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Chapter

Overview of Brain Metastasis and Treatment Modalities

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Abstract

Brain metastasis (BM) is the commonest form of intracranial malignancy, historically considered a single disease entity with a gloomy outcome, often resulting in a palliative approach to clinical management. Primary cancers that most frequently spread to the brain are lung, breast, and renal carcinomas as well as malignant melanomas. Global incidence of brain metastasis is on the rise but may still be underestimated. About 67% of patients with BM present with either generalized or focal symptoms and sometimes both. A thorough clinical workup and application of verified prognostic scores lead to optimal stratification and strongly influences therapeutic decisions and patients’ outcomes. Management is multidisciplinary and involves symptomatic treatment, use of best supportive care, radiotherapy, surgery as well as targeted therapy.

Keywords: brain metastasis, cancer, brain tumors, neurological symptoms, whole brain radiotherapy, stereotactic radiosurgery

1. Introduction

Brain metastasis (BM) is the commonest group of intracranial tumors and is considered a direct neurological complication of cancer. It is 10 times more frequent than primary brain neoplasms [1], occurring at a median time of 8.5–12 months from primary diagnosis. About 20–40% of adult cancer patients develop brain metastases, with 40% of these presenting with a limited number of lesions (i.e., 1–4 lesions whereas 60% present with multiple lesions. Brain metastasis is the direct cause of death in 30–50% of cases [2]. Improved cancer survival is one of the key reasons for the rise in prevalence of brain metastasis (Reference). Brain metastasis generally has poor prognosis, causes significant morbidity and is fatal if left untreated. Median survival time ranges from 4.9 to 16.4 months [3]. Localization of brain metastases is influenced by the arterial blood flow distribution with about 80% localized in the cerebral hemispheres, 15% in the cerebellum and 5% in the brainstem [4]. Research has shown a strong correlation between the localization of brain metastases and clinical outcomes, as such infratentorial metastases though not frequent have the worst prognosis [5].
2. Epidemiology

Population-based studies show global incidence ranging from 8.3 to 14.3 per 100,000 population per year. This is likely underestimated owing to significant inaccuracies associated with these population and pathologic studies [6]. Any type of cancer can metastasize to the brain, however the three commonest primary tumors associated with brain metastases are lung (20–56%), breast (5–20%) and malignant melanomas (7–16%) [2, 6, 7]. Data from the Surveillance, Epidemiology, and End Results (SEER) Program indicate that patients with either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) have the highest rates of brain metastases at diagnosis, whilst patients with malignant melanomas have the highest risk of presenting with metastatic brain disease. By contrast cancers of the prostate, head and neck, skin (non-melanoma skin cancer), and esophagus rarely metastasize to the brain (Figure 1) [6].

3. Risk factors

Tumor site and molecular subtype of primary tumors are important factors that influence the risk of distant brain metastases among cancer patients. Some tumors have very high propensity to metastasize to the brain whereas other tumors rarely spread to the brain. For instance, ALK-rearranged NSCLC specifically metastasizes to the brain. Patients with human epidermal growth factor receptor 2 (ERBB2 or HER2) amplification or triple-negative breast cancers (TNBC) have a higher risk of developing brain metastases than those with other molecular subtypes of breast cancer [9]. Other risk factors include advanced age, sex, ethnicity, and geographic location.

4. Pathobiology

The blood-brain barrier (BBB) protects the brain from the effect of chemicals in the blood circulatory system. The BBB maintains normal brain function by tight
regulation of transfer of molecules and ions between blood and the brain. The BBB is made up of endothelial cells. Its basement membrane is adjoined by tight cell-to-cell junction proteins with specific transport mechanisms and pinocytic vesicles. The endothelium is further surrounded by cellular elements including pericytes and astroglia foot processes (end foot processes), forming an additional continuous stratum that reinforces the barrier [10]. This barrier permits only small uncharged compounds to diffuse from blood into the brain without a specific transporter.

Metastasis of cancer cells is a multifaceted process that has been simplified in several critical steps. It involves epithelial to mesenchymal transition (EMT) of cancer cells at their primary site, extracellular matrix modulation, intravasation, circulation, extravasation, homing, formation of the premetastatic niche for organotypic colonization and mesenchymal–epithelial transition (MET) at the secondary site. This stepwise process takes into account the interaction between the tumor and the tumor micro-environment, host immunity and secondary site micro-environment.

Multiple hypotheses have been proposed to explain metastatic patterns observed among different primary cancers. Two longstanding theories on the metastatic spread of cancer are the “seed and soil” hypothesis and mechanical theory [11, 12]. The “seed and soil hypothesis” seems to best explain the pathophysiology of brain metastases with the following steps.

1. A normal cell undergoes multiple genetic mutations or epigenetic changes to transform into a malignant cell.

2. The transformed cell proliferates uncontrollably and undergoes angiogenesis.

3. There is invasion of normal tissue stroma and intravasation of tumor cells into blood vessels or lymph channels.

4. Tumor cells in blood vessels overcome the shear stress of blood circulation and evade immune cells.

5. Surviving tumor cells get to the capillary bed and then gain access to arterial circulation.

6. Extravasation and seeding of the brain, usually at the gray-matter/white-matter junction.

7. If the “soil” (brain) microenvironment is favorable, the tumor cells may leave brain capillaries form a metastatic brain lesion.

BM requires synergy between cancer cells and the parenchymal tissue of the central nervous system (CNS). Different primary tumors are characterized by distinct patterns of brain metastasis. Clonal cells of primary tumors undergo a series of genetic changes as they accumulate more and more mutations in their DNA with subsequent divisions and damage of repair mechanisms. This contributes to genomic instability which is associated with the activation of genes that promote abnormal cellular growth and the silencing of genes that regulate the cell cycle. Ultimately, this culminates in the immortalization of cancer cells. This is classically seen in the inactivation of the Retinoblastoma (Rb) protein and destruction of the p53 protein which plays a key role in the pathogenesis of Human Papilloma Virus 16 (HPV 16)-associated head and neck
cancers as well as HPV-positive cervical cancers [13]. Mutations downstream from the parent stem cell with subsequent mutations result in a heterogeneous tumor with some cells having the propensity to metastasize. As tumors continue to proliferate and increase in size, increased demand for nutrition and oxygenation to maintain growth triggers angiogenesis. Switch for angiogenesis requires a tip of the balance between pro and anti-angiogenic factors towards the former. This occurs as hypoxia sets in at tumor regions far from blood supply. Under hypoxic conditions, Hypoxia Inducible Factor (HIF) is activated. HIF-1α is stabilized because of the lack of oxygen and dimerizes with HIF-1β to bind to the hypoxia response element (HRE; 5'-G/ACGTG30'). HIF-1 activates the transcription of target genes by interacting with co-activator CBP/p300. These genes regulate and promote glucose transporters and glycolysis, angiogenesis, proliferation, invasion and metastasis [14]. HIF controls the activity of VEGF over-expression promoting angiogenesis; however, blood vessels are poorly formed and defective. Newly formed blood vessels are tortuous and dilated with endothelial cells forming a monolayer and resting on a basement membrane of variable thickness and pericytes forming loose associations of endothelial cells [14, 15]. This results in leakiness of the vessel formed and gives rise to chronic hypoxia in the tumor. This leakiness in the newly formed vasculature also serves as an easy portal for cancer cells to circulate in the bloodstream. HIF-dependent upregulation of transcription repressors of E-cadherin, such as zinc finger protein SNAI1 (SNAIL), twist related protein 1 (TWIST1), transcription factor 3 (TCF3), zinc finger E-box-binding homeobox 1 and 2 (ZEB1 and ZEB2) results in loss of receptors [14, 16]. E-cadherin among others is a major component of adherent junctions that maintain the integrity of the epithelium. This loss is a functional requirement for EMT [14].

EMT is a natural phenomenon that is employed during embryogenesis. Cancer cells employ this principle to aid distant spread. It is a biochemically stimulated process during which epithelial cells acquire a mesenchymal phenotype through EMT transcription factors (these repress epithelial genes and promote mesenchymal genes) [15]. It encompasses changes in multiple phenotypic characteristics including but not limited to apicobasal polarity, cell-cell adhesion, cytoskeleton remodeling and cell-matrix adhesion as well as the gain of mesenchymal markers such as vimentin and alpha smooth muscle actin (αSMA) [16]. All these changes promote the detachment of cancer cells from the parent tumor into the extracellular matrix. Using proteolytic enzymes such as metalloproteinase degrades the extracellular matrix and travels through the extracellular matrix to reach blood and lymphatic vessels [17].

Neo-vascularization by tumor is ineffective as described earlier hence cancer cells easily enter the lumen of blood vessels. In areas where blood vessels do not have the defect of leakiness, intravasation is achieved by use of enzymes such as heparinase which degrades the basement membrane of vessels and allows cancer cells to enter circulation. Circulation is not a friendly environment for the cell because of host immune system that attacks and lyases these cancer cells. Cancer cells have developed strategies for evasion of host immune defense mechanisms through immune mimicry [15]. This is achieved by upregulating specific receptors such as integrins and protein death ligand 1 (PD-L1) that bind to platelets and host leukocytes to form a complex structure which facilitates immune evasion and also protects cancer cells from mechanical damage [17].

Metastatic tumor cells travel along blood vessels and can get trapped in smaller vessels (end arteries of the brain). Here they adhere to the endothelial lining and have to break through the BBB described earlier. There are various hypotheses that have been generated over the years to explain how this occurs. Three of these hypotheses
are; First, tumor adhere to proteins expressed by endothelial cells allowing them to cross the BBB into the perivascular space; Second, tumor cells adhere to systemic immune cells via receptor-ligand interactions and cross through the BBB with the “hijacked” cells; Third, tumor cells modify the endothelial cell wall by stimulating expression of matrix metalloproteases (MMPs), allowing extravasation into the perivascular space [10]. Hereafter there is local extracellular matrix (ECM) remodeling to suit the tumor cells and this is achieved through paracrine interactions between the brain stromal, endothelial wall and invading tumor cells [18]. Proteolytic degradation of the ECM by enzymes such as heparinase concentrated mainly around the region of the advancing cancer cell membrane promotes the breakdown of the endothelial wall into the brain parenchyma. Astedt et al noted urokinase-type plasminogen activator (uPA) is produced and released from cancer cells. Also, tumor associated serine protease plasmin, its activator uPA, the receptor uPA-R (CD87), and plasminogen activator inhibitor type 1 and 2 (PAI-1/2) are linked to cancer invasion and metastasis [19]. At the BBB Urokinase converts the zymogen plasminogen to plasmin, a trypsin-like enzyme with broad substrate specificities. uPA binds to the surface of the cell membrane and causes localized cell surface proteolytic activity, which is required for the destruction of the ECM. PAI-1 modulates the activity of uPA. Plasmin on the other hand activates the other proteolytic enzymes (such as metalloproteases) and degrades components of the ECM as well [18]. In the brain perivascular or parenchymal space, tumor cells adhere for survival through the E-cadherin-catenin complex. This process is a reversal of the epithelial to mesenchymal transition that was seen at the initial stages of metastasis [10]. Through interaction between the tumor cells, ECM and stroma, multiple cytokines, growth factors and enzymes are secreted by microglia and macrophages to promote inflammation, growth and survival of the tumor cells. For instance, vascular endothelial factor (VEGF) promotes angiogenesis, epidermal growth factor (EGF) promotes tumor proliferation and matrix metalloproteases promotes further invasion of tumor cells in the brain. Vessels are poorly formed in this process as described earlier and this results in leakage of water, proteins, and inflammatory mediators at the site of metastasis resulting in edema (perilesional edema as seen on imaging studies).

Specifically in malignant melanoma, expression of programmed death ligand 1 (PD-L1) by microglia promotes invasion of tumor cells and inhibits cytotoxic T cell activity [20]. Furthermore, there is production of proinflammatory chemokine CXCL10 and release of Interleukin 23 (IL-23) as a result of interaction between tumor cells and astrocytes. CXCL10 chemokine attracts T lymphocyte cells as well as tumor cells via CXC3R. Thus, malignant melanoma is the seed and astrocytes make the brain a suitable soil for metastasis. Both malignant melanoma and neural cells originate from neural crest cells hence express neurotrophin receptors (such as P75NRT and TrkC) [21]. This is regulated by neural growth factor (NGF) and neurotrophin 3 secreted by astrocytes and resulting in promoting invasion [20].

Brain tissue uniquely appears to downregulate the expression of the tumor suppressor “phosphatase and tensin homolog” (PTEN) culminating in the growth of tumor in the brain microenvironment in lung cancer. MicroRNA (specifically miR-19) released from astrocytes plays a role in downregulating PTEN expression in invading tumor cells [22]. Over-expression of a disintegrin and metalloprotease 9 (ADAM9) protein promotes migration and expression of integrin 1 on lung cancer cells. This results in adhesion to endothelial cells. It may also increase the activity of tissue plasminogen activator (tPA) culminating in angiogenesis, tumor invasion and proliferation [23]. The chemokine CXCL12 binds the G-protein-coupled receptor
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CXCR4 and stimulates the pathways leading to chemotaxis, enhanced intracellular calcium, tumor growth, invasion, homing, angiogenesis and metastasis [24].

In breast cancer, activation of the AKT/MAPK signaling pathway stimulates upregulation of interleukin 6 and 8 (IL-6 and IL-8), B-cell lymphoma 2L1 (BCL2L1), TWIST1, and glutathione S-transferase A5 (GSTA5) anti-apoptotic genes that are responsible for breast cancer metastases to the brain [25]. Phospholipid-binding proteins such as annexin A1 (ANXA1 or lipocortin) ignite CXCR4-mediated migration of breast cancer cells in response to stromal cell derived factor 1α (SDF-1α) which incorporates with CXCR4 [26]. This promotes penetration of breast cancer cells into human brain microvascular endothelial cells [27].

Wyler et al. studied the chemokine and chemoreceptors in 246 autopsy specimens that could explain the frequency and patterns of brain metastasis in renal cell carcinoma (RCC) at autopsy [28]. In all, 15% of the sample had brain metastasis. CXCR4 expression levels were 85.7% and 91.7% in primary RCC and brain metastases respectively. CCR2 and CCL7 expression were 52.1% and 75% respectively metastatic brain cells as compared with primary tumors (15.5% and 16.7%, respectively; P<0.0001 each). CD68+ tumor-associated macrophages (TAMs) were similar in primary RCC and brain metastases. However, TAMs were more frequently CCR2-positive in brain metastases than in primary RCC (P < 0.001) [28]. This further confirms the changes seen in chemokine and chemoreceptor expression seen in metastatic brain tumor cells.

There is uneven distribution of metastatic lesions in the brain. This distribution is partly explained by the tissue volume in these areas. The lesions are distributed along the grey-white matter junctions and tumor emboli lodges in capillary beds with smaller diameter (thus the watershed distribution). However, it should be noted that the within the cerebral hemisphere, distribution in the frontal and parietal region is higher than the temporal and occipital region as related to the mass of these regions. In the cerebrum, some literature have suggested that the Batson venous plexus via a retrograde pathway through the basilar plexus of veins plays a role in the preferential metastasis of abdominal and pelvic primary lesions [29]. The incidence of vertebral bone metastasis also via this pathway is well documented in literature for prostate, renal, breast, lung and colon cancers [30].

Stephen Paget first proposed that metastatic development was a consequence of particular tumor cells (‘seeds’) finding a suitable environment (‘soil’) in order to develop and grow. James Ewing on the other hand proposed that circulatory patterns between the primary tumor and specific secondary organs are sufficient to explain the majority of organ-specific metastatic spread thus the mechanical hypothesis. Interplay between tumor molecular, epigenetic, genetic factors and that of secondary site all contribute to the metastasis of specific tumors to the brain. Presented here is a brief overview of this in-depth picture.

5. Clinical presentation

The clinical manifestation of distant metastatic brain lesions is associated with a wide array of signs and symptoms that are influenced by the region of the brain involved as well as the extent of peritumoral edema. There is a need for high index of suspicion among cancer patients because some of these symptoms can be as vague as mild headaches or mood changes and may be easily taken for granted. Some lesions may be asymptomatic and discovered as incidental findings on brain imaging studies done for other unrelated reasons. Progression of intraparenchymal metastasis may lead to...
leptomeningeal spread [31]. Leptomeningeal spread occurs in both adults and children especially those with acute leukemia and lymphomas. Intracranial metastasis can present as hemorrhagic or cystic lesions on imaging. The former is likely to occur in cancer types such as renal cell carcinoma, choriocarcinoma, thyroid carcinoma as well as malignant melanoma whereas the latter is predominantly associated with gastro-intestinal malignancies. Common signs and symptoms presented by patients include the following.

5.1 Headache

Headache is a common presenting complaint among 32% - 54% of cancer patients who are diagnosed with brain metastasis [31, 32]. As many as 71% of brain neoplasms are associated with tension headache. Under normal physiologic conditions, the brain is largely insensate demonstrated in neurosurgical procedures in which stimulation of the brain parenchyma in awake patients caused no pain. Projections from the trigeminal [33] and upper cervical dorsal root ganglia innervate the pial, dural, and extracranial blood vessels. Therefore, metastatic brain lesions with their associated peritumoral edema cause pressure and stretching of the pia and dura matter resulting in stimulation of the unmyelinated C fibers (afferent neurons). These fibers transmit the nociceptive information mediated by glutamate through the trigeminal ganglia to synapses on second-order neurons within the trigeminal nucleus. Headache associated with increased ICP typically worsens in the morning and is aggravated with coughing, carotid massage, or Valsalva maneuver. Multiple brain lesions and localization in the posterior cranial fossa are associated with more frequent headaches.

5.2 Increased intracranial pressure (ICP)

The skull bone provides a fixed space that accommodates a person's brain tissue and associated meninges, CSF and vasculature. The presence of a lesion that is increasing size increases the ICP in this fixed space. As a result, there are symptoms that occur due to increased ICP such as altered level of consciousness (confusion), headache, nausea, vomiting and visual disturbance in the form of blurred vision or diplopia. Vomiting is more common with children than adults.

5.3 Seizure

Seizures are potential life-threatening complications of brain metastases; and are a presenting symptom in up to 40% of patients [34]. The risk of developing a seizure is influenced by the tumor type, the location and its proximity to the cortical gray matter. Prophylactic anticonvulsants are not recommended for routine use by the ASCO guidelines in patients with brain metastases who have not undergone surgical resection and who are otherwise seizure free. It's routine use in the post craniotomy setting for seizure-free patients with brain metastases is not recommended either (Level 3 evidence).

5.4 Cerebrovascular accident (CVA)

Hemorrhagic strokes can occur from metastatic brain lesions with intrallesional bleeding, vascular invasion, or embolization of tumor cells. Cancers such as malignant melanoma, choriocarcinoma, thyroid and renal carcinoma are associated with this kind of presentation.
5.5 Altered level of consciousness

The reticular activating system (RAS) is a component of the reticular formation, found in the brainstem. The reticular formation receives afferent neurons from the spinal cord, sensory pathways, thalamus, and cortex and has efferent connections throughout the nervous system. The RAS is composed of four groupings of nuclei namely locus coeruleus, raphe nuclei, posterior tuberomammillary hypothalamus and pedunculopontine tegmentum. The locus coeruleus is located within the upper dorsolateral pons [35] whiles raphe nuclei are located midline throughout the brainstem within the pons, midbrain, and medulla [36]. The tuberomammillary nucleus is located within the posterior aspect of the hypothalamus [37]. The lateral and dorsal pedunculopontine tegmentum lies within the midbrain and pons [38]. Each is unique in the neuropeptides they release, however these centers are largely activated by the lateral hypothalamus (LH), via the release of the neuropeptide orexin in response to the light hitting the eyes, which then stimulates arousal and the transition from sleep to waking [39]. Disruption and inactivation of the intricate network of the RAS decreases the release of neurotransmitters (serotonin, histamine, norepinephrine and nitric oxide) needed for arousal and wakefulness. This results in altered level of consciousness manifested by inattentiveness, drowsiness, decreased cognition, memory impairment, confusion and even hallucinations.

5.6 Focal neurological symptoms

Focal neurological symptoms may manifest on the side of the body opposite to the location of the lesion in the brain. Metastatic brain lesions are usually located in cerebral cortex (80%), cerebellum (15%) and brainstem (5%) [40, 41]. Focal symptoms may manifest as unilateral limb weakness known as Todd's paralysis. Some neurological symptoms are directly dependent on the exact localization of metastatic lesions in the lobes of the brain.

5.6.1 Frontal lobe lesions

Tumor metastasis in the frontal lobe can affect motor function, speech, attention, planning, change in personality and ability to solve problems. Focal weakness is common.

5.6.2 Parietal lobe

Parietal lobe lesions can affect one or several of the core functions of the parietal lobe namely, vision, perception, sensation and spatial-visual coordination. This results in symptoms such as apraxia, right-left confusion, inability to read, write or complete simple calculations.

5.6.3 Temporal lobe

Important cerebral structures in the temporal lobe include the hippocampus, auditory cortex as well as Wernicke's area. Lesions in the temporal lobe may affect the function of these structures leading to receptive aphasia, impaired speech recognition and inability to store new memories.
5.6.4 Occipital lobe

The occipital lobes house the visual cortex. Metastatic lesions affecting this lobe can result in hemianopsia or cortical blindness.

6. Clinical workup

The initial workup of patients with metastatic brain lesions must include a complete history and physical examination. Immediate relatives and close friends are also a good source of information concerning changes in mental state which the patient may not appreciate as important. During this exercise, the clinician probes into the onset and clinical course of symptoms as well as any history of a previous diagnosis of cancer, previous surgeries and their indication and biopsy taken. A high index of suspicion is present if patient has a known history of cancer and presents with a change in mentation. Physical examination is performed to document firstly the patient’s current neurologic deficit and this serves as a baseline for assessment to treatment responds later.

Imaging studies help to confirm a lesion in the brain. Magnetic resonance imaging (MRI) with a gadolinium (Gd)-containing contrast agent is the imaging modality of choice for brain metastasis. Gd-based contrast leaks into parenchyma in areas with BBB breakdown, and the paramagnetic properties of Gd generate hyperintense signal on T1 weighted images. These images are better at demonstrating the anatomy and areas of contrast enhancement just like a contrast enhanced CT scan (which in place of MRI is helpful in a low resource setting) however a better tumor delineation is seen on MRI. T2 weighted and FLAIR images are more sensitive for detecting edema and tumor infiltration.

Computed tomography (CT) scan can be used in situations in which MRI is contraindicated, such as implanted pacemaker, metal fragment or metallic implants. In low-resource countries, a Ct scan done in a planning position saves cost as this can be used to confirm diagnosis radiologically and for radiation treatment. A biopsy of the primary lesion and further immunohistochemistry is essential in the management of brain metastasis as this helps determine the choice of treatment and may predict the responds to treatment.

Examination of blood and serum should include full blood count, renal and liver function tests, and, if any risk factors are present such as HIV antibody status.

7. Prognostic classification

Prognostic classification of brain metastatic disease patients has important implications for patient education and choice of treatment approach. A recursive partitioning analysis of 1200 patients enrolled in one of three consecutive Radiation Therapy Oncology Group (RTOG) trials established three classes (I -III) of patients with different survival estimates based on four key prognostic factors: age, Karnofsky performance status (KPS), evidence of control of the primary tumor and the status of extracranial metastases.

Additional prognostic classification systems have provided an initial framework for estimating a patient’s overall survival. These systems include firstly, the Score
Index for Radiosurgery (SIR), which was developed for the classification of patients undergoing Stereotactic radiosurgery (SRS) and hence placed importance on the number and the volume of brain metastases [42]. Secondly, the Basic Score for Brain Metastases in which Karnofsky Performance Score, control of the primary tumor and presence of extracranial disease are used to estimate survival [43].

8. Management

The management of metastatic brain disease requires a multimodality approach involving radiation oncologists, neurosurgeons, neurologists and clinical psychologists amongst others. Treatment options for brain metastases include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), conventional surgery, and systemic therapies (chemotherapy, immunotherapy).

8.1 General management

The general management of patients with metastatic brain lesions includes control of increased intracranial pressure (ICP) and seizures. ICP is due the lesion growing in a fixed space with associated perilesional edema. This manifests as headaches, blurred vision or diplopia, nausea, vomiting and seizures as seen in primary brain lesions. If left unresolved increased ICP can eventually result in coning. Steroids are employed to control the neurologic signs and symptoms associated with cerebral edema caused by metastatic brain lesions.

Kofman first used prednisone for the management of perilesional edema due to brain metastasis in 1957 [44]. Years afterwards, dexamethasone revolutionized care of brain lesions by alleviating cerebral edema. Dexamethasone like other glucocorticoids interacts with the glucocorticoid receptor (GR) which is encoded by a gene located on chromosome 5 [45]. Ligand binding of GR can result in a direct induction or repression of target gene expression and this in turn gives rise to a multitude of steroid exerted effects. The result is a reduction of perilesional edema and a decrease in the permeability of the blood brain barrier [46]. Though there are other medications in this group, dexamethasone is the most commonly used. It has a biological half-life of more than 30 hours with minimal mineralocorticoid effect as compared to hydrocortisone, prednisone, cortisone and methylprednisolone [45]. Steroids are metabolized in the liver in a cytochrome P450-dependent manner therefore a p450 inducer affects the bioavailability of the medication as seen in combined use with anti-seizure medication such as phenytoin carbamazepine and phenobarbital [47]. Non-enzyme-inducing anticonvulsants, such as levetiracetam, lacosamide, lamotrigine, and pregabaline, are preferred in the management of seizures associated with brain metastasis.

Veicht et al in a randomized trial compared 8 mg dexamethasone versus 16 mg dexamethasone or 4 mg versus 16 mg in patients with brain metastases [48]. A similar improvement of the Karnofsky performance status was observed in all groups. However, side effects were significantly more frequent in patients treated with 16 mg dexamethasone per day. Steroids can be stopped without tapering down for a short period of time however prolonged administration lasting for weeks or months requires tapering over a longer period of time to avoid hypocortisolism due to suppression of adrenal function [49]. Effects of long-term use of steroids include osteoporosis, steroid-induced diabetes, myopathy, thromboembolic event, psychiatric disorders and immunosuppression. Furthermore, Patients on glucocorticoids may
experience symptoms of gastric irritation which may not translate into an increased risk of peptic ulcer disease (PUD) with only 0.4% of this group developing it [50]. However, the combination of glucocorticoids with nonsteroidal anti-inflammatory medication increases the risk for PUD [51]. Proton pump inhibitors are started to counter this effect.

8.2 Radiotherapy

Different types of cancers have different sensitivities to radiation. Small cell lung cancer and germ cell tumors are very sensitive to radiation whereas lung and breast cancers are only moderately sensitive to radiation. Malignant melanoma and renal cell carcinoma are less sensitive to radiation.

8.2.1 WBRT

WBRT involves irradiating the entire brain and is considered to be a standard of care in select patients with diffuse brain metastasis (≥5 brain metastases). It is also considered for patients in whom surgery or stereotactic radiosurgery (SRS) is not recommended, for example, those with leptomeningeal disease, innumerable metastases, low RTOG DS-GPA scores or medical contraindications. It has the advantage of simplicity of delivery and the ability to treat both local and distant intracranial disease. There is no consensus on the optimal dose and fractionation schedule for WBRT, despite multiple studies to determine the optimal delivery.

An updated Cochrane review from 2018 support the use of a biologically effective WBRT doses, with respect to consequences for survival and improvement in neurological function. WBRT dose of 30 Gy in 10 fractions, as opposed to a lower total of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions continue to remain the standard for a vast majority of patients receiving WBRT. Nieder et al. reported the radiographic overall response rate with this fractionation scheme to be 59%. For patients with poor performance status, and/or uncontrolled extracranial disease, a shorter fractionation scheme (e.g., 20 Gy in 5 fractions) or best supportive care can be considered.

A phase III randomized, noninferiority study, the QUARTZ (Quality of Life after Treatment of Brain Metastases) trial, compared the Quality Adjusted Life Years (QALY) between optimal supportive care (OSC) alone and OSC + WBRT (20 Gy in 5 daily fractions) for NSCLC patients with brain metastases unsuitable for resection or stereotactic radiotherapy. OSC consisted of dexamethasone titrated based on patient's symptoms as well as patient access to palliative care clinicians and nurses. Results revealed a difference in mean QALY of 4.7 days (46.4 QALY days for OSC + WBRT vs. 41.7 QALY days for OSC), which was within the prespecified noninferiority margin of 7 days. Overall survival was not significantly different between randomization arms (OSC + WBRT: 9.2 weeks vs. OSC alone: 8.5 weeks). Subgroup analysis suggested a survival benefit in favor of OSC + WBRT for patients younger than 60, KPS ≥ 70, and controlled extracranial primary disease.

The role of surgery and WBRT in patients with a single metastatic lesion in the brain has been demonstrated to improve both OS and local control (LC) in several trials. In a study by Patchell et al, the efficacy of biopsy sampling plus WBRT was compared with that of WBRT and complete resection in 48 patients with a single metastatic lesion in the brain. Both OS (median 40 weeks versus 15 weeks; P < 0.01) and local control (median 38 weeks versus 8 weeks; P<0.005) were improved with surgical resection [52]. In another study by Noordijk et al. similar outcomes were
reported in a trial involving 63 patients randomized to either surgical resection plus WBRT or to WBRT alone (median OS 10 months versus 6 months; \( P = 0.04 \)), with those with controlled extracranial disease having the best outcomes [53].

Acute adverse effects of WBRT include skin erythema, alopecia, fatigue, serous otitis and an altered sense of smell and taste. Late-onset adverse effects, such as memory loss, confusion and leukoencephalopathy. The late effects are of most concern to patients, caregivers and health care providers. Effects of WBRT on neurocognitive function (NCF) are best assessed using objective psychometric tests such as Hopkins Verbal Learning Tests (HVLT), Controlled Oral Word Association, Grooved Pegboard test, and Trail Making Tests Parts A and B.

Strategies to mitigate neurocognitive decline from WBRT include the use of Memantine (a non-competitive NMDA receptor antagonist that retains activated NMDA receptors in an open-channel state, thus preserving long-term potentiation) and hippocampal avoidance (HA-WBRT).

In the RTOG 0614 trial, Memantine was started once daily with WBRT and increased to 10 mg twice daily over a few weeks, for a total of 24 weeks. The primary end point was preservation of cognitive function particularly memory function, which was assessed using the revised HVLT (HVLT-R) to measure changes in delayed recall at 24 weeks. Patients in the memantine arm had less decline in performance on HVLT-R delayed recall at 24 weeks: median decline was 0 in the memantine arm versus –0.9 in the placebo arm at 24 weeks, although this difference was not statistically significant \( P = 0.059 \) [54].

8.2.2 Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a minimally invasive treatment option in the management of brain metastases with efficacy demonstrated in several randomized trials and multi-institutional studies. It is associated with similarly high efficacy for both radiosensitive and radioresistant tumors. SRS is a preferred option mainly because of the limited area irradiated. It is however limited by its small therapeutic ratio in lesions \( \geq 4 \text{cm} \) and/or tumor localization in the brainstem. This limitation has recently been solved with the use of fractionated SRS given in 3–7 fractions which typically results in a good therapeutic ratio with high local control rates (75–85%) and lower toxicity rates for large lesions.

SRS can be used alone or as a combined modality with WBRT or surgery. SRS has demonstrated superior local tumor control and functional autonomy for patients with brain metastases when combined with WBRT compared with WBRT alone. Patients with single metastatic brain lesions also experience longer survival with the use of SRS combined with WBRT. The reported survival for patients with RPA prognostic class I is 18–24 months, RPA class II from 9 to 11 months and RPA class III only 3 months.

Postoperative SRS is an alternative to WBRT for patients who undergo resection of brain metastases, with a reduced risk of neurocognitive decline; however, preoperative SRS might be favored given the lower risks of radiation necrosis and leptomeningeal disease. SRS is highly recommended in the American Society of Radiation Oncology (ASTRO) and International Stereotactic Radiosurgery Society (ISRS) consensus guidelines owing to the absence of compromise in survival outcomes with no increase in neurocognitive toxicities, unlike with WBRT. SRS is now the primary treatment for patients with either limited or multiple brain metastases, with potential synergistic effects when combined with certain immunotherapeutic agents or targeted therapies.
8.3 Principles of surgical management

Cancer patients with single metastatic lesions have been shown to benefit more from treatment with surgical resection plus radiotherapy compared to radiotherapy alone. This benefit includes incidence of fewer recurrences, better quality of life and longer overall survival time [52]. Surgery offers rapid and effective symptom control for patients with large tumors or those associated with significant peritumoral edema or mass effect. For patients with active extracranial disease or older age > 60 years, surgery has not been shown to provide benefit. Even though age has been identified as a risk factor for high surgery related mortality, it has not been demonstrated to be a strict basis for withholding surgical treatment [53, 55]. Surgical complications encountered include infection, post-op CVA and intracranial bleeding.

Prior to the early nineties, surgery only had a controversial role in the management of brain metastasis. The benefit of surgery as a modality for treatment of brain metastasis was established by two randomized prospective trials published by Patchell et al and Vecht et al. in 1990 and 1994 respectively [48, 51]. Clinical studies show that about 30–50% of all patients with brain metastasis present with multiple lesions [16, 56]. Multiple lesions are known to have poorer prognosis as compared to singular or solitary metastatic brain lesions. Surgery is indicated for patients with single lesions ≤ 3 cm whereas SRS is preferred for larger lesions [51]. Tumors must be located outside the speech and motor cortices with controlled extracranial disease to be deemed resectable. Surgery is contraindicated for multiple brain lesions and patients who have serious comorbidities as there is no class I evidence in support of surgery among patients with multiple metastatic brain lesions [57].

Microsurgical resection of metastatic brain lesions is effective in relieving brainstem compression and reducing peritumoral edema as well as decreasing ICP caused by “mass effect” of the gross tumor in the brain parenchyma. This translates into improved functional state and overall survival of patients [3, 58, 59]. Microsurgical resection followed by whole brain radiation therapy (WBRT) has been shown to result in prolonged median overall survival compared with WBRT alone in patients with brain metastasis [48, 51]. Furthermore, microsurgical resection results in improvement of neurological function. It enhances quality of life of patients with brain metastasis and may lead to improvement of performance status as evaluated with the Karnofsky score as well as improvement in Recursion Partition Analysis (RPA) score [60]. This benefit is more in elderly patients with symptomatic metastatic brain tumors. Eradication of the gross macroscopic lesion also contributes to the normalization of brain microenvironment further reducing patient’s symptoms. Microsurgical brain tumor resection also serves the purpose of tissue sampling for histological, molecular and mutational analysis.

Surgical resection of metastatic brain lesions is associated with a morbidity rate of 2–10%. In the past, this rate was as high as 24.8% [48, 51, 55, 57, 61–65]. The observed reduction in morbidity associated with brain surgery is due to improved surgical techniques, prophylactic anticoagulation, appropriate seizure prophylaxis as well as availability of contemporary imaging modalities [66, 67]. The commonest complications are postoperative hemorrhage (2.7%), pulmonary embolism (2.2%), CSF leakage (0.8%) and cardiovascular accident (0.6%) [61]. Permanent neurological complications range from 6% to 11% [59, 61, 65]. These events are associated more with tumors in eloquent areas of the brain. Contrary to what was previously thought, advanced age > 65 years has not been found to be associated with significantly higher morbidity rate for patients who undergo brain microsurgery [55]. Surgical mortality rates used to
be as high as 8–11% but have been shown in recent studies to have improved to about 2–4% [48, 62, 63].

9. Conclusions

BM is a heterogeneous group of diseases with increasing prevalence. The three most common cancers associated with brain metastasis are lung cancer, breast cancer and malignant melanoma. Use of prognostic functional scales such as KPS, RPA and GPA are necessary for the comprehensive evaluation of patients with brain metastasis. Control of extracranial malignant disease is an important survival factor in the management of these patients. The therapeutic decision for each patient must be individualized and a multi-disciplinary approach applied.

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Conflict of interest

The authors declare no conflict of interest.

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