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]. Heads 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 specific 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 hypoenhancement 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 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 $0.8 \pm 0.25$ 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. Caponetto 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
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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 encaumement 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 deprecating 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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References

[1] Alexandru D, Bota DA, Linskey ME. Epidemiology of central nervous system metastases. In: Current and Future Management of Brain Metastasis. Vol. 25. Basel, Switzerland: Karger Publishers; 2012. pp. 13-29

[2] Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Current Oncology Reports. 2012;14(1):48-54

[3] Smedby KE, Brandt L, Bäcklund ML, Blomqvist P. Brain metastases admissions in Sweden between 1987 and 2006. British Journal of Cancer. 2009;101(11):1919

[4] Bachmann C et al. CNS metastases in breast cancer patients: Prognostic implications of tumor subtype. Medical Oncology. 2015;32:400

[5] Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. Journal of Clinical Oncology. 2004;22(14):2865-2872

[6] Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA, Eheman C, et al. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. Journal of the National Cancer Institute. 2011;103:714-736

[7] LAG R, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al., editors. SEER Cancer Statistics Review, 1975-2000. Bethesda, MD: National Cancer Institute; 2003. Available from: https://seer.cancer.gov/csr/1975_2000/

[8] Feng W, Zhang P, Zheng X, Chen M, Mao WM. Incidence and treatment of brain metastasis in patients with esophageal carcinoma. World Journal of Gastroenterology—WJG. 2015;21(19):5805

[9] Villano JL, Durbin EB, Normandseau C, Thakkar JP, Moirangthem V, Davis FG. Incidence of brain metastasis at initial presentation of lung cancer. Neuro-Oncology. 2014;17(1):122-128

[10] Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al., editors. SEER Cancer Statistics Review, 1975-2015. Bethesda, MD: National Cancer Institute. Available from: https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018

[11] Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases: Histology, multiplicity, surgery, and survival. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1996;78(8):1781-1788

[12] Sawaya R, Bindal RK, Lang FF, Abi-Said D. Metastatic brain tumors. In: El K, editor. Brain Tumors: An Encyclopedic Approach. 2nd ed. London: Churchill Livingstone; 2001

[13] Posner JB, Chernik NL. Intracranial metastases from systemic cancer. Advances in Neurology. 1978;19:579-592

[14] Schouten LJ, Rutten J, Huveneneers HA. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer Institute. 2002;105:551-562

[15] Counsell CE, Collie DA, Grant R. Incidence of intracranial tumors in the Lothian region of Scotland 1989-90. Journal of Neurology, Neurosurgery, and Psychiatry. 1996;61:142-150

[16] Suki D, Khoury Abdulla R, Ding M, et al. Brain metastases in patients
diagnosed with a solid primary cancer during childhood: Experience from a single referral cancer center. Journal of Neurosurgery. Pediatrics. 2014;14:372-385

[17] Curless RG, Toledano SR, Ragheb J, Cleveland WW, Falcone S. Hematogenous brain metastasis in children. Pediatric Neurology. 2002;26:219-221

[18] Paulino AC, Nguyen TX, Barker JL Jr. Brain metastases in children with sarcoma, neuroblastoma, and Wilms’ tumor. International Journal of Radiation Oncology, Biology, Physics. 2003;57:177-183

[19] Graus F, Walker RW, Allen JC. Brain metastases in children. The Journal of Pediatrics. 1983;105:558-561

[20] Kebudi R, Ayan I, Gorgun O, Agaoglu FY, Vural S, Darendeliler E. Brain metastasis in pediatric extracranial solid tumors: Survey and literature review. Journal of Neuro-Oncology. 2005;71:43-48

[21] Jemal A, Miller KD, Ma J, Siegel RL, Fedewa SA, Islami F, et al. Higher lung cancer incidence in young women than young men in the United States. New England Journal of Medicine. 2018;378:21

[22] Surveillance Epidemiology and End Results (SEER) Program. SEER*Stat Database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases. Nov 2015 Sub (1973-2013 varying) – Linked To County Attributes – Total U.S., 1969-2014 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on November 2015 submission; 2016

[23] Kaal EC, Taphoorn MJ, Vecht CJ. Symptomatic management and imaging of brain metastases. Journal of Neuro-Oncology. 2005;75(1):15-20

[24] Christiaans MH, Kelder JC, Arnoldus EP, Tijssen CC. Prediction of intracranial metastases in cancer patients with headache. Cancer. 2002;94(7):2063-2068

[25] Pfund Z, Szapary L, Jaszberenyi O, Nagy F, Czopf J. Headache in intracranial tumors. Cephalalgia. 1999;19(9):787-790

[26] Saha A, Ghosh SK, Roy C, Choudhury KB, Chakrabarty B, Sarkar R. Demographic and clinical profile of patients with brain metastases: A retrospective study. Asian Journal of Neurosurgery. 2013;8(3):157

[27] Wilne SH, Ferris RC, Nathwani A, Kennedy CR. The presenting features of brain tumours: A review of 200 cases. Archives of Disease in Childhood. 2006;91(6):502-506

[28] Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, et al. Brain metastases. In: European Handbook of Neurological Management. Oxford, England, UK: Wiley-Blackwell; 2010. pp. 437-445

[29] Wu SG, Rao MY, Zhou J, et al. Distribution of metastatic disease in the brain in relation to the hippocampus: A retrospective single-center analysis of 6064 metastases in 632 patients. Oncotarget. 2015;6(41):44030-44036

[30] Wu SG, Sun JY, Tong Q, Li FY, He ZY. Clinical features of brain metastases in breast cancer: An implication for hippocampal-sparing whole-brain radiation therapy. Therapeutics and Clinical Risk Management. 2016;12:1849-1853

[31] Graf AH, Buchberger W, Langmayr H, Schmid KW. Site preference of metastatic tumours of the brain. Virchows Archiv A. 1988;412(5):493-498

[32] Nguyen DX et al. WNT/TCF signaling through LEF1 and HOXB9
mediates lung adenocarcinoma metastasis. Cell. 2009;138:51-62

[33] Bos PD et al. Genes that mediate breast cancer metastasis to the brain. Nature. 2009;459:1005-1009

[34] Lee HW, Seol HJ, Choi YL, Ju HJ, Joo KM, Ko YH, et al. Genomic copy number alterations associated with the early brain metastasis of non-small cell lung cancer. International Journal of Oncology. 2012;41:2013-2020

[35] Benedettini E, Sholl LM, Peyton M, Reilly J, Ware C, Davis L, et al. Met activation in non-small cell lung cancer is associated with de novo resistance to EGFR inhibitors and the development of brain metastasis. The American Journal of Pathology. 2010;177:415-423

[36] Chen G, Wang Z, Liu XY, Liu FY. High-level CXCR4 expression correlates with brain-specific metastasis of non-small cell lung cancer. World Journal of Surgery. 2011;35:56-61

[37] Li B, Wang C, Zhang Y, Zhao XY, Huang B, Wu PF, et al. Elevated PLGF contributes to small-cell lung cancer brain metastasis. Oncogene. 2013;32:2952-2962

[38] Martinez-Aranda A et al. FN14 and GRP94 expression are prognostic/predictive biomarkers of brain metastasis outcome that open up new therapeutic strategies. Oncotarget. 2015;6:44254-44273

[39] Li B et al. Elevated PLGF contributes to small-cell lung cancer brain metastasis. Oncogene. 2013;32:2952-2962

[40] Sevenich L et al. Analysis of tumour- and stroma-supplied proteolytic networks reveals a brain-metastasis-promoting role for cathepsin S. Nature Cell Biology. 2014;16:876-888

[41] Wrage M et al. Identification of HERC5 and its potential role in NSCLC progression. International Journal of Cancer. 2015;136:2264-2272

[42] Jilaveanu LB et al. PLEKHA5 as a biomarker and potential mediator of melanoma brain metastasis. Clinical Cancer Research. 2015;21:2138-2147

[43] Shen L, Chen L, Wang Y, Jiang X, Xia H, Zhuang Z. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. Journal of Neurooncology. 2015;121:101-108

[44] Dagogo-Jack I et al. Brain metastasis: Clinical implications of branched evolution. Trends in Cancer. 2016;2:332-337

[45] Valiente M et al. Serpins promote cancer cell survival and vascular co-option in brain metastasis. Cell. 2014;156:1002-1016

[46] Lorger M, Felding-Habermann B. Capturing changes in the brain microenvironment during initial steps of breast cancer brain metastasis. The American Journal of Pathology. 2010;176:2958-2971

[47] Wang X et al. Astrocytic Fas ligand expression is required to induce T-cell apoptosis and recovery from experimental autoimmune encephalomyelitis. European Journal of Immunology. 2013;43:115-124

[48] Wanner LB et al. Glial scar borders are formed by newly proliferated, elongated astrocytes that interact to corral inflammatory and fibrotic cells via STAT3-dependent mechanisms after spinal cord injury. The Journal of Neuroscience. 2013;33:12870-12886

[49] Kienast Y et al. Real-time imaging reveals the single steps of brain metastasis formation. Nature Medicine. 2010;16:116-122
[50] Carbonell WS et al. The vascular basement membrane as 'soil' in brain metastasis. PLoS One. 2009;4:e5857

[51] Rafi S et al. Angiocrine functions of organ-specific endothelial cells. Nature. 2016;529:316-325

[52] Loulier K et al. Beta1 integrin maintains integrity of the embryonic neocortical stem cell niche. PLoS Biology. 2009;7:e1000176

[53] Shen Q et al. Adult SVZ stem cells lie in a vascular niche: A quantitative analysis of niche cell-cell interactions. Cell Stem Cell. 2008;3:289-300

[54] Garcia MA et al. Discovery of additional brain metastases on the day of stereotactic radiosurgery: Risk factors and outcomes. Journal of Neurosurgery. 2017;126:1756-1763

[55] Xing F et al. Reactive astrocytes promote the metastatic growth of breast cancer stem-like cells by activating notch signaling in brain. EMBO Molecular Medicine. 2013;5:385-396

[56] Chen Q et al. Carcinoma-astrocyte gap junctions promote brain metastasis by cGAMP transfer. Nature. 2016;533:493-498

[57] Lin Q et al. Reactive astrocytes protect melanoma cells from chemotherapy by sequestering intracellular calcium through gap junction communication channels. Neoplasia. 2010;12:748-754

[58] Priego N et al. STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis. Nature Medicine. 2018;24:1024-1035

[59] Dolgushin M, Kornienko VN, Pronin IN. Brain Metastases—Advance Neuroimaging. Cham, Switzerland: Springer International Publishing; 2018

[60] Maroldi R, Ambrosi C, Farina D. Metastatic disease of the brain: Extra-axial metastases (skull, dura, leptomeningeal) and tumour spread. European Radiology. 2005;15:617-626

[61] Lin JP, Kricheff II, Laguna J, et al. Brain tumors studied by computerized tomography. Advances in Neurology. 1976;15:175-199

[62] Kornienko VN, Pronin IN. Diagnostic Neuroradiology. Berline-Heidelberg: Springer-Verlag; 2009

[63] Kornienko VN, Pronin IN. Diagnostic neuroradiology. In: Tumors of the Skull Base. Vol. 4. Moscow: Alexeeva TM; 2012

[64] Kornienko VN et al. A study of brain tissue perfusion by computed tomography. Journal of Medical Imaging. 2007;2:70-81

[65] Miles K, Charnsangavej C, Cuenod C. Multi-Detector Computed Tomography in Oncology CT Perfusion Imaging. London: Informa Healthcare; 2007

[66] Lev M, Nichols S. Computer tomographic angiography and computed tomographic perfusion imaging of hyperacute stroke. Topics in Magnetic Resonance Imaging. 2000;11:283-287

[67] König M. Brain perfusion CR in acute stroke: Current status. European Journal of Radiology. 2003;45(1):11-22

[68] Pronin IN et al. The use of CT perfusion imaging in stereotactic biopsy of diffuse gliomas. In: Nevsky Radiological Forum. St Petersburg; 2005

[69] Dolgushin M et al. Use of CT perfusion to discriminate between brain metastases from different primaries. Clinical Imaging. 2015;39:9-14

[70] Dolgushin M et al. A CT perfusion method in the differential diagnosis of a secondary tumor lesions of the
brain. Journal of Medical Imaging. 2007;4:100-106

[71] Dolgushin MB et al. Perfusion CT in dynamic evaluation of the effectiveness of radiation therapy in secondary brain tumors. N.N. Blokhin Russian Cancer Research Centre. 2008;19(4):36-46

[72] Schellinger P, Meinck H, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. Journal of Neuro-Oncology. 1999;44(3):275-281

[73] Barajas RF Jr, Cha S. Imaging diagnosis of brain metastasis. Progress in Neurological Surgery. 2012;25:55-73

[74] Seute T, Leffers P, ten Velde GP, et al. Detection of brain metastases from small cell lung cancer: Consequences of changing imaging techniques (CT versus MRI). Cancer. 2008;112:1827-1834

[75] Kruger S, Mottaghy FM, Buck AK, et al. Brain metastasis in lung cancer. Nuklearmedizin. 2010;50:101-106

[76] Seidl Z, Vymazal J, Mechl M, et al. Does higher gadolinium concentration play a role in the morphologic assessment of brain tumors? Results of a multicenter intraindividual crossover comparison of gadobutrol versus gadobenate dimeglumine (the MERIT study). American Journal of Neuroradiology. 2012;33:1050-1058

[77] Anzalone N, Essig M, Lee SK, et al. Optimizing contrast-enhanced magnetic resonance imaging characterization of brain metastases: Relevance to stereotactic radiosurgery. Neurosurgery. 2013;72:691-701

[78] Togao O, Hiwatashi A, Yamashita K, et al. Additional MR contrast dosage for radiologists’ diagnostic performance in detecting brain metastases: A systematic observer study at 3T. Japanese Journal of Radiology. 2014;32:537-544

[79] Hoult DI, Lauterbur PC. The sensitivity of the zeugmatographic experiment involving human samples. Journal of Magnetic Resonance. 1979;34:425-433

[80] Ba-Ssalamah A, Nobauer-Huhmann IM, Pinker K, et al. Effect of contrast dose and field strength in the magnetic resonance detection of brain metastases. Investigative Radiology. 2003;38:415-422

[81] Krautmacher C, Willinek WA, Tschampa HJ, et al. Brain tumors: Full-and half-dose contrast-enhanced MR imaging at 3.0 T compared with 1.5 T-initial experience. Radiology. 2005;237:1014-1019

[82] Noebauer-Huhmann IM, Szomolanyi P, Kronnerwetter C, et al. Brain tumours at 7T MRI compared to 3T-contrast effect after half and full standard contrast agent dose: Initial results. European Radiology. 2015;25:106-112

[83] Deelchand DK, Van de Moortele PF, Adriany G, et al. In vivo 1H NMR spectroscopy of the human brain at 9.4 T: Initial results. Journal of Magnetic Resonance. 2010;206:74-80

[84] Kushnirsky M, Nguyen V, Katz JS, et al. Time-delayed contrast-enhanced MRI improves detection of brain metastases and apparent treatment volumes. Journal of Neurosurgery. 2016;124:489-495

[85] Yang S, Nam Y, Kim MO, et al. Computer-aided detection of metastatic brain tumors using magnetic resonance black-blood imaging. Investigative Radiology. 2013;48:113-119

[86] Szwarc P, Kawa J, Rudzki M, et al. Automatic brain tumour detection and neovasculature assessment with multiseries MRI analysis. Computerized Medical Imaging and Graphics. 2015;46:178-190
[87] Leenders W, Kusters B, Pikkemaat J. Vascular endothelial growth factor-A determines detectability of experimental melanoma brain metastasis in GD-DTPA-enhanced MRI. International Journal of Cancer. 2003;105:437-443

[88] Cascino T, Byrne T, Deck M, Posner JB. Intra-arterial BCNU in the treatment of metastatic brain tumors. Journal of Neuro-Oncology; 1(3):211-218

[89] Roberts T. Physiologic measurements by contrast-enhanced MR imaging: Evaluate expectations and limitations. Journal of Magnetic Resonance Imaging. 1997;7:82-90

[90] Blouw B et al. The hypoxic response of tumors is dependent on their microenvironment. Cancer Cell. 2003;4:133-146

[91] Ostergaard L. Principles of cerebral perfusion imaging by bolus tracking. Journal of Magnetic Resonance Imaging. 2005;24(2):180

[92] Saremi F. Perfusion Imaging in Clinical Practice. A Multimodality Approach to Tissue Perfusion Analysis. New York: Wolters Kluwer; 2015

[93] Tofts P. Quantitative MRI of the Brain. Chichester: Wiley; 2004

[94] Griffith B, Jain R. Perfusion in neuro- oncology basic techniques and clinical applications. The Journal of Pathology. 2015;53(3):497-511

[95] Grade M, Hernandez Tamames JA, Pizzini FB, et al. A neuroradiologist’s guide to arterial spin labeling MRI in clinical practice. Neuroradiology. 2015;57:1181-1202

[96] Tourdias T, Rodrigo S, Oppenheim C, et al. Pulsed arterial spine labeling applications in brain tumors: Practical review. Journal of Neuroradiology. 2008;35:79-89

[97] Lowther E, Whitlow C, Maldjian J. Clinical applications of ASL brain perfusion imaging, chapter 14. In: Saremi F, editor. Perfusion Imaging in Clinical Practice. A Multimodality Approach to Tissue Perfusion Analysis. New York: Wolters Kluwer; 2015

[98] Boxerman JL, Shiroishi MS, Ellingston BM, et al. Dynamic susceptibility contrast MR imaging in glioma: Review of current clinical practice. Magnetic Resonance Imaging Clinics of North America. 2016;24:649-670

[99] Sorensen A, Reimer P. Cerebral MR Perfusion Imaging: Principles and Current Applications. New York: Thieme; 2000

[100] Jones T, Rabiner EA, Company PETRA. The development, past achievements, and future directions of brain PET. Journal of Cerebral Blood Flow and Metabolism. 2012;32:1426-1454

[101] Li Z, Conti PS. Radiopharmaceutical chemistry for positron emission tomography. Advanced Drug Delivery Reviews. 2010;62:1031-1051

[102] Oriuchi N, Higuchi T, Ishikita T, Miyakubo M, Hanoka H, Iida Y, et al. Present role and future prospects of positron emission tomography in clinical oncology. Cancer Science. 2006;97:1291-1297

[103] Fischman AJ. PET imaging of brain tumors. In: Blake MA, Kalra MK, editors. Imaging in Oncology. Boston, MA: Springer; 2008

[104] Juhasz C, Dwivedi S, Kamson DO, et al. Comparison of amino acid positron emission tomographic radiotracers for molecular imaging of primary and metastatic brain tumors. Molecular Imaging. 2014;13:13
[105] Ohno Y, Koyama H, Nogami M, et al. Whole-body MR imaging vs FDG-PET: Comparison of accuracy of M-stage diagnosis for lung cancer patients. Journal of Magnetic Resonance Imaging. 2007;26:498-509

[106] Rohren EM, Provenzalle JM, Barbiorak DP, et al. Screening for cerebral metastases with FDG PET in patients undergoing whole-body staging of non-central nervous system malignancy. Radiology. 2003;226:181-187

[107] Patronas NJ, Di Chiro G, Kufta C, et al. Prediction of survival in glioma patients by means of positron emission tomography. Journal of Neurosurgery. 1985;62:816-822

[108] Chao S, Suh JH, Raja S, et al. The sensitivity and specificity of FDG PET in distinguishing recurrent brain tumor from radionecrosis in patients treated with stereotactic radiosurgery. International Journal of Cancer. 2001;96:191-197

[109] Hutterer M, Nowosielski M, Putzer D, et al. [18F]-fluoro-ethyl-L-tyrosine PET: A valuable diagnostic tool in neuro-oncology, but not all that glitters is glioma. Neuro-Oncology. 2013;15:341-351

[110] Allen AM, Ben-Ami M, Reshef A, Steinmetz A, Kundel Y, Inbar E, et al. Assessment of response of brain metastases to radiotherapy by PET imaging of apoptosis with (1) (8) F-ML-10. European Journal of Nuclear Medicine and Molecular Imaging. 2012;39(9):1400-1408

[111] Chen W. Clinical applications of PET in brain tumors. Journal of Nuclear Medicine. 2007;48(9):1468-1481

[112] Brandao LA, Castillo M. Adult brain tumors: Clinical applications of magnetic resonance spectroscopy.

[113] Rapalino O, Ratai EM. Multiparametric imaging analysis: Magnetic resonance spectroscopy. Magnetic Resonance Imaging Clinics of North America. 2016;24:781-809

[114] De Edelenyi FS, Rubin C, Esteve F, et al. A new approach for analyzing proton magnetic resonance spectroscopic imaging of brain tumors: Nosologic images. Nature Medicine. 2000;6:1287-1289

[115] Fan G, Sun B, Wu Z, Guo Q, Guo Y. In vivo single-voxel proton MR spectroscopy in the differentiation of high-grade gliomas and solitary metastases. Clinical Radiology. 2004;59:77-85

[116] Ishimaru H, Morikawa M, Iwanaga S, Kaminogo M, Ochi M, Hayashi K. Differentiation between high-grade glioma and metastatic brain tumor using single-voxel proton MR spectroscopy. European Radiology. 2001;11:1784-1791

[117] Guzman-de-Villoria JA, Sanchez-Gonzalez J, Munoz L, et al. 1H MR spectroscopy in the assessment of gliomatosis cerebri. American Journal of Roentgenology. 2007;188:710-714

[118] Kuznetsov YE, Caramanos Z, Antel SB, et al. Proton magnetic resonance spectroscopic imaging can predict length of survival in patients with supratentorial gliomas. Neurosurgery. 2003;53:564-574

[119] Sjobakk TE, Johansen R, Bathen TF, et al. Metabolic profiling of human brain metastases using in vivo proton MR spectroscopy at 3T. BMC Cancer. 2007;7:141

[120] Murase K. Dynamic contrast-enhanced perfusion CT: Basic of mathematical tracer kinetic models and
applications. Chapter 4. In: Saremi F, editor. Perfusion Imaging in Clinical Practice. A Multimodality Approach to Tissue Perfusion Analysis. New York: Wolters Klumer; 2015. pp. 62-76

[121] Le Bihan D, Breton E. Imagier de diffusion in-vivo par resonance magnetique. Comptes rendus de l’Academie des sciences. Serie II. 1985;15:1109-1112

[122] Le Bihan D, Turner R, Mooner C, et al. Imaging of diffusion and microvasculature with gradient sensitization: Design, strategy and significance. Journal of Magnetic Resonance Imaging. 1991;1:7-28

[123] Chang S, Parney IF, McDermott M, et al. Perioperative complications and neurological outcome of first versus second craniotomy among patients enrolled in the Glioma outcomes project. Journal of Neurosurgery. 2003;98:1175-1181

[124] Deveaux BC, O’Fallon JR, Kelly PR. Resection, biopsy, and survival in malignant glial neoplasms: A retrospective study of clinical parameters, therapy, and outcome. Journal of Neurosurgery. 1993;78(5):767-775

[125] Fadul C, Wood J, Thaler H, et al. Morbidity and mortality for excision of supratentorial gliomas. Neurology. 1988;38:1374-1379

[126] Sawaya R, Hammoud M, Schoppa D, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment parenchymal tumors. Neurosurgery. 1998;42:1044-1055

[127] Mueller W. DTI for neurosurgeons: Cases and concepts. In: International Brain Mapping and Intraoperative Surgical Planning Society (IBMISPS) Brain, Spinal Cord Mapping and Image Guided Therapy Conference; 27 May 2010; Bethesda, MN. 2010

[128] Essayed WI, Zhang F, Unadkat P, Cosgrove GR, Golby AJ, O’Donnell LJ. White matter tractography for neurosurgical planning: A topography-based review of the current state of the art. NeuroImage: Clinical. 2017;15:659-672

[129] Wu JS, Zhou LF, Tang WJ, Mao Y, Hu J, Song YY, et al. Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation. Neurosurgery. 2007;61(5):935-949

[130] Duffau H et al. Intraoperative mapping of the subcortical language pathways using direct stimulations. Brain. 2002;125(1):199-214

[131] Berman JI. Advanced diffusion MR tractography for surgical planning. In: Pillai JJ, editor. Functional Brain Tumor Imaging. New York, NY: Springer; 2014. pp. 183-192

[132] Alexander AL, Hasan K, Kindlmann G, Parker DL, Tsuruda JS. A geometric analysis of diffusion tensor measurements of the human brain. Magnetic Resonance in Medicine. 2000;44(2):283-291

[133] Schilling KG, Janve V, Gao Y, Stepniewska I, Landman BA, Anderson AW. Histological validation of diffusion MRI fiber orientation distributions and dispersion. NeuroImage. 2018;165:200-221

[134] Grussu F, Schneider T, Yates RL, Tachrount M, Tur C, Newcombe J, et al. Quantitative histological validation of NODDI MRI indices of neurite morphology in multiple sclerosis spinal cord. Multiple Sclerosis Journal. 2015;21(S11):204-205

[135] Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage.
[136] Jacobs B, Schall M, Prather M, Kapler E, Driscoll L, Baca S, et al. Regional dendritic and spine variation in human cerebral cortex: A quantitative golgi study. Cerebral Cortex. 2001;11:558-571

[137] Jacobs B, Driscoll L, Schall M. Life-span dendritic and spine changes in areas 10 and 18 of human cortex: A quantitative golgi study. The Journal of Comparative Neurology. 1997;386:661-680

[138] Evanglou N, Esiri MM, Smith S, Palace J, Matthews PM. Quantitative pathological evidence for axonal loss in normal appearing white matter in multiple sclerosis. Annals of Neurology. 2000;47:391-395

[139] Bruijn LI, Miller TM, Cleveland DW. Unraveling the mechanisms involved in motor neuron degeneration in ALS. Annual Review of Neuroscience. 2004;27:723-749

[140] Broad RJ, Gabel MC, Dowell NG, et al. Neurite orientation and dispersion density imaging (NODDI) detects cortical and corticospinal tract degeneration in ALS. Journal of Neurology, Neurosurgery, and Psychiatry. 2018

[141] Paula-Barbosa MM, Mota Cardoso R, Guimaraes ML, Cruz C. Dendritic degeneration and regrowth in the cerebral cortex of patients with Alzheimer’s disease. Journal of the Neurological Sciences. 1980;45(1):129-134

[142] Jespersen SN, Bjarkam CR, Nyengaard JR, Chakravarty MM, Hansen B, Vosegaard T, et al. Neurite density from magnetic resonance diffusion measurements at ultrahigh field: Comparison with light microscopy and electron microscopy. NeuroImage. 2010;49:205-216

[143] Yoshihito K, Hirai T, Azuma M, Hattori Y, Khant ZA, Hori M, et al. Differentiation between glioblastoma and solitary brain metastasis using neurite orientation dispersion and density imaging. Journal of Neuroradiology. 2018. DOI: 10.1016/j.neurad.2018.10.005

[144] Caverzasi E, Papinutto N, Castellano A, Zhu AH, Scifo P, Riva M, et al. Neurite orientation dispersion and density imaging color maps to characterize brain diffusion in neurologic disorders. Journal of Neuroimaging. 2016;26(5):494-498. DOI: 10.1111/jon.12359 [Epub 2016/05/24]

[145] Maximov II, Tonoyan AS, Pronin IN. Differentiation of glioma malignancy using diffusion MRI. Physica Medica. 2017;40:24-32

[146] Yaeger KA, Nair MN. Surgery for brain metastases. Surgical Neurology International. 2013;4(Suppl 4):S203

[147] Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. New England Journal of Medicine. 1990;322(8):494-500

[148] Yoo H, Kim YZ, Nam BH, Shin SH, Yang HS, Lee JS, et al. Reduced local recurrence of a single brain metastasis through microscopic total resection. Journal of Neurosurgery. 2009;110(4):730-736

[149] Ali A, Goffin JR, Arnold A, Ellis PM. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. Current Oncology. 2013;20(4):e300

[150] Vávra P, Roman J, Zonča P, Ihnát P, Němec M, Kumar J, et al. Recent development of augmented reality in
surgery: A review. Journal of Healthcare Engineering. 2017

[151] Wen R, Chui CK, Ong SH, Lim KB, Chang SKY. Projection-based visual guidance for robot-aided RF needle insertion. International Journal of Computer Assisted Radiology and Surgery. 2013;8(6):1015-1025

[152] Lapeer RJ, Jeffrey SJ, Dao JT, García GG, Chen M, Shickell SM, et al. Using a passive coordinate measurement arm for motion tracking of a rigid endoscope for augmented-reality image-guided surgery. The International Journal of Medical Robotics and Computer Assisted Surgery. 2014;10(1):65-77

[153] Besharati Tabrizi L, Mahvash M. Augmented reality-guided neurosurgery: Accuracy and intraoperative application of an image projection technique. Journal of Neurosurgery. 2015;123(1):206-211

[154] Mert A, Buehler K, Sutherland GR, Tomanek B, Widhal G, Kasprian G, et al. Brain tumor surgery with 3-dimensional surface navigation. Operative Neurosurgery. 2012;71(suppl_2):286-295

[155] Badiola G, Ferrari V, Cutolo F, Freschi C, Caramella D, Bianchi A, et al. Augmented reality as an aid in maxillofacial surgery: Validation of a wearable system allowing maxillary repositioning. Journal of Cranio-Maxillofacial Surgery. 2014;42(8):1970-1976

[156] Madhavan K, Kolcun JG, Chieng L, Wang MY. Augmented-reality integrated robotics in neurosurgery: Are we there yet? Neurosurgical Focus FOC. 2017;42(5):E3

[157] Komarnicky LT, Phillips TL, Martz K, Asbell S, Isaacson S, Urtasun R. A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). International Journal of Radiation Oncology, Biology, Physics. 1991;20(1):53-58

[158] Sause WT, Scott C, Krisch R, Rotman M, Sneed PK, Janjan N, et al. Phase I/II trial of accelerated fractionation in brain metastases RTOG 85-28. International Journal of Radiation Oncology, Biology, Physics. 1993;26(4):653-657

[159] Phillips TL, Scott CB, Leibel SA, Rotman M, Weigensberg IJ. Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases report of RTOG trial 89-05. International Journal of Radiation Oncology, Biology, Physics. 1995;33:339-348

[160] Murray KJ, Scott C, Greenberg HM, Emami B, Seider M, Vora NL, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: A report of the radiation therapy oncology group (RTOG) 9014. International Journal of Radiation Oncology, Biology, Physics. 1997;39(3):571-574

[161] Tsao MN, Lloyd N, Wong RK, Chow E, Rakovich E, Laperriere N, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database of Systematic Reviews. 2012;4:1-106. DOI: 10.1002/14651858.CD003869.pub4

[162] Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. JAMA. 1998;280(17):1485-1489

[163] Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised
controlled trial. The Lancet Oncology. 2009;10(11):1037-1044

[164] Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. Journal of Clinical Oncology. 2010;29(2):134-141

[165] Aoyama H, Tago M, Shirato H. For the Japanese radiation oncology study group 99-1 (JROSG 99-1) investigators. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases secondary analysis of the JROSG 99-1 randomized clinical trial. JAMA Oncology. 2015;1(4):457-464

[166] Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: A randomized clinical trial by the Radiation Therapy Oncology Group. International Journal of Radiation Oncology, Biology, Physics. 1981;7(7):891-895 [Epub 1981/07/01]

[167] Ogawa K, Yoshii Y, Nishimaki T, Tamaki N, Miyaguni T, Tsuchida Y, et al. Treatment and prognosis of brain metastases from breast cancer. Journal of Neuro-Oncology. 2008;86(2):231-238

[168] Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): Results from a phase 3, non-inferiority, randomised trial. Lancet. 2016;388(10055):2004-2014

[169] Brown PD, Ballman KV, Cerhan J, et al. N107C CEC.3: A phase III trial of post-operative stereotactic radiosurgery (SRS) compared with whole brain radiotherapy (WBRT) for resected metastatic brain disease. International Journal of Radiation Oncology. Biology. Physics. 2016;96:937

[170] Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: A randomized clinical trial. JAMA. 2016;316:401-409

[171] Mehta MP, Rodrigus P, Terhaard CH, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. Journal of Clinical Oncology. 2003;21:2529-2536

[172] Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: A randomized, double-blind, placebo-controlled trial. Neuro-Oncology. 2013;15:1429-1437

[173] Rapp SR, Case LD, Peiffer A, et al. Donepezil for irradiated brain tumor survivors: A phase III randomized placebo-controlled clinical trial. Journal of Clinical Oncology. 2015;33:1653-1659

[174] Trifiletti DM, Lee CC, Kano H, Cohen J, Janopaul-Naylor J, Alonso-Basanta M, et al. Stereotactic radiosurgery for brainstem metastases: An international cooperative study to define response and toxicity. International Journal of Radiation Oncology, Biology, and Physics. 2016;96(2):280-288

[175] Koyfman SA, Tendulkar RD, Chao ST, Vogelbaum MA, Barnett GH, Angelov L, et al. Stereotactic radiosurgery for single brainstem metastases: The Cleveland clinic experience. International Journal of
Radiation Oncology, Biology, and Physics. 2010;78(2):409-414

[176] Muacevic A, Kreth FW, Horstmann GA, et al. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. Journal of Neurosurgery. 1999;91:35-43

[177] Muacevic A, Wowra B, Siefert A, et al. Microsurgery plus whole brain irradiation versus gamma knife surgery alone for treatment of single metastases to the brain: A randomized controlled multicenter phase III trial. Journal of Neuro-Oncology. 2008;87:299

[178] Schöggel A, Kitz K, Reddy M, et al. Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases. Acta Neurochirurgica. 2000;142:621

[179] O’Neill BP, Iturria NJ, Link MJ, et al. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. International Journal of Radiation Oncology, Biology, Physics. 2003;55:1169-1176

[180] Rades D, Bohlen G, Pluemer A, Veninga T, Hanssens P, Dunst J, et al. Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. Cancer. 2007;109:2515-2521

[181] Baschnagel AM, Meyer KD, Chen PY, et al. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with gamma knife surgery. Journal of Neurosurgery. 2013;119:1139-1144

[182] Wolf A, Kvint S, Chachoua A, et al. BRAF V600E mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases. Journal of Neurosurgery. 2017;126:726-734

[183] Narayana A, Mathew M, Tam M, et al. Vemurafenib and radiation therapy in melanoma brain metastases. Journal of Neuro-Oncology. 2013;113:411-416

[184] Ahmed KA, Freilich JM, Sloat S, et al. LINAC-based stereotactic radiosurgery to the brain with concurrent vemurafenib for melanoma metastases. Journal of Neuro-Oncology. 2015;122:121-126

[185] Ahmed KA, Abuodeh YA, Echevarria MI, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. Annals of Oncology. 2016;27:2288-2294

[186] Shin SM, Cooper BT, Chachoua A, et al. Survival but not brain metastasis response relates to lung cancer mutation status after radiosurgery. Journal of Neuro-Oncology. 2016;126:483-491

[187] Xu Z, Lee C, Ramesh A, et al. BRAF V600E mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases. Journal of Neurosurgery. 2017;126:726-734

[188] Patel KR, Chowdhary M, Switchenko JM, et al. BRAF inhibitor and stereotactic radiosurgery is associated with an increased risk of radiation necrosis. Melanoma Research. 2016;26:387-394

[189] Ly D, Bagsshaw HP, Anker CJ, et al. Local control after stereotactic radiosurgery for brain metastases of small diameter. Journal of Neurosurgery. 2015;91:35-43

[190] Kiess AP, Wolchok JD, Barker CA, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: Safety profile and efficacy of combined treatment.
International Journal of Radiation Oncology. 2015;92:368-375

[191] Cohen-Inbar O, Shih HH, Xu Z, et al. The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab. Journal of Neurosurgery. 2017;127:1-8

[192] Barlesi F, Gervais R, Lena H, Hureaux H, Berard H, Paillotin D, et al. Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: A multicenter phase II trial (GFPC 07-01). Annals of Oncology. 2011;22(11):2466-2470

[193] Dinglin XX, Huang Y, Liu H, et al. Pemetrexed and cisplatin combination with concurrent whole brain radiotherapy in patients with brain metastases of lung adenocarcinoma: A single-arm phase II clinical trial. Journal of Neuro-Oncology. 2013;112:461-466

[194] Robinet G, Thomas P, Breton JL, Léna H, Gouva S, Dabouis G, et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Français de Pneumo-Cancérologie (GFPC) Protocol 95-1*. Annals of Oncology. 2001;12(1):59-67

[195] Boogerd W, Dalesio O, Bais EM, et al. Response of brain metastases from breast cancer to systemic chemotherapy. Cancer. 1992;69:972-980

[196] Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. Journal of Clinical Oncology. 2004;22:3608-3617

[197] Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH. Convection-enhanced delivery of macromolecules in the brain. Proceedings of the National Academy of Sciences of the United States of America. 1994;91:2076-2080

[198] Walter KA, Tamargo RJ, Oliver A, Burger PC, Brem H. Intratumoral chemotherapy. Neurosurgery. 1995;37:1128-1145

[199] Lieberman DM, Laske DW, Morrison PF, Bankiewicz KS, Oldfield EH. Convection-enhanced distribution of large molecules in gray matter during interstitial drug infusion. Journal of Neurosurgery. 1995;82:1021-1029

[200] Bodell WJ, Giannini DD, Singh S, Pietronigro D, Levin VA. Formation of DNA adducts and tumor growth delay following intratumoral administration of DTI-015. Journal of Neuro-Oncology. 2003;62:251-258

[201] Ramsay GS. Interstitial irradiation of the pituitary. Proceedings of the Royal Society of Medicine. 1960;53:641-644

[202] Chase NE, Atkins HL, Correll JW. Interstitial irradiation of brain tumors with iridium 192. Radiology. 1961;77:842-843. DOI: 10.1148/77.5.842

[203] Hosobuchi Y, Phillips TL, Stupar TA, Gutin PH. Interstitial brachytherapy of primary brain tumors. Preliminary report. Journal of Neurosurgery. 1980;53:613-617

[204] Ware ML, Larson DA, Sneed PK, Wara WW, McDermott MW. Surgical resection and permanent brachytherapy for recurrent atypical and malignant meningioma. Neurosurgery. 2004;54: 55-63. Discussion 63-54

[205] Vitaz TW, Warnke PC, Tabar V, Gutin PH. Brachytherapy for brain tumors. Journal of Neuro-Oncology. 2005;73:71-86

[206] Wernicke AG, Smith AW, Taube S, Yondorf MZ, Parashar B, Trichter S, et al. Cesium-131 brachytherapy for
[207] Wernicke AG, Yondorf MZ, Peng L, Trichter S, Nedialkova L, Sabbas A, et al. Phase I/II study of resection and intraoperative cesium-131 radioisotope brachytherapy in patients with newly diagnosed brain metastases. Journal of Neurosurgery. 2014;121:338-348

[208] Xia Y, Mashouf LA, Baker BR, et al. Outcomes of metastatic brain lesions treated with radioactive Cs-131 seeds after surgery: Experience from one institution. Cureus. 2018;10(7):e3075

[209] Hawasli AH, Bagade S, Shimony JS, Miller-Thomas M, Leuthardt EC. Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: Single-institution series. Neurosurgery. 2013;73:1007-1017

[210] Carpentier A, McNichols RJ, Stafford RJ, Itzcovitz J, Guichard JP, Reizine D, et al. Real-time magnetic resonance-guided laser thermal therapy for focal metastatic brain tumors. Neurosurgery. 2008;63:ONS21-ONS28

[211] Ahluwalia M, Barnett GH, Deng D, Tatter SB, Laxton AW, Mohammadi AM, et al. Laser ablation after stereotactic radiosurgery: A multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. Journal of Neurosurgery. 2018;130:804-811

[212] Ashraf O, Patel NV, Hanft S, Danish SF. Laser-induced thermal therapy in neuro-oncology: A review. World Neurosurgery. 2018;112:166-177

[213] Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. Science. 2016;353:766-771

[214] Berghoff AS et al. Density of tumor-infiltrating lymphocytes correlates with extent of brain edema and overall survival time in patients with brain metastases. Oncoimmunology. 2016;5:e1057388

[215] Berghoff AS et al. Characterization of the inflammatory response to solid cancer metastases in the human brain. Clinical and Experimental Metastasis. 2013;30:69-81

[216] Wyler L et al. Brain metastasis in renal cancer patients: Metastatic pattern, tumour-associated macrophages and chemokine/chemoreceptor expression. British Journal of Cancer. 2014;110:686-694

[217] Berghoff AS et al. Tumor infiltrating lymphocytes and PD-L1 expression in brain metastases of small cell lung cancer (SCLC). Journal of Neuro-Oncology. 2016;130:19-29

[218] Duchnowska R et al. Immune response in breast cancer brain metastases and their microenvironment: The role of the PD-1/PD-L axis. Breast Cancer Research. 2016;18:43

[219] Pardoll D. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews. Cancer. 2012;12:252-264

[220] Brochez L et al. The rationale of indoleamine 2,3-dioxygenase inhibition for cancer therapy. European Journal of Cancer. 2017;76:167-182

[221] Ferris RL et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. The New England Journal of Medicine. 2016;375:1856-1867

[222] Borghaei H et al. Nivolumab versus docetaxel in advanced nonsquamous nonsmall-cell lung cancer. The New England Journal of Medicine. 2015;373:1627-1639
[223] Motzer RJ et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial. The Lancet Oncology. 2015;16(5):1473-1482

[224] Herbst RS et al. Lung master protocol (Lung-MAP)—A biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. Clinical Cancer Research. 2015;21(7):1514-1524

[225] Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): An open-label, multicentre, phase 1b trial. The Lancet Oncology. 2016;17(7):956-965

[226] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. The New England Journal of Medicine. 2015;372:2521-2532

[227] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. The New England Journal of Medicine. 2015;372:320-330

[228] Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. The New England Journal of Medicine. 2018;379(8):722-730

[229] Caponnetto S, Draghi A, Borch TH, Nuti M, Cortesi E, Svane IM, et al. Cancer immunotherapy in patients with brain metastases. Cancer Immunology, Immunotherapy. 2018;67(5):703-711

[230] Kanai O, Fujita K, Okamura M, Nakatani K, Mio T. Severe exacerbation or manifestation of primary disease related to nivolumab in non-small-cell lung cancer patients with poor performance status or brain metastases. Annals of Oncology. 2016;27(7):1354-1356

[231] Goldman JW, Crino L, Vokes EE, Holgado E, Reckamp K, Pluzanski A, et al. P2.36: Nivolumab (nivo) in patients (pts) with advanced (adv) NSCLC and central nervous system (CNS) metastases (mts): Track: Immunotherapy. Journal of Thoracic Oncology. 2016;11(10S):S238-S239

[232] Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480:480-489

[233] Hodi FS, O’Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. The New England Journal of Medicine. 2010;363(8):711-723

[234] Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: An open-label, phase 2 trial. The Lancet Oncology. 2012;13(5):459-465

[235] Long GV, Atkinson V, Menzies AM, Lo S, Guminski AD, Brown MP, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases (mts): The anti-PD1 brain collaboration (ABC). In: Abstract from the American Society of Clinical Oncology (ASCO) Annual Meeting. 2017

[236] Haanen J, Hwu WJ, Martín-Algarra S, Hodi FS, Bhatia S, Slights CL, et al. Efficacy and safety of nivolumab (NIVO) alone or combined with ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain in a phase 1 study. In: Poster from the Society for Melanoma Research Annual Meeting. 2016
[237] Silva IP, Johnpulle RAN, Banks PD, Grass GD, Smith JL, Everett AS, et al. Incidence, features and management of radionecrosis (RN) in melanoma patients (pts) treated with cerebral radiotherapy (RT) and anti-PD-1 antibodies (PD1). In: Abstract from the American Society of Clinical Oncology (ASCO) Annual Meeting. 2017

[238] Zang YW, Gu XD, Xiang JB, Chen ZY. Clinical application of adoptive T cell therapy in solid tumors. Medical Science Monitor. 2014;20:953-959. Epub 2014/06/11

[239] Weber JS. At the bedside: Adoptive cell therapy for melanoma—clinical development. Journal of Leukocyte Biology. 2014;95(6):875-882

[240] Hong JJ, Rosenberg SA, Dudley ME, Yang JC, White DE, Butman JA, et al. Successful treatment of melanoma brain metastases with adoptive cell therapy. Clinical Cancer Research. 2010;16(19):4892-4898

[241] Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science. 2015;348:62-68. A comprehensive review of the clinical development and potentially transformative impact of adoptive T-cell therapy on cancer by one of its pioneers; see also ref. [42]

[242] Mehta GU, Malekzadeh P, Shelton T, et al. Outcomes of adoptive cell transfer with tumor-infiltrating lymphocytes for metastatic melanoma patients with and without brain metastases. Journal of Immunotherapy. 2018;41(5):241-247

[243] Mullinax JE, Hall M, Prabhakaran S, et al. Combination of ipilimumab and adoptive cell therapy with tumor-infiltrating lymphocytes for patients with metastatic melanoma. Frontiers in Oncology. 2018;8:44. This is an interesting study and its design is a little similar to that of phase I study. The results showed that combination of ipilimumab and tumor-infiltrating lymphocytes was well tolerated and the efficacy is higher than those of any of the regimen itself in contrast to historical control

[244] Valiente M et al. The evolving landscape of brain metastasis. Trends in Cancer. 2018;4:176-196

[245] Cheng X, Hung MC. Breast cancer brain metastases. Cancer Metastasis Reviews. 2007;26:635-643

[246] Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. Journal of Clinical Oncology. 2009;27:5278-5286

[247] Bendell JC et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 2003;97:2972-2977

[248] Melisko ME, Glantz M, Rugo HS. New challenges and opportunities in the management of brain metastases in patients with ErbB2-positive metastatic breast cancer. Nature Clinical Practice. Oncology. 2009;6:25-33

[249] Lin NU et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. Journal of Clinical Oncology. 2008;26:1993-1999

[250] Lin NU et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clinical Cancer Research. 2009;15:1452-1459

[251] Bachelot T et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): A single-group
[252] Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Research and Treatment. 2008;112(3):533-543

[253] Kaufman B, Crown J, Chan A, Campone M, Viens P, Davidson N, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: Updated efficacy and biomarker analyses. Breast Cancer Research and Treatment. 2008;112(3):533-543

[254] Freedman RA et al. Translational breast Cancer research consortium (TBCRC) 022: A phase II trial of neratinib for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. Journal of Clinical Oncology. 2016;34:945-952

[255] Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes. Journal of Clinical Oncology. 2010;28:3271-3277

[256] Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings. Molecular Oncology. 2011;5:387-393

[257] Anders CK, Winer EP, Ford JM, Dent R, Silver DP, Sledge GW, et al. Poly(ADP-ribose) polymerase inhibition: “Targeted” therapy for triple-negative breast cancer. Clinical Cancer Research. 2010;16:4702-4710

[258] Lane AA, Chabner BA. Histone deacetylase inhibitors in cancer therapy. Journal of Clinical Oncology. 2009;27:5459-5468

[259] Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. Journal of Clinical Oncology. 2005;23:6207-6219

[260] Palmieri D, Lockman PR, Thomas FC, Hua E, Herring J, Hargrave E, et al. Vorinostat inhibits brain metastatic colonization in a model of triple-negative breast cancer and induces DNA double-strand breaks. Clinical Cancer Research. 2009;15:6148-6157

[261] Qian Y, Hua E, Bisht K, Woditschka S, Skordos KW, Liewehr DJ, et al. Inhibition of polo-like kinase 1 prevents the growth of metastatic breast cancer cells in the brain. Clinical and Experimental Metastasis. 2011;28:899-908

[262] Liu Z, Sun Q, Wang X. PLK1, a potential target for cancer therapy. Translational Oncology. 2017;10(1):22-32. Epub 2016/11/27

[263] Holohan C et al. Cancer drug resistance: An evolving paradigm. Nature Reviews. Cancer. 2013;13:714-726

[264] Albritton JL, Miller JS. 3D bioprinting: Improving in vitro models of metastasis with heterogeneous tumor microenvironments. Disease Models and Mechanisms. 2017;10(1):3-14

[265] Shi W, Lawrence YR, Choy H, Werner-Wasik M, Andrews DW, Evans JJ, et al. Vorinostat as a radiosensitizer for brain metastasis: A phase I clinical trial. Journal of Neuro-Oncology. 2014;118:313-319

[266] Ricciardi S, de Marinis F. Multimodality management of non-small cell lung cancer patients with
brain metastases. Current Opinion in Oncology. 2010;22(2):86-93

[267] Slotman BJ, Mauer ME, Bottomley A, Faivre-Finn C, Kramer GW, Rankin EM, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: Short-term health-related quality of life and patient reported symptoms: Results of an international phase III randomized controlled trial by the EORTC radiation oncology and lung cancer groups. Journal of Clinical Oncology. 2009;27:78-84

[268] Cagney DN et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: A population-based study. Neuro-Oncology. 2017;19:1511-1521

[269] Iuchi T et al. Frequency of brain metastases in nonsmall-cell lung cancer, and their association with epidermal growth factor receptor mutations. International Journal of Clinical Oncology. 2015;20:674-679

[270] Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. New England Journal of Medicine. 2004;350(21):2129-2139

[271] Porta R et al. Brain metastases from lung cancer responding to erlotinib: The importance of EGFR mutation. The European Respiratory Journal. 2011;37:624-631

[272] Iuchi T et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. Lung Cancer. 2013;82:282-287

[273] Wu YL et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: A phase II study (CTONG-0803). Annals of Oncology. 2013;24:993-999

[274] Heon S, Yeap BY, Britt GJ, Costa DB, Rabin MS, Jackman DM, et al. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. Clinical Cancer Research. 2010;16:5873-5882

[275] Mok TS et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. The New England Journal of Medicine. 2017;376:629-640

[276] Metro G et al. CSF concentration of crizotinib in two ALK-positive non-small-cell lung cancer patients with CNS metastases deriving clinical benefit from treatment. Journal of Thoracic Oncology. 2015;10:e26-e27

[277] Kim DW et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: A randomized, multicenter phase II trial. Journal of Clinical Oncology. 2017;35:2490-2498

[278] Gadgeel SM et al. Pooled analysis of CNS response to alectinib in two ALK-positive non-small-cell lung cancer studies of pretreated patients with ALK-positive non-small-cell lung cancer. Journal of Clinical Oncology. 2016;34:4079-4085

[279] Bafaloukos D, Gogas H. The treatment of brain metastases in melanoma patients. Cancer Treatment Reviews. 2004;30:515-520

[280] Long GV et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): A multicentre, open-label, phase 2 trial. The Lancet Oncology. 2012;13:1087-1095
[281] Davies MA et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): A multicentre, multicohort, open-label, phase 2 trial. The Lancet Oncology. 2017;18:863-873

[282] McArthur GA et al. Vemurafenib in metastatic melanoma patients with brain metastases: An open-label, single-arm, phase 2, multicentre study. Annals of Oncology. 2017;28:634-641

[283] Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. The New England Journal of Medicine. 2010;363:809-819

[284] Long GV, Kefford RF, Carr PJ. Phase 1/2 study of GSK2118436, a selective inhibitor of V600 mutant (MUT) BRAF kinase; evidence of activity in melanoma brain metastases (METS). Annals of Oncology. 2010;21(Suppl. 8):viii12

[285] Jain KK. Applications of Biotechnology in Oncology. New York: Springer; 2014

[286] Jain KK. Recent advances in nanooncology. Technology in Cancer Research & Treatment. 2008;7:1-13

[287] LeBrun A, Zhu L. Magnetic nanoparticle hyperthermia in cancer treatment: History, mechanism, imaging-assisted protocol design, and challenges. In: Shrivastava D, editor. Theory and Applications of Heat Transfer in Humans. Hoboken, NJ: Wiley; 2018:631-667

[288] Son KH, Hong JH, Lee JW. Carbon nanotubes as cancer therapeutic carriers and mediators. International Journal of Nanomedicine. 2016;11:5163-5185

[289] Al-Jamal WT, Kostarelos K. Liposomes: From a clinically established drug delivery system to a nanoparticle platform for theranostic nanomedicine. Accounts of Chemical Research. 2011;44:1094-1104

[290] Bozzuto G, Molinari A. Liposomes as nanomedical devices. International Journal of Nanomedicine. 2015;10:975-999

[291] Hamill RJ. Amphotericin B formulations: A comparative review of efficacy and toxicity. Drugs. 2013;73:919-934

[292] O’Brien MER. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX®/Doxil®) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Annals of Oncology. 2004;15:440-449

[293] Rafiyath SM, Rasul M, Lee B, et al. Comparison of safety and toxicity of liposomal doxorubicin vs. conventional anthracyclines: A meta-analysis. Experimental Hematological Oncology. 2012;1:10

[294] Gabizon A, Goren D, Horowitz AT, et al. Long-circulating liposomes for drug delivery in cancer therapy: A review of biodistribution studies in tumor-bearing animals. Advanced Drug Delivery Reviews. 1997;24:337-344

[295] Zhigaltsev IV, Maurer N, Akhong QF, et al. Liposome-encapsulated vincristine, vinblastine and vinorelbine: A comparative study of drug loading and retention. Journal of Controlled Release. 2005;104:103-111

[296] Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. Journal of Controlled Release. 2010;148:135-146

[297] Torchilin VP. Passive and active drug targeting: Drug delivery to
Innovations in Metastatic Brain Tumor Treatment
DOI: http://dx.doi.org/10.5772/intechopen.86047

[298] Passero FC, Grapsa D, Syrigos KN, Saif MW. The safety and efficacy of Onivyde (irinotecan liposome injection) for the treatment of metastatic pancreatic cancer following gemcitabine-based therapy. Expert Review of Anticancer Therapy. 2016;16:697-703

[299] Gaillard PJ, Appeldoor P, Dorland R, van Kregten J, Manca F, Vugts DJ, et al. Pharmacokinetics, brain delivery, and efficacy in brain tumor-bearing mice of glutathione pegylated liposomal doxorubicin (2B3-101). PLoS One. 2014;9(1):e82331

[300] Linot B, Campone M, Augereau P, Delva R, Abadie-Lacourtoisie S, Nebout-Mesgouez N, et al. Use of liposomal doxorubicin-cyclophosphamide combination in breast cancer patients with brain metastases: A monocentric retrospective study. Journal of Neuro-Oncology. 2014;117(2):253-259

[301] Akbarzadeh A, Rezaei-Sadabady R, Davaran S, et al. Liposome: Classification, preparation, and applications. Nanoscale Research Letters. 2013;8:102

[302] Stummer W, Pichlmeyer U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: A randomised controlled multicentre phase III trial. The Lancet Oncology. 2006;7(5):392-401

[303] Roy M, Niu CJ, Chen YH, McVeigh PZ, Shuhendler AJ, Leung MK, et al. Estimation of minimum doses for optimized quantum dot contrast-enhanced vascular imaging in vivo. Small. 2012;8:1780-1792

[304] Zhou RH, Li M, Wang SL, Wu P, Wu L, Hou XD. Low-toxic Mn-doped ZnSe/ZnS quantum dots conjugated with nano-hydroxyapatite for cell imaging. Nanoscale. 2014;6:14319-14325

[305] Li ZS, Xu W, Wang YT, Shah BR, Zhang CL, Chen YJ, et al. Quantum dots loaded nanogels for low cytotoxicity, pH-sensitive fluorescence, cell imaging and drug delivery. Carbohydrate Polymers. 2015;121:477-485

[306] Lee J, Kang HJ, Jang H, Lee YJ, Lee YS, Ali BA, et al. Simultaneous imaging of two different cancer biomarkers using aptamer-conjugated quantum dots. Sensors. 2015;15:8595-8604

[307] Sureshkumar S, Jothimani B, Sridhar TM, Venkatachalapathy B. Synthesis and characterization of gadolinium doped ZnSe quantum dots for fluorescence imaging of cancer cells. RSC Advances. 2016;6:16081-16086

[308] Karamanos Y, Pottiez G. Proteomics and the blood-brain barrier: How recent findings help drug development. Expert Review of Proteomics. 2016;13:251-258

[309] Huang N, Cheng S, Zhang X, Tian Q, Pi JL, Tang J, et al. Efficacy of NGR peptide-modified PEGylated quantum dots for crossing the blood-brain barrier and targeted fluorescence imaging of glioma and tumor vasculature. Nanomedicine. 2017;13:83-93

[310] Wu CF, Hansen SJ, Hou Q, Yu JB, Zeigler M, Jin YH, et al. Design of highly emissive polymer dot bioconjugates for in vivo tumor targeting. Angewandte Chemie (International Edition). 2011;50:3430-3434

[311] Maguire AM et al. Age-dependent effects of RPE65 gene therapy for Leber’s congenital amaurosis: A phase 1 dose-escalation trial. Lancet. 2009;374:1597-1605
[312] Marks WJ Jr et al. Gene delivery of AAV2-neurturin for Parkinson’s disease: A double-blind, randomised, controlled trial. Lancet. 2010;9:1164-1172

[313] Green NK, Seymour LW. Adenoviral vectors: Systemic delivery and tumor targeting. Cancer Gene Therapy. 2002;9:1036-1042

[314] Ostertag D, Amundson KK, Espinoza FL, Martin B, Buckley T, Galvao da Silva AP, et al. Brain tumor eradication and prolonged survival from intratumoral conversion of 5-fluorocytosine to 5-fluorouracil using a nonlytic retroviral replicating vector. Neuro-Oncology. 2012;14(2):145-159

[315] Perez OD et al. Design and selection of Toca 511 for clinical use: Modified retroviral replicating vector with improved stability and gene expression. Molecular Therapy. 2012;20:1689-1698

[316] Hickey MJ, Kasahara N, Mueller BM, Kruse CA. Combining cellular and gene therapy approaches for treatment of intracranial tumors. Oncoimmunology. 2013;2(10):e25989

[317] Reinshagen C, Bhere D, Choi SH, Hutten S, Nesterenko I, Wakimoto H, et al. CRISPR-enhanced engineering of therapy-sensitive cancer cells for self-targeting of primary and metastatic tumors. Science Translational Medicine. 2018;10(449)

[318] Cooper ML, Choi J, Staser K, Ritchey JK, Devenport JM, Eckardt K, et al. An ‘off-the-shelf’ fratricide-resistant CAR-T for the treatment of T cell hematologic malignancies. Leukemia. 2018;32(9):1970-1983

[319] Mukherjee S. The Emperor of All Maladies: A Biography of Cancer. New York: Simon & Schuster; 2010

[320] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: A Cancer Journal for Clinicians. 2018;68(1):7-30

[321] Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Goncalves A. Recent trends in epidemiology of brain metastases: An overview. Anticancer Research. 2012;32(11):4655-4662

[322] Gordon RJ. Why has economic growth slowed when innovation appears to be accelerating? CEPR Discussion Papers 13039, C.E.P.R. Discussion Papers. 2018

[323] Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. Nature Reviews. Drug Discovery. 2012;11(3):191-200

[324] Dubois P, de Mouzon O, Scott-Morton F, Seabright P. Market size and pharmaceutical innovation. The RAND Journal of Economics. 2015;46(4):844-871

[325] Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. JAMA Internal Medicine. 2017;177(11):1569-1575

[326] Shambaugh J, Nunn R, Breitwieser A, Liu P. The state of competition and dynamism: Facts about concentration, start-ups, and related policies. The Hamilton Project. 2018:1-36

[327] Vaishampayan UN. Changing face of metastatic prostate cancer: The law of diminishing returns holds true. Current Opinion in Oncology. 2017