeters beyond the dissection plane. Importation of DTI mapping data into neuronavigation systems allow real-time interaction with spatial relationships between lesions and functional nerve pathways.

2.7 Advanced diffusion imaging

High angular diffusion imaging (HARDI) method detects diffusion greater directions than DTI. HARDI implements 55 to over 100 gradient directions as compared to the standard 6 gradient directions in DTI [130]. The HARDI model estimates fiber orientations (orientation distribution function) that minimizes scan acquisition time compared to other methods (diffusion spectrum imaging). By changing from an ellipsoid model to orientation distribution function, HARDI appreciates multiple fibers in a single voxel. Scan acquisition time for DTI is roughly 3–10 minutes, whereas HARDI requires a minimum of 12 minutes. HARDI scan times are more reasonable for research and clinical use as opposed to other novel techniques [130].

By propagating fiber trajectories in multiple alternative directions, HARDI is more sensitive in picking up fibers displaced by brain lesions. White matter critical for speech, language, and motor functions better delineated by HARDI in cases where lesion-induced deviation or interruption may occur. Corticospinal tracts (CST) near the centrum semiovale run against crossing white matter tracts from the corpus callosum and superior longitudinal fasciculus [131]. Identifying motor fibers represented by CST is critical for presurgical brain mapping in tumor resection cases.

Neurite orientation dispersion and density imaging (NODDI) is a recent diffusion MRI technique detecting microstructural features of brain tissue with higher resolution than DTI [132, 133]. NODDI maps both gray and white matter microstructure. Detection of diffusion for both dendrites and axons constitutes the term neurite. Neurite density (intracellular volume fraction) and orientation dispersion are calculated using 17 b values and 153 gradient directions, making it tedious for clinical translation [134]. Quantifying neurite morphology in terms of density and orientation provides alternative information for the structural basis of brain

disorders. Branching complexity can be computed in terms of dendritic density. Areas with less complex dendritic structures tend to engage in early information processing, while regions with greater complexity participate in the end stages of information processing [135]. Changes in neurite morphology is associated with development as humans age [136], numerous neurological disorders including multiple sclerosis [137], amyotrophic lateral sclerosis [138, 139], and Alzheimer's disease [140].

Prior to the advent of NODDI, changes in the brain microstructure from brain disorders were studied using scarce postmortem tissue samples. There is growing evidence that neurite morphology from NODDI methods is comparable to independent measures derived from histology [141]. NODDI provides a promising tool for differentiating glioblastomas from solitary brain metastases and assessing tumor malignancy grades [142–144].

3. Metastatic brain tumor therapeutics

3.1 Surgery

Despite advances in other technologies, surgical resection of BMs remains a mainstay of treatment. Surgical resection provides a number of immediate benefits to patients including symptomatic relief from BMs through resolution of mass effect and reducing edema [145]. Often this is for emergent situations in which complications, like increased intracranial pressure, become life threatening. Surgical resection of the tumor can also be a non-pharmacological solution to seizures. The epileptic medications can have significant interactions with chemotherapy due to inhibition of the cytochrome p450. Another valuable product of surgical resection is histological evaluation of the tumor. This gives pathologist a change to determine the source of metastatic tumors in the event of undiagnosed primary disease, and also the opportunity to evaluate the genetic variations to help guide further clinical decision making.

Aggressive surgical resection of BMs of solitary tumors has gained greater popularity in the last few decades. This type of management gained more traction in the 90s and early 2000s when studies began to show benefits for surgical resection over radiation therapies. Studies demonstrated a reduction in local recurrence, increase life expectancy, and improved quality of life [146–148]. The difficulties in assessing the indications for surgical resection over other treatment modalities have led to the development of nonograms like recursive partitioning analysis (RPA) that classify MBT patients into three classes. Class I patients have a Karnofsky Performance Status (KPS) ≥ 70, are younger than 60 years of age, have a well-controlled primary tumor and metastatic disease that is limited to the brain [149]. These patients have been shown to be the best surgical candidates of the RPA classes. This has demonstrated that subgroups of this patient population will benefit from more aggressive treatment. Various nonograms have been developed in more recent years to help define this population of patients more clearly. This has been somewhat of a moving target as surgical advancements have been made which can improve outcomes through reduced surgical complication and more accurate resection of tumors and tumor margins.

3.2 Augmented reality

A number of technological advancements over the last couple of decades have culminated to allow for new developments in the realm of augmented reality (AR)

use in surgery. Modeling of patient-specific anatomy and pathology has become easier to produce and more accurate. With this and other advancements like smaller, less bulky AR hardware, intraoperative use of AR more feasible. One of the most difficult obstacles AR is facing is determining the best method for image alignment and maintaining this alignment during tissue movement [150]. Several studies have demonstrated that some of these techniques have an accuracy that meets the clinical requirement of under 2 mm [151, 152]. One study even demonstrated an accuracy of 0.8 ± 0.25 mm for projecting images on the skull and brain [153]. This can allow the surgeon direct visualization of the tumor and has the potential to increase the accuracy of resection. It has been demonstrated that AR has shown to be beneficial of a 2D approach in rates of correct localization and in efficiency [154]. It has also been demonstrated that there may be no difference in terms of error between operators [155].

AR technology requires much more work before being used routinely in the operative setting. Larger scale studies are needed to compare AR in tumor resection to other techniques like fluorescence guided surgery. These studies need to determine whether AR improves clinical outcomes, such as reducing morbidity, mortality, and local tumor recurrence. Headset technology and computing platform limitations with regard to field of view, positional tracking and coregistration with moving tissue need further development. The larger hope for developers is integrating artificial intelligence, robotics and AR technology to merge machine-learning with pre-programmed trajectories and spatial parameters from the overlay [156].

3.3 Whole brain radiotherapy

Whole-brain radiotherapy had long been the standard of care for the management of patients with brain metastases (BM). Toxicities associated with whole-brain radiotherapy has led to greater selectivity for its use. Multiple Radiation Therapy Oncology Group (RTOG, now NRG) have examined optimal WBRT dose regimen [157–160]. Typical WBRT fractionation schedule consisted of 20 Gy in five fractions, 30 Gy in 10 fractions, or 37.5 Gy in 15 fractions to produce noticeable effects on imaging [161]. Multiple randomized trials have shown WBRT is an effective treatment for controlling intracranial metastases and preventing new occurrences [162–165]. Studies have also reported that WBRT is associated with both stabilized or improvements in neurological signs and symptoms [166–168]. Despite the benefits of tumor control and neurological improvements, routine use of WBRT for all patients is still controversial. The QUARTZ trial examined patients with nonsmall cell lung cancer (NCLC) patients with BM [168]. Over 500 patients were evaluated comparing patients receiving WBRT with supportive care. The trial reported no difference in survival, quality-adjusted life years, or steroid use. This study suggests that WBRT provides little to no benefit for patients unsuitable for surgical resection.

Routine use of WBRT as an adjuvant for patients with BM following resection remains controversial [162]. A randomized trial in 1998 examined WBRT after surgery and found WBRT was associated with lower rates of recurrence and less neurologic death, however, no improvement in overall survival was reported. A phase III randomized trial evaluating adjuvant WBRT after surgery versus solely stereotactic radiosurgery (SRS) or surgical resection in patients with one to three MBTs found greater control by WBRT than the alternatives [164]. In 2016, another phase III trial compared postoperative SRS with post-resection WBRT and found 6-month cognitive deterioration was worse in the WBRT group [169]. Although cognitive deterioration was worse following WBRT, intracranial control was still better in the WBRT group than the SRS group. No overall survival benefit was reported for WBRT and quality of life was worse.

In an effort to prevent new metastases WBRT has been combined with SRS in multiple randomized control trials (RCTs). Despite increased tumor control, multiple trials have shown no survival benefit by adding WBRT [163, 164, 170]. Furthermore, patients with WBRT following SRS had worse memory, verbal fluency and quality of life outcomes [170]. Novel WBRT techniques have been developed to preserve neurocognitive and quality-of-life by avoiding the hippocampus during treatment. RTOG studied the effect of hippocampal avoidance and found much lower declines in Hopkins Verbal Learning Test—Revised compared to traditional WBRT [171]. Pharmacologic therapy has provided another method for greater neuroprotection after WBRT. Memantine and donepezil have shown some potential in reducing the rate of cognitive decline and memory loss in patients [172]. Limitations in these studies necessitate more RCTs to validate these protective therapies [173].

3.4 Stereotactic radiosurgery

SRS is a treatment for MBTs that converges multiple, well-collimated beams of ionizing radiation to tumors, while reducing toxic exposure to surrounding brain tissues. In many cases, SRS can be performed as a direct alternative to surgical resection. SRS is often preferred over surgical resection for tumor located within or near eloquent brain structure for in areas that may be challenging to access such as the brainstem, thalamus, and basal ganglia [174, 175]. In addition SRS, may be used as an adjuvant following resection. Several retrospective studies and one incomplete RCT have compared SRS + WBRT versus resection + WBRT and SRS versus resection + WBRT. Generally, these studies show no significant difference in outcomes between treatment groups for median survival, neurologic death, or functional outcome [176–180]. Since survival outcomes are the same for surgical resection and SRS, many institutions perform resection in cases with unclear histology, significant mass effect or patients with neurological deficits. Radiosurgery is the primary option for tumors smaller than 3 cm in diameter. Overall, SRS provides high local tumor control rates, low toxicity, and reduced risk of hemorrhage, infection, and tumor seeding [181, 182].

More recently, MBC is managed with SRS in combination with targeted agents and immunotherapies. SRS and BRAF inhibitors have been safely combined for cases of melanoma brain metastases with no resulting toxicity [183, 184]. Several studies demonstrated greater median survival for patients treated with SRS and targeted therapies in melanoma and nonsmall cell lung cancer brain metastases [185–187]. However, some studies have not shown a benefit when combining SRS with targeted agents [188, 189]. Concurrent delivery of SRS and immunotherapy may enhance the effectiveness of SRS. Several studies have reported better outcomes after treating metastatic brain melanoma with combination radiosurgery and immunotherapy [221, 222]. One downside to this treatment is the inflammatory response may be overactive resulting in elevated peritumoral edema and more severe neurologic symptoms [190, 191]. Efficacy and safety of concurrent SRS and immunotherapy needs further investigation.

3.5 Chemotherapy

Cytotoxic chemotherapy for metastatic brain cancer is currently considered when surgical resection and radiation therapies are not adequate or sufficient for treatment. This is often the case for patients with lower prognostic factors such as patients in RPS class II or III. Patient who have no targetable genetic factors and for which immunotherapeutic agents are inappropriate or contraindicated are

considered for cytotoxic chemotherapeutic agents. The agent(s) change based on the primary tumor. A number of phase II and III trials have evaluated the role of chemotherapy for NSCLC MBTs. Patients were treated with six cycles of cisplatin and pemetrexed followed by WBRT in one trial and recorded a response rate of 34.9% [192]. Median survival in the same study was 7.4 months. A more recent cisplatin/pemetrexed study examined patients with BM from lung adenocarcinoma. Overall response rates were comparable to the aforementioned study with median overall survival of 12 months [193].

A randomized phase III trial reversed the order of treatment in patients with NSCLC MBTs where WBRT was followed by chemotherapy [194]. In this study, patients received cisplatin and vinorelbine for six cycles. Intracranial response rates were similar for both the group receiving chemotherapy alone and those receiving WBRT early and concurrently [194]. Another study evaluated paclitaxel and cisplatin chemotherapy in MBTs from NSCLC. The response rate after completion of the course resulted in slightly higher response rates (38%) compared to previous trials. Multiple chemotherapeutic agents have been studied for the treatment of MBTs from breast cancer. Cisplatin, etoposide, cyclophosphamide, high dose methotrexate and 5-fluorouracil have achieved response rates over 50% [195, 196]. Innovation to systemic chemotherapy for brain metastases has been modest with regard to drug development. Modifications to drug delivery ranging from direct injection, convection-enhanced, and implantable seeds have been examined for efficacy [197–200].

3.6 Brachytherapy

Brachytherapy delivers high doses of radiation with small pieces of radioactive material placed within the resection cavity for treating residual tumor. Brachytherapy enables delivery of customizable doses for sparing of functional tissue. Brachytherapy seeds have been used in neurosurgery for over a half-century with mixed results [201–203]. Isotypes used in brachytherapy changed since the 1960s. More recently, cesium-131 and iodine-125 are now replacing gold and iridium-based isotypes. Modern brachytherapy has been studied for the treatment of meningiomas, gliomas, and metastases [204, 205]. Intraoperative brachytherapy may also be used as salvage treatment for recurrent cancers [206]. Recently, a randomized trial evaluated cesium-131 for the treatment of MBTs [207]. Twenty-four patients underwent total resection followed by intraoperative placement of cesium-131 with a planned dose of 80 Gy [207, 208]. The patients had no local recurrence, symptomatic radiation necrosis, and minimal surgical morbidity. Despite limitations in the study including small sample size, these promising results confirm the need for more robust trials.

3.7 Laser interstitial thermal therapy

MR-guided laser interstitial thermal therapy (LITT) builds upon previous thermal ablation technology with safer and more accurate results. LITT is performed by implanting a laser catheter into the tumor and heating it to temperatures monitored by MRI thermography. Patients often return home the day after treatment. Two studies have shown promising results for tumors failing to respond to radiotherapy. LITT is minimally invasive and requires only a 2-mm access port. Four patients with six tumors were treated with LITT without complications and no recurrence within 90-day follow up [209]. Another study demonstrated similar results using LITT for five metastases [210]. More recent studies have bolstered LITT in larger sample sizes as an alternative option for

patients unresponsive to radiotherapy. Ahluwalia et al. reported LITT stabilized the Karnofsky Performance Scale (KPS) score, prolonged quality of life, reduced steroid usage with minimal complications [211]. With the advent of real-time monitoring and damage estimation, LITT has emerged as a valuable management modality for metastatic tumors. Larger scale trials need to standardize protocols and specify indications [212].

3.8 Checkpoint inhibitors

Immunotherapies are treatments that activate the immune system to destroy cancer and have been around for over a century. The brain has limited infiltration of leukocytes [213]. Following an injury or metastasis, infiltration of non-resident cell will take place. Metastatic brain infiltrate consists of a mixed array of immune cells, specifically, CD3+, CD4+, CD8+, FoxP3+, CD45RO+ lymphocytes, natural killer (NK) cells, and macrophages [214, 215]. Patient survival is correlated to the quantity of tumor-infiltrating leukocytes in peritumoral edema [214]. In the last decade, exciting advancements from a group of monoclonal antibody treatments called checkpoint inhibitors. Checkpoint inhibitors act to prevent lymphocyte suppression. Several clinical trials have studied immune checkpoint inhibitors efficacy on patients with MBC [216–218].

Programmed cell death proteins (PD-1) are immunomodulatory molecules expressed on the surfaces of immune cells to prevent T-cell overactivation [219]. There are two ligands for PD-1 (PD-L1 and PD-L2) found on the surface of tissue macrophages that regulate the immune response of T cells against pathogens and foreign cells [220]. Cancers are known to express PD-L1 and PD-L2 on their surface to suppress the cytotoxic T lymphocytes (CTLs) response. Nivolumab and pembrolizumab are both anti-PD-1 antibodies that selectively block PD-1 receptor interaction with ligands PD-L1 and PD-L2. These antibodies were approved by the FDA based on efficacy data from phase III trials for the treatment of melanoma, NSCLC, renal cell carcinoma, and head-neck cancer [221–228]. Three new PD-1 antibodies against PD-L1 (durvalumab, atezolizumab, and avelumab) are currently being investigated in phase III trials. Despite a large number of studies examining. Caponnetto et al. provide a timely overview of immunotherapy studies for the treatment of brain metastases [229]. PD-L1 antibodies have been studied on NSCLC brain metastases that resulted in the majority of participants discontinuing treatment from exacerbation of neurologic symptoms [230]. A study by Goldman et al., did not report high toxicity rates in the treatment of NSCLC BM with nivolumab and observed improved overall survival for patients [231]. Large prospective studies will be needed to confirm initial results.

Cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) is another similar checkpoint molecule regulating CTL activity. CTLA-4 is on the surface of CTLs, which connect with CD28 and deactivate T cells [232]. Ipilimumab, an anti-CTLA-4 antibody, has demonstrated promising results in multiple trials in patients with metastatic melanoma [233, 234]. Another Phase III trial reported enhanced overall survival in patients with advanced melanoma and BM [233]. More tests will be required to determine if ipilimumab provides durable responses against melanoma, which is a limitation for BRAF inhibitors. Combination ipilimumab and nivolumab has shown promising results in several studies [228, 235, 236]. Unfortunately, there are no studies testing combination therapy on non-melanoma tumor types. Combination immunotherapy with radiotherapy is limited MBT studies, but radiation necrosis is an emerging concern [237]. Long-term effects of combination treatment and more robust studies to determine its efficacy.

3.9 Adoptive cellular therapy

Adoptive Cellular Therapy (ACT) for the treatment of BM extracts T cells from the patient, genetically modify and culture the cells in vitro before returning them to the same patient. Growth factors are usually added to the cells prior to reintroduction to stimulate survival and expansion in vivo [238]. There are three forms of ACT that use T cells including tumor-infiltrating lymphocyte (TIL) therapy, chimeric antigen receptor (CAR) T-cell therapy, and endogenous T-cell (ETC) therapy. Similar to the process described previously, TIL therapy removes T cell from the patient's tumor, expands them in vitro with an immune signaling molecule (Interleukin-2), before being infused back into the patient [239]. CAR T-cell therapy genetically engineer T cells to recognize specific tumor antigens. ETC neither requires a tumor source nor genetic engineering. Rather, ETC selects intrinsically tumor-reactive T cells in the peripheral blood and expands them. These cells are exceptionally rare and require intense processing methods. Several studies have reported successful treatment of melanoma brain metastases with ACT or combination therapy that includes ACT [240–243].

3.10 Targeted cancer therapy

Targeted cancer treatments are treatments that target specific proteins, processes, and pathways that have become pathological in cancer cells. Generally, targeted entities involve surface proteins on cancer cell membranes, faulty or overactive enzymes in cytoplasm, or faulty cell signaling pathway. The majority of these therapies can be classified under two categories, namely, monoclonal antibodies or kinase inhibitors. It is estimated that 18% of patients with MBTs are susceptible to targeted therapies [244]. Recent developments in the field of tumor biology have presented new therapeutic targets with greater BBB penetrance for a variety of metastatic brain cancers.

3.11 Breast cancer and brain metastases

MBTs occur in 10–15% of patients with breast cancer, although studies based on findings at autopsy suggest that the incidence is closer to 40% of cases [245]. Human epidermal growth factor receptor-2 (HER2) is overexpressed in approximately 15–20% of patients with breast cancer [246]. HER2-positive breast cancer is associated with higher rates of MBTs and prolonged survival than HER2-negative breast cancer [246]. Trastuzumab, a recombinant monoclonal antibody against HER2, improves tumor control and confers a survival benefit for HER2-positive patients [246]. However, the relative higher incidence of BM when treated with trastuzumab has prompted development of alternative therapies with enhanced blood-brain barrier (BBB) penetrance [247]. Lapatinib, a dual tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR) and HER2, has been used for treating patients with resistance to trastuzumab [248]. In contrast to trastuzumab, lapatinib can penetrate the BBB when combined with capecitabine. The intracranial response rate was 66% in a Phase II study of HER2-positive breast cancer patients with brain metastases [249–251]. By comparison, lapatinib as a single agent demonstrates only modest activity [249, 252]. Similar findings were observed with neratinib in combination with capecitabine [253, 254].

Triple-negative breast cancer (TNBC) does not express hormone receptors and presents a greater challenge identifying molecular targets. Approximately, 10–15% of breast cancers are TNBC, which have higher incidence and reduced survival [245, 255]. One potential target is poly adenosine diphosphate ribose polymerase (PARP) inhibitors

that potentiate chemotherapy and radiotherapy [256]. PARP inhibitors can be effective as single agents for BRCA associated breast and ovarian cancers. Iniparib has begun Phase II trials and in combination with irinotecan yielded a modest benefit for treatment of TNBC [257]. Another potential candidate for TNBC are histone deacetylase (HDAC) inhibitors that prevent transcription of particular genes and expression of cellular activities [258, 259]. Vorinostat, an HDAC inhibitor, has prevented brain metastatic colonization by over 62% in mouse models [260]. Polo-like kinase 1 (Plk1) is another well-performing molecular target in BM from breast cancer. Inhibitors of Plk1 prevented the development of large BMs by 62% and prolonged survival by 17% in mouse models with breast cancer [261]. Plk1 inhibitors may be a new target for MBT prevention and treatment [262].

However, studies reported to date have not demonstrated improvements to overall survival with these treatments. An important factor for these findings may be the failure of targeted therapies to achieve complete responses in the brain [263]. To address these shortcomings, researchers are unraveling the mechanisms for therapeutic resistance, revising brain metastasis models, and developing more penetrative treatments. Specifically, these modifications include patient-derived xenografts, 3D bioprinted metastatic models, genetically-modified mouse models, and nanoparticles for enhanced drug delivery [264]. Vorinostat has undergone a Phase I clinical trial to study its use as a radiosensitizer for WBRT [265]. Treatment was well-tolerated by patients and is expected to enter a Phase II study.

3.12 Lung cancer and brain metastases

Approximately 40–50% of patients with lung cancer are diagnosed with MBC during their disease course [266]. Small cell lung cancer (SCLC) has a greater tendency to metastasize early in its development [267]. MBTs are more commonly encountered in this histological type than NSCLC. Overall, lung cancer patients commonly present with brain metastases at diagnosis [268]. As of today, no targeted therapies have been developed for BM in SCLC.

Roughly, 2–4% of lung cancer brain metastases originate from EGFR mutant [269]. Another 5% of lung cancer MBTs derive from ALK-translocated primary tumors (ibid). Gefitinib and Erlotinib are two first-generation EGFR TKIs approved for the management of EGFR mutant NSCLC [270]. Recent evidence has validated its effectiveness in decreasing the tumor burden by over 30% in over 80% of patients [271, 272]. The median time to progression was also extended for patients treated with erlotinib from 11.7 to 5.8 months [271]. Other studies have confirmed these findings with overall progression-free survival (PFS) of 15.2 months versus 4.4 months for patients without the mutation [273]. Gefitinib or erlotinib may be useful as prophylaxis since they were found to reduce the risk of progression in patients with NSCLC [274]. Similar findings have been observed for another EGFR inhibitor, osimertinib [275]. Osimertinib outperformed patients receiving chemotherapy in a Phase III trial with brain metastasis patients (ibid). Crizotinib is the first TKI approved for ALK-translocated lung cancer [276]. However, it exhibited suboptimal BBB penetration. Next-generation TKIs (e.g., brigatinib and alectinib) targeting translocated ALK have greater penetrance with greater intracranial responsiveness [277, 278].

3.13 Melanoma and brain metastases

Melanoma brain metastases have also benefited from targeted therapies. MBTs are found approximately in 10–20% of patients with melanoma, although autopsies suggest the incidence is as high as 70% in such patients [279]. Targeted therapies

such as BRAF V600 TKI dabrafenib have exhibited 39% intracranial response in BMs that increased to 58% in studies combining dabrafenib and trametinib [280, 281]. Another BRAF inhibitor, vemurafenib, recorded a response rate of 18% in another trial [282]. In a previous study, vemurafenib resulted in complete or partial tumor regression and improved overall survival in patients positive for BRAF V600E metastatic melanoma [283]. The downside with BRAF inhibitors is that the majority of melanoma patients develop drug resistance and eventual relapse [284]. Combination therapies with targeted approaches will be necessary to counteract cancer resistance.

4. Experimental therapies

4.1 Nanooncology

Biotechnologies are increasingly used in cancer research [285]. The application of nanotechnology in cancer research is termed nanooncology and has generated promising solutions to address our current limitations in imaging and treatment of brain tumors [286]. Currently, two nanotechnology-based products are approved for the treatment of cancer, e.g., Doxil (liposomal doxorubicin) and Abraxane (nanoparticle formulated paclitaxel). Novel cancer therapeutics ranging from tiny carbon nanotubes and polymeric nanoparticles to large-scale thermal therapies such as magnetic nanoparticle-based hyperthermia [287, 288]. This field of research is growing rapidly with approximately 150 drugs currently in development that incorporate nanotechnology. The purpose of this section is to provide exposure to the field of nanooncology and highlight some promising materials.

4.2 Liposome-based nanoparticles

Liposomes are one of the most established nanomedicines in cancer therapy and theranostics. It is an effective delivery system with their flexibility, versatility, biocompatibility, and biodegradability [289]. Liposomes resemble biological membranes by adopting a lipid bilayer structure and house a wide range of cytotoxic drugs and imaging agents. The vesicle structure of liposomes permits encasement of a variety of lipophilic and hydrophilic cargos. The drug adopts the pharmacokinetic properties of the liposomal carrier until they are released [290]. This feature results in enhanced therapeutic index and reduction in systemic toxicity [291–293]. Additionally, hydrophilic polymers and ligands may be attached to the liposomes to modulate circulation time and targeting capabilities [294, 295]. Several studies have reported enhanced uptake and efficacy of ligand-targeted liposomes in diseased tissue versus non-targeted liposomes. Ligands are selected that have high affinity for highly-expressed receptor on cancer cells [296, 297].

Different strategies have been developed to promote the loading and release of therapeutics for cancer treatments. Liposomes act to protect encapsulated drugs from degradation, dilution and premature release [298]. As a consequence, therapeutic efficacy of anticancer drugs are increased since higher amounts reach the destination [299, 300]. Liposomal doxorubicin-cyclophosphamide for the treatment of breast cancer patients with MBTs demonstrated greater response rates and median survival time for both mouse models and human patients [299, 300]. One challenge for liposome-based nanoparticles is the encapsulation inefficiency (<30%) for passive loading of hydrophilic therapeutics [301]. In contrast, hydrophobic drugs tend to load with much higher efficiency because they readily dissolve inside the lipid bilayer.

4.3 Quantum dots

Quantum dots (QDs) are extremely small nanoparticles measuring a few nanometers in size. QDs emit light of specific frequencies modifiable by altering the size, shape, and material of the dots. QDs possess great potential for tumor fluorescence imaging and delivering therapies. Fluorescence imaging is a potent tool for cancer diagnosis and achieves more complete resections [302]. Biomolecules can be used to modify QDs which provides several improvements from other organic fluorophores, e.g., higher photoluminescence efficiency, greater photostability, and sharp emission profile. QD-based fluorescence also has good biocompatibility and low toxicity [303–307].

Visible fluorescence imaging uses light in the visible wavelength spectrum (400–700 nm) and is adept at cancer diagnosis and enhancing spatial resolution. For in vivo tumor fluorescence imaging, imaging agent delivery to brain tumors is challenging because the BBB restricts the passage of large molecules [308]. Thus, BBB prevents the transposition of many imaging agents and cancer therapeutics ergo attenuating their effect on tumor treatment and illumination. QDs provide a workaround for these physiological constraints due to their miniscule dimensions. Recent studies have developed QD nanoprobes that cross the BBB and target tumors specifically [309, 310]. These QDs cross the BBB and target cancer cells for in vivo imaging.

4.4 Gene therapy

Gene therapy of the nervous system is now a commonplace tool used around the world. Widely used to generate preclinical models, gene therapy is now demonstrating success in the clinic for both safety and efficacy for the treatment of congenital blindness and neurodegenerative disorders [311, 312]. A major component to gene therapeutics is the delivery system known as vectors. Vectors are commonly categorized as viral and non-viral vectors. Adenoviral vectors have proven valuable in the development of anticancer agents by selectively replicating within cancer cells [313]. Retroviral vectors are another useful delivery system for cancer treatment. Previous studies have demonstrated its ability to activate enzymes that convert 5-fluorocytosine (5FC) into toxic 5-fluorouracil (5FU) for treatment of gliomas [314, 315]. RRV with prodrug is currently being tested in randomized trials, however, this concept may be tested on MBTs in combination with immunotherapy [316]. Another rising technology is Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) that allows gene editing within organisms. Recently, CRISPR was used to engineer tumor cells to exhibit homing behavior [317]. After engineering, cells are released back into circulation and return back to the main tumor site. Cells were designed to secrete death receptor-targeting ligands that destroy the main tumor cells. Self-homing cells were also programmed with a drug-triggered cellular suicide system to eliminate them following tumor death. CRISPR has also been used to enhance therapeutic T cells in cancer immunotherapy [318]. These new capacities may expand into brain metastatic treatment in the near future.

5. Conclusion

In 1971, the National Cancer Act was signed to strengthen the National Care Institute with the objective to eliminate cancer as a leading cause of death in the United States [319]. This was expected to be achieved by funding research for

understanding the mechanisms of cancer biology and developing effective treatments. Although cancer death rates have declined for the past 25 years in the United States, the results have overall been disappointing when considering total cancer deaths and mortality rate. Much of the progress against cancer can be attributed to the decline in tobacco use and the development of screening tools for earlier detection [320]. Since 1971, there has been expansion of knowledge in cancer biology and diversification of diagnostic tools and treatment options. With respect to brain metastases, the median survival has improved modestly [321] and innovative approaches to MBC management continue to emerge in the fields of imaging, biotechnology, and pharmaceuticals. Having said that, it is fair to question whether the rate of progress for cancer patient outcomes and innovation is decelerating and whether subsequent inventions will be as impactful as those previous [322, 323]. As Gordon has pointed out, successive Industrial Revolutions after the 1960s have made depreciating impacts on productivity and economic growth [322]. A similar trend is observed in pharmaceuticals with a noticeable decline in research and development (R&D) efficiency defined as the number of new drugs approved for every billion dollars spent on R&D [323]. Studies have haggled over the cost for one new drug approval with estimates between roughly $700 million and $2.5 billion dollars [324, 325]. This trend is referred to as Eroom's Law, which means drug discovery becomes slower and more expensive with time. Additionally, we have seen a decline in the state of competition and economic dynamism characterized by rising mergers and declining start-up rates [323, 326]. Even with newer treatments reaching market, we see evidence of diminishing returns for the treatment of cancer [327]. Despite these problematic economic and healthcare patterns, innovation in MBC management remains resilient producing robust tools for improving treatment safety and efficacy.

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