Brain Metastases: An Update on Multi-disciplinary Approach of Clinical Management

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Abstract

Importance: Brain metastasis (BM) is the most common malignant intracranial neoplasm in adults with over 100,000 new cases annually in the United States and outnumbering primary brain tumors 10:1.

Observations: The incidence of BM in adult cancer patients ranges from 10-40%, and is increasing with improved surveillance, effective systemic therapy, and an aging population. The overall prognosis of cancer patients is largely dependent on the presence or absence of brain metastasis, and therefore, a timely and accurate diagnosis is crucial for improving long-term
outcomes, especially in the current era of significantly improved systemic therapy for many common cancers. BM should be suspected in any cancer patient who develops new neurological deficits or behavioral abnormalities. Gadolinium enhanced MRI is the preferred imaging technique and must be distinguished from other pathologies. Large, symptomatic lesion(s) in patients with good functional status are best treated with surgery and stereotactic radiosurgery (SRS). Due to neurocognitive side effects and improved overall survival of cancer patients, whole brain radiotherapy (WBRT) is reserved as salvage therapy for patients with multiple lesions or as palliation. Newer approaches including multi-lesion stereotactic surgery, targeted therapy, and immunotherapy are also being investigated to improve outcomes while preserving quality of life.

**Conclusion:** With the significant advancements in the systemic treatment for cancer patients, addressing BM effectively is critical for overall survival. In addition to patient’s performance status, therapeutic approach should be based on the type of primary tumor and associated molecular profile as well as the size, number, and location of metastatic lesion(s).

**Keywords:** Brain metastasis, Cancer, Radiation, Neurosurgery, Chemotherapy, Lung cancer

**Introduction**

Brain metastases (BM) are the most common intracranial neoplasms in adults and are the primary cause of neurologic complications resulting from systemic cancers [1]. Left untreated, afflicted patients suffer a dismal 3-month median survival, however, the rapid advancement in imaging and therapeutics, including systemic treatments in the form of immunotherapy in combination with radiotherapy, have resulted in significantly improved survival [2-4]. Despite this improvement in longevity, quality of life for these patients remains poor secondary to neurologic and cognitive impairment [5-7].
It is estimated that 2% of cancer patients are diagnosed with BM at the same time as their primary tumor, with an annual incidence of 24,000 in the U.S. [6]. However, the true annual incidence is likely >100,000 as 8.5-9.6% of cancer patients will acquire BM at some point during treatment [8] and an additional 25% of patients are found to have BM at autopsy [9]. Interestingly, an increase in incidence has been attributable to improved systemic cancer treatment resulting in longer survival of cancer patients, improved and increased utilization of surveillance imaging, as well as an aging population [7]. The effective treatment of HER2+ breast cancer with trastuzumab, provides an example of how systemic therapeutic control of a primary malignancy has led to an increased number of breast cancer survivors who later develop BM due to trastuzumab’s poor blood brain barrier (BBB) penetration. As a result, up to one third of patients with HER2+ early stage breast cancers will go on to develop BM despite adequate control of their primary malignancy [10]. Furthermore, the incidence of BM is dependent on the type of primary tumor, as cancers of the lung and breast as well as melanoma demonstrate a high incidence of cerebral metastasis, whereas head and neck, prostate and non-melanoma skin cancers infrequently metastasizing to the brain (Figure 1) [6, 11]. With numerous new clinical trials and a rapidly evolving frontier in systemic and localized treatment modalities, it can be difficult to determine the best approach to patients with BM. Because of the importance of this subject matter and the richness of the literature, recently several entire books have been dedicated to topic [12, 13]. This current review hopes to serve as a concise guide to aid clinicians in the diagnosis and up to date management of these patients.

Pathophysiology

The metastasis of primary tumor cells to the CNS is a complex multi-step event where circulating cancer cells find a suitable environment in which to establish a new cancer niche
through interactions with the microenvironment. A thorough understanding of the details of this metastatic cascade is important in the development and consideration of appropriate therapeutic strategies (Figure 2) [14-30]. For example, neuroinflammation and deregulation of the tissue damage response resulting in increased permeability of the blood brain barrier and recruitment of immune cells have recently been implicated in facilitating the development of cerebral metastasis [28]. This is particularly important when considering the explosive development of immunotherapeutic agents in recent years. Broadly, the majority of cerebral metastasis occur via hematogenous spread to the brain parenchyma, however, metastasis to other sites such as the leptomeninges (pia and arachnoid), dura and skull is not uncommon [31]. Cerebral blood flow is an important determinate of localization and the proportion of lesions localizing to specific regions is correlated with the blood flow to each area [31]. As such, 80% of BM occur in the cerebral hemispheres, which have the highest blood flow, whereas 15% and 3% localize to the cerebellum and basal ganglia, respectively [31, 32]. Within the parenchyma, BM are most commonly found in the gray/white junction and the “watershed areas” of arterial circulation [31].

Another important factor influencing the development of cerebral metastasis is the type of primary tumor. Five types of primary tumors (lung cancer, renal cell carcinoma, breast cancer, melanoma, gastrointestinal tract adenocarcinoma) account for 80% of all brain metastases [33]. A study of 169,444 patients, spanning over nearly 30 years found that 10% of patients diagnosed with one of these five primary tumors will eventually develop brain metastases [8]. The specific type of primary malignancy also appears to play a role in the localization of metastatic lesions [31]. For example, posterior fossa metastasis occurs at a disproportionately higher incidence with pelvic and gastrointestinal tumors, whereas leptomeningeal spread is more commonly associated with small cell lung cancer, melanoma and breast cancer [31]. The type of primary tumor also
influences the number of metastatic lesions, with small cell lung cancer and melanoma being most likely to present with multiple lesions and breast, renal and colorectal carcinomas are more commonly associated with solitary lesions [31]. Furthermore, certain molecular subtypes of primary tumors may be associated with an increased propensity for cerebral metastasis. For example, within non-small cell lung cancer, subtypes harboring epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase rearrangements or HER2 mutations are particularly prone to the development of BM [34-37]. Likewise, hormone receptor negativity and HER2 positivity in breast cancer is also associated with an increased propensity for brain metastasis [38, 39].

Clinical Presentation

Brain metastases are most commonly diagnosed in patients with a previously identified primary malignancy, but they are also found in up to 30% of patients at the time of primary tumor diagnosis [40]. Additionally, metastatic lesions may be detected prior to the identification of a primary malignancy and the primary site is unknown in roughly 15% of patients. [40]. While the increased use of MRI in staging of primary tumors has increased detection of asymptomatic BM, 60-75% of patients with brain metastases will be symptomatic at some point during the course of their disease (Figure 1D) [40-43]. When present, symptoms resemble those seen in patients with primary brain tumors with the most common presenting symptoms being fatigue (~75%), headache (40-50%) and focal neurological deficits (30-40%) [44, 45]. With respect to headache quality, morning headaches have classically been associated with brain lesions, especially when characterized by pain worsening with positional changes, sneezing, coughing, bearing down, or when accompanied by nausea and vomiting – all of which can be attributed to the increased
intracranial pressure [46]. However, the classic morning headache, while highly suggestive, is not commonly present and up to 77% of patients describe their headaches as tension-type headaches that occur randomly throughout the day. Much like primary cerebral neoplasms, the specific focal neurological deficit associated with BM is dependent on the location of the lesion(s). Lesions in the cortex and subcortex may present with weakness, sensory deficit, language dysfunction, behavior changes and visual field deficits, whereas involvement of the cerebellum often presents with ataxia, vertigo, nystagmus, deficits of coordination or slurred speech. Lesions involving the brainstem may present with clinical features similar to those of cerebellar dysfunction and additionally, dysphagia and dysarthria may also be present. Patients with BM from hypervascular primary tumors, such as melanoma or renal cell carcinoma, may experience acute intratumoral and/or intracranial hemorrhage resulting in the sudden onset of stroke-like symptoms as well as an acute change in headache quality, depressed mental status, coma, or death [47].

Other symptoms such as seizures and cognitive impairment may also occur either as a presenting symptom or throughout the course of the disease process. Seizures are the presenting symptom in 15-20% of patients and an additional ~16.1% of patients will develop seizures during the course of their disease [41, 48]. Studies have suggested that a wide range of cognitive functions may also be impaired, and that the degree and frequency of cognitive impairment in patients with BM is underestimated [49, 50]. While impairments in language (46%), executive function (31%) and fine motor dexterity (33%) occur in an appreciable portion of patients, memory impairment appears to be the most pronounced cognitive deficit [49, 50]. In support of this, two studies found that a majority of patients (>70%) with BM had impairment on the recall portion of the Hopkins Verbal Learning Test [49, 50]. Overall, in a study of 32 patients with BM, fewer than 20% were completely cognitively intact, with no impairments demonstrated on any of the administered tests.
Conversely, 80% of patients who were still largely able to participate in self-care activities demonstrated impairment of one or more cognitive measures, 75% were impaired on two measures and over 56% were impaired on greater than three cognitive measures [50]. It is important to appreciate that despite patients having high performance scores and being able to complete activities of daily living, cognitive impairment is present in a large portion of patients with BM and this can have a significant impact on quality of life [49, 50].

Although less common than parenchymal metastasis, leptomeningeal metastasis (LM) can occur and when present, classically presents with multifocal neurological deficits that affect multiple motor/sensory functions depending on the specific areas of involvement[51, 52]. Cerebral involvement most commonly manifests with symptoms of increased ICP such as headaches, nausea/vomiting and altered level of consciousness, whereas cranial nerve and spinal involvement may present with diplopia, changes in facial sensation, hearing loss or weakness and paresthesia, respectively [51-53].

It is important to note that many patients with BM may not complain of any neurological symptoms and may have a normal or subtle neurological examination [54]. Therefore, one should have high index of suspicion and practice close observation for subtle clinical changes in high risk cancer patients, especially patients with primary tumors characterized by a high propensity to metastasize to the brain.

Assessment and Diagnosis

Suspicion for brain metastasis should be heightened in any cancer patient who presents with new neurological symptoms or behavioral abnormalities (Figure 3) and signs of increased intracranial pressure, if present, (e.g. papilledema, nausea, and vomiting) warrant urgent neurosurgical evaluation [40]. Imaging should be performed in these patients and, additionally, the
National Comprehensive Cancer Network recommends brain metastasis screening utilizing MRI in patients with stage II-IV NSCLC, small cell lung cancer of any age and stage IIIC-IV melanoma [55]. While there are currently no established BM screening recommendations for patients with other neoplasms, a recent retrospective study suggests that further investigation of MRI screening in certain patients with metastatic breast cancer is warranted [56]. Broadly, BM screening in patients harboring primary tumors known to have a high propensity to metastasize to the brain is important to consider given the significant impact of BM on quality of life and in guiding therapeutic strategy, which may include less invasive interventions if BM are identified early [56]. Future work will be needed to identify specific patient populations for which initial BM screening should occur and the presence or absence of certain molecular alterations that increase the propensity of primary tumors to metastasize to the brain should be taken into consideration in addition to the type of primary malignancy. With the exception of the above referenced recommendations, the decision to screen patients for BM is currently based on physician preference. Here we will discuss the range of imaging modalities available for both screening in asymptomatic patients as well as evaluation of patients presenting with clinical features concerning for BM.

**Computed Tomography (CT)**

Non-contrast enhanced CT (NECT) is often the first imaging study a patient undergoes and while it is suboptimal for visualizing the tumor itself, it is useful for ruling out other emergent cases (e.g. hemorrhage, hydrocephalus, and severe mass effect) and is superior to (Magnetic Resonance Imaging) MRI in the evaluation of bony destruction secondary to calvarial metastasis [57, 58]. On non- or pre-contrast CT, BM may appear isodense, hypodense or hyperdense when compared to the normal brain parenchyma and are associated with variable amounts of vasogenic
edema [59]. Likewise, BM on post-contrast CT demonstrate variable enhancement. Furthermore, in cases where it is contraindicated for a patient to undergo contrast enhancing MRI (e.g. pacemaker), contrast enhancing CT can also be used as an alternative.

*Magnetic Resonance Imaging (MRI)*

Contrast-enhanced MRI (CEMRI) is the gold standard for diagnosing brain metastases and is more sensitive than contrast-enhanced CT (CECT) at differentiating metastasis from other brain lesions [32, 57]. The use of gadolinium contrast is essential for identifying smaller metastases as well as distinguishing tumors from non-neoplastic diseases such as microvascular ischemic disease [32]. On pre-contrast T1-weighted images, BM are typically iso- or hypointense, with the exception of hemorrhagic lesions and non-hemorrhagic melanoma metastases, which may appear hyperintense [58]. Intensity of BM is variable on pre-contrast T2-weighted imaging, however, most parenchymal lesions appear as hyperintense foci on fluid-attenuated inversion recovery (FLAIR) [58]. Due to the lack of blood-brain and blood-tumor barriers, BM typically enhance on contrast-enhanced T1-weighted images unless characterized by non-enhancing cystic or hemorrhagic components [58, 60].

For post-contrast T1-weighted imaging, inversion recovery fast gradient echo (IR-GRE) is widely available for both 1.5T and 3T systems and offers anatomical depiction with good gray-white differentiation. There are, however, several disadvantages in the use of IR-GRE that should be noted [60]. Compared to spin echo (SE) sequences, the appearance of contrast enhancing brain lesions is slightly less prominent on spoiled GRE sequences (FLASH, SPGR) [61]. IR-GRE is also characterized by a lower contrast ratio, which may result in increased difficulty in identifying brightly enhancing BM within bright white matter [60]. Additionally, normal cortical vessels appear as bright foci in cross-sectional images, which may impair the ability to distinguish these
normal vessels from smaller, enhancing metastatic lesions [60]. Lastly, fat saturation is not possible in IR-GRE pulse sequences and this can impair identification of enhancing osseous lesions within the fat containing skull, skull base and vertebral marrow [60]. Conversely, SE-based pulse sequences, which include 3D turbo SE T1-weighted (3D TSE) SPACE, CUBE and VISTA are characterized by lower white matter signal intensity, inherent flow suppression and the ability to be fat saturated [60, 62]. Due to difficulty with acquisition at 1.5T, the additional cost of sequence installation on older machines and the increased susceptibility to motion artifact associated with 3D TSE, IR-GRE is often preferred [60].

The selection of the best sequences for the evaluation of BM can be burdensome, however, a recent publication, which builds upon the standardized brain tumor imaging protocol (BTIP), has defined an imaging protocol for brain metastases (BTIP-BM) based on consensus recommendations [60]. The recommendations for a minimum standard protocol include the following:

1. Parameter matched pre- and post-contrast inversion recovery 3D T1-weighted gradient echo (IR-GRE) performed in axial, sagittal and coronal planes, with recommended parameters for both 1.5T and 3T scanners found in the original publication [60].
2. Axial, 2D T2-weighted turbo spin echo to be acquired after gadolinium-based contrast agent (GBCA) administration, but before post-contrast 3D T1-weighted images
3. Axial 2D or 3D T2-weighted FLAIR
4. Axial 2D, 3-directional DWI
5. Post-contrast 2D T1-weighted spin echo images

Additional sequences that possess increased sensitivity to specific metastatic characteristics or that provide additional metrics can also be utilize in the evaluation of cerebral metastasis.
Susceptibility-weighted images (SWI), for example, have been shown to improve the detection of hemorrhagic metastases >1 mm in size [63, 64]. Furthermore, perfusion imaging can be accomplished via multiple approaches, with dynamic susceptibility contrast (DSC) and dynamic contrast-enhanced (DCE) being the most common. Both DSC and DCE measure relative cerebral blood volume (rCBV) which correlates with tumor vascularity [32, 58]. Signal recovery evaluation in DSC perfusion imaging can also provide information regarding vascular permeability to aid in the differentiation of BM from high-grade glial neoplasms and abscesses [32, 58]. Arterial spin labeling (ASL) is an alternative to DSC/DCE that does not require the administration of contrast and may help distinguish primary brain tumors from metastatic lesions [58, 65]. Diffusion weighted imaging (DWI) may also be helpful in distinguishing metastatic lesions from primary brain tumors and abscesses [32]. On DWI, pyogenic abscesses will demonstrate diffusion restriction, whereas metastases and glioblastoma rarely restrict diffusion [58]. Similarly, Diffusion tensor imaging (DTI) can aid in distinguishing between gliomas and metastases[66, 67].

The detection of small metastatic lesions is critical for the development of an effective therapeutic strategy, which may involve less invasive approaches when BM are identified early. There are several approaches that can be used to enhance the detection of small metastatic lesions on MRI including, increasing the gadolinium-based contrast agent (GBCA) dose and increasing the time delay between contrast administration and image acquisition [58]. Previous studies have demonstrated that increasing GBCA dose increases the sensitivity for small (<5 mm) lesions and a post-injection delay of 20 minutes appears optimal for the detection of lesions <10mm [68, 69]. However, both of these methods of optimization are characterized by disadvantages including an increase in false-positive results and increased time of study acquisition, respectively [68, 69]. The utilization of other T1 sequences, such as magnetization-prepared rapid gradient echo (MP-RAGE)
and volumetric fast spin echo (SPACE), may also be used to enhance the detection of smaller metastases [58, 70, 71]. Similarly, small metastatic lesions may present with peritumoral edema that is disproportionate to the lesion size and the best sequences for detecting this edema are T2-weighted images and T2-FLAIR. With respect to contrast-enhanced T1-weighted sequences, previous studies demonstrated superior brain metastasis detection using 3D fast spoiled gradient echo (FSPGR; e.g. FLASH) or 3D magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) with 1-1.4 mm slice thickness compared to 2D SE imaging (6-7 mm) [61, 72, 73]. However, several studies including a meta-analysis of five studies comparing 3D TSE (e.g. SPACE/CUBE/VISTA) and 3D MPRAGE at equal thickness of 1 mm, have found 3D spin echo to be superior to GRE sequences [62, 70, 71, 74-79]. Furthermore, an additional recent study also found that 3D fast spin echo (e.g. SPACE) is superior to both 2D spoiled gradient echo (e.g. FLASH) and MPRAGE specifically in the detection of small metastatic lesions [80]. As such, in instances where 3D IR-GRE is used, it is recommended that an additional post-contrast 2D SE or fast spin-echo (FSE) T1-weighted series be added as with slice thickness <4 mm and no interslice gap [60]. The use of a second post-contrast T1 series can increase identification of small metastatic lesions and this is especially important in the planning and consideration of SRS [60]. Lastly, though rare, pachymeningeal (dural) and leptomeningeal (pia, arachnoid, or subarachnoid space) metastases can also be detected on MRI and may be visible on FLAIR sequences, however, previous studies suggest that post-contrast FLAIR and contrast-enhanced 3D T1 SPACE sequences demonstrate improved sensitivity [58, 81, 82].

**MR spectroscopy**

MR spectroscopy, which allows for the evaluation of the presence and concentration of various metabolites in tissues, has been shown to be useful in distinguishing neoplastic from non-
neoplastic brain lesions [32]. MR spectroscopy can be performed via single- or multivoxel (volume of interest) spectroscopy, but multivoxel spectroscopy offers the advantage of improved spatial resolution and greater coverage [32, 58]. As such, multivoxel spectroscopy allows for the evaluation of different volumes of interest and is particularly useful in the setting of heterogeneous masses [32, 58]. Choline, N-acetyl aspartate (NAA), lactate and lipid are commonly measured metabolites and provide information regarding cellular density, neuronal integrity, anaerobic metabolism, necrosis, respectively [32, 58]. Levels and ratios of these metabolites have been evaluated in their ability to differentiate gliomas from brain metastasis [83, 84]. While some studies suggest that evaluation of the metabolite profile of the T2-hyperintense region surrounding the lesion may aid in differentiation, the ability for MR spectroscopy to reliability distinguish between high-grade gliomas and metastatic lesions has not been consistently demonstrated [32, 58, 83, 84].

**Positron Emission Tomography (PET)**

While FDG-PET and PET-CT are frequently used in the staging of cancer, its sensitivity for detecting BM is inferior to that of contrast-enhanced MRI [32, 85-87]. The utility of FDG-PET in identifying small metastatic lesions has been reported to be especially limited, however, when identified, BM most commonly appear as focal areas of hypometabolism, but hypermetabolism is also possible [32, 58, 86]. Recently, the Response Assessment in Neuro-Oncology (RANO) working group published recommendations to guide the use of PET imaging in patients with cerebral metastasis [88]. Their findings suggest that, although data is limited, amino acid PET has superior diagnostic accuracy compared to FDG-PET in (1) the identification of newly diagnosed BM, (2) the differential diagnosis of newly diagnosed BM (3) distinguishing between radiation-
or immunotherapy-induced changes from recurrent BM and (4) in the assessment of treatment response [88].

**Treatment**

Historically, whole brain radiation therapy (WBRT) was the standard treatment for patients with brain metastasis, however, recent advances in both radiosurgery and systemic therapies have further expanded the spectrum of available treatment modalities for these patients [89, 90]. Current management strategies consist of true multi-disciplinary approach with various combinations of surgery, radiotherapy, targeted agents and immunotherapy (Table 1).

**Surgical Resection**

Despite being the most invasive option, surgical intervention offers several benefits in the management of patients with BM. Immediately, surgical resection of metastatic lesions can provide relief from symptoms arising from mass effect and increased intracranial pressure, especially those that are refractory to corticosteroids, and can allow for the removal of large tumors requiring decompression resulting in likely improvement in neurological and cognitive function [91, 92]. Additionally, tissue obtained during resection can be used for diagnostic confirmation and plays an especially important role in patients who do not have a previously identified primary malignancy [91, 92]. In addition, genomic analyses of BM and matching primary tumor and other extracranial metastases have revealed that BM harbor potentially actionable driver mutations that are unique to them and hence targeted therapies against these mutations can potentially improve survival outcomes for BM patients [93]. Support for surgical intervention came with the landmark study published by Patchell et al., which found that the combination of surgical resection plus radiotherapy in patients with single metastatic lesion improved overall survival, decreased rate of recurrence of cerebral metastasis and improved quality of life compare to patients treated with
radiotherapy alone [94]. In the setting of multiple metastatic lesions, surgical intervention may be beneficial in patients who have \( \leq 4 \) metastases where complete resection of all lesions is possible [95, 96]. In support of this, a study published by Bindal et al. concluded that the surgical removal of all tumors in patients with multiple cerebral metastases increased survival time and confers a prognosis that is similar to that of patients undergoing resection for a single metastatic lesion [96]. In the setting of recurrent BM, factors that influence survival benefit include (1) time to recurrence of > 200 days, (2) the number of lesions (single vs. multiple), (3) Recursive partitioning analysis (RPA)-classification and (4) completeness of resection [97]. Overall, several studies suggest a survival benefit with surgical resection, and thus support its consideration for patients who have good functional scores with absent or controlled extracranial tumor activity and in whom complete resection of all lesions is possible [94, 96, 98]. While studies support gross total over subtotal resection, aggressive resection may result in significant neurological deficits, especially when lesions are located in eloquent regions [96, 98]. However, the risk of significant and permanent neurological deficits associated with total resection is decreasing with modern innovations in surgical techniques that have yielded approaches utilizing intraoperative neuronavigation and brain mapping [99], laser interstitial thermal therapy (LITT) [100], convection-enhanced delivery [101], and focused ultrasonography [102], all of which aim to maximize tumor resection while minimizing potential morbidity [103].

Surgical techniques are also important in limiting the risk of local recurrence and leptomeningeal dissemination. En bloc resection, which involves the total removal of the tumor along the brain-tumor interface without violation of the tumor capsule, is preferred over piecemeal resection for the prevention of recurrence and dissemination [104, 105]. While en bloc resection may not be possible in certain situations, such as with large or infiltrative tumors, when performed,
it has not been shown to be inferior to piecemeal resection and it is not associated with increased risk of neurological injury [105].

**Stereotactic Radiosurgery (SRS)**

Prior to the development of SRS, the use of ionizing radiation for the treatment of cancer involved delivering radiation to the tumor as well as to a significant volume of the surrounding normal tissue. As this method relied on the superior DNA-repair capacity of normal tissues compared to tumor cells for therapeutic efficacy, the total dose of radiation had to be delivered in smaller fractions over a period of several weeks in order to allow normal tissues to recover prior to administration of the next dose. This approach of repeated administration of small doses of ionizing radiation to a larger target area is known as fractionated radiation therapy (FRT) and can be further divided into whole-brain radiation therapy (WBRT) or focal radiation therapy (Focal RT). Advances in stereotactic localization have allowed for ionizing radiation to be selectively delivered to a sharply defined target lesion while simultaneously decreasing the radiation delivered to the normal, surrounding tissue [106]. This delivery of a single, large dose of radiation through the use of multiple, non-parallel radiation beams converging on a precisely-defined target lesion is known as stereotactic radiosurgery (SRS) [107]. By delivering the radiation through multiple, non-parallel radiation beams, the full therapeutic dose is delivered only where the beams overlap. This allows for a larger dose of radiation to be administered to a specific target lesion, while the surrounding, normal tissue receives much smaller doses from a single or limited number of radiation beams [106].

SRS is becoming a leading modality in the treatment of brain metastases in a variety of clinical scenarios including, as a single, definitive treatment for patients with a limited number of brain metastases, and as an adjuvant treatment modality in the pre- and postoperative setting [108-
The use of SRS requires the consideration of several factors including the number, size and location of the lesion(s), as well as the timing of SRS treatment (i.e. pre-operative vs. post-operative). Historically, a maximum of four lesions was considered the cut-off for treatment with SRS. Several recent studies, however, have provided support for the use of SRS in patients with >4 lesions [15, 113, 114]. These studies have found that patients with 5-10 metastases, as well as those with >10, have survival outcomes that are comparable to those of patients with 2-4 lesions when treated with SRS [113, 114]. Furthermore, there are currently several active clinical trials (NCT03075072, NCT04277403, NCT03775330) comparing the use of WBRT vs. SRS with or without WBRT in the treatment of patients with ≥5 metastatic lesions.

SRS is particularly suitable for metastatic lesions due to their smaller size, circular shape and well-circumscribed margins and it can be successfully used regardless of tumor cell radiosensitivity [107, 112, 115]. While SRS, which is typically administered in a single session, is optimal for treating small intracranial lesions, for large lesions or those near critical structures, it can be difficult to obtain tumor control while simultaneously avoiding damage to normal tissue. This is because the size of the tumor(s) influences the amount of radiation delivered to the surrounding, normal tissue and as the tumor size increases, so does the incidental irradiation delivered to the surrounding tissues [106]. Several studies have evaluated the maximum size of metastatic lesions that can be successfully treated with SRS to achieve sufficient local control without exposing the surrounding, normal tissue to unacceptable levels of radiation [116-123]. The Radiation Therapy Oncology group (RTOG 90-05), previously determined the maximum tolerated dose for non-brainstem BM with diameters ≤2cm, >2-3cm and >3-4 cm to be 24 Gy, 18 Gy and 15 Gy, respectively [121, 122]. This study also determined that the use of SRS could not achieve adequate local control without an unacceptable degree of toxicity to the normal, surrounding tissue.
when tumors were >4 cm in diameter [121, 122]. Several studies that followed the RTOG 90-05 study further supported the finding that the rate of local failure was higher in larger tumors treated with SRS [116-120]. While it has been proposed that improved local control could be achieved with higher doses of radiation, the administration of sufficiently high doses of radiation in a single fraction to a large volume would increase the exposure of normal tissues to unacceptable levels of radiation toxicity [116, 123-126]. In settings where larger lesions are present, single-fraction SRS can be split into 2 to 5 fractions (termed “fractionated SRS” or “hypo-fractionated stereotactic radiation therapy), which can provide both adequate tumor control and acceptable toxicity [127-131]. Not surprisingly, studies evaluating the use of fractionated SRS in patients with larger BM, suggest that it is associated with improved local control compared to the use of single-fraction SRS in this patient population [130, 132]. In addition to delivering smaller fractions of radiation via fractionated SRS, volume-staged SRS (VS-SRS) in which specific portions of large lesions are treated over time, has also been proposed as a technique for achieving superior local control in patients with larger BM [133-135]. The support for the use of VS-SRS comes predominantly from its evaluation in the treatment of large arteriovenous malformations (AVMs) and as such, future studies examining the utility of VS-SRS in the setting of large metastatic lesions are needed [136].

In addition to number and size, the location of metastatic lesions is also an important factor to consider when developing a therapeutic strategy involving surgery or SRS. As a result, lesions located in areas associated with the lowest risk of permanent post-radiosurgery neurological sequelae (i.e. frontal/temporal lobes) are generally treated with higher radiation doses than lesions located in high risk areas, such as the thalamus, basal ganglia or brainstem [106, 123, 137]. The use of lower radiation doses should also be considered in the treatment of BM located in the eloquent areas of the cortex which include the primary motor cortex (precentral gyrus), primary
somatosensory cortex (postcentral gyrus), primary visual cortex (posterior pole of occipital lobe), primary auditory cortex (superior temporal gyrus), Broca’s area (posterior inferior frontal gyrus) and Wernicke’s area (posterior superior temporal gyrus) [106, 123, 137]. Cranial nerves are also especially sensitive to the effects of incidental irradiation and factors that increase risk of cranial nerve radiation neurotoxicity include (1) previous surgery or radiation, (2) large target volume and (3) a high total dose of radiation [138, 139]. Cranial nerves (CN) II and VIII appear to be the most sensitive to radiation injury and radiosurgery is generally contraindicated in lesions that are either intrinsic to or abutting the optic apparatus (i.e. optic chiasm and nerve) [106, 140, 141]. Previous recommendations suggested avoiding SRS when the dose of radiation delivered to the optic apparatus would be >10 Gy. Recent studies, however, suggest that the optic apparatus is not as sensitive as previously thought and that the risk of radiation-induced optic neuropathy was less than 1% when doses of 12 Gy, 20 Gy and 25 Gy were delivered in 1, 3 and 5 fractions, respectively [142, 143]. CN III, IV, VI, VII are proposed to be less sensitive than CN II and VIII, with studies suggesting that doses <15 Gy do not result in significant radiation-induced CN neuropathy (RICN) [144, 145]. Similarly, CN IX, X, XI are associated with a <2% incidence of RICN when exposed to <12 Gy [146-148]. The previously discussed findings suggest that in settings where single-fraction SRS is likely to compromise sensitive structures and result in significant, permanent post-radiosurgery neurological deficits, fractionated SRS should be considered instead.

With respect to timing of SRS treatment, several trials have supported the use of post-operative SRS and provided insights into its benefit over the use of post-operative WBRT. The Alliance NCCTG N107C/CEC·3 trial (NCT01372774) found that post-operative SRS was superior to post-operative WBRT in preservation of cognitive function and a phase III trial conducted by M.D. Anderson Cancer Center (NCT00950001) demonstrated that SRS administered
to resection cavities significantly lowers the risk of recurrence compared to observation [108, 109]. However, while the post-operative use of SRS has been associated with superior neurocognitive preservation compared to WBRT and allows for the treatment of BM that are not able to be surgically resected or are located in regions where surgical resection confers a high risk of neurological injury (e.g. deep-seated lesions or involving eloquent areas), it is also associated with an increased risk of intracranial failure when used without WBRT [115, 149]. Factors that are suggested to influence the efficacy of SRS in achieving local control include the dose of radiation and tumor volume [150, 151]. Unlike WBRT, however, the efficacy of SRS in achieving control does not appear to be influenced by the type of primary tumor. This is supported by the finding that conventionally radio-resistant tumors, such as renal cell carcinoma and melanoma, achieve control rates comparable to breast cancer and NSCLC, which are considered to be relatively radiosensitive [152-158]. Several studies have evaluated the factors that can be used to predict recurrence in patients treated with SRS alone [159]. These predictive factors include (1) patient age, (2) cancer type (e.g. HER2- breast cancer, colorectal cancer, melanoma), (3) number of brain metastases, (4) progressive systemic disease/increasing extracranial disease burden [159, 160]. Additionally, a retrospective study found that patients with HER2+ breast cancer had the longest time to recurrence requiring salvage WBRT, whereas patients with melanoma or poorly differentiated lung cancer had the shortest [161]. Given the higher rate of recurrence in patients treated with SRS alone, it is important to closely follow patients with surveillance imaging, preferably with MRI or CECT when MRI is not possible. It is important to note, that while the incidence of recurrence has been found to be significantly higher when SRS is used alone, the addition of WBRT to SRS does not appear to result in improved overall survival in patients with ≤ 4 lesions [115, 126]. Additionally, in an attempt to develop an approach to decrease the
likelihood of post-surgical local failure, the efficacy of pre-operative SRS followed by surgical resection is currently being evaluated in several clinical trials (NCT03398694, NCT03741673, NCT04474925, NCT03750227, NCT04422639).

In addition to the disadvantages mentioned above, the use of SRS is also associated with the development of radiation necrosis and development of leptomeningeal dissemination (LMD). Radiation necrosis (RN) is one of the most significant complications associated with the use of SRS and is reported to occur between 6 months to several years after treatment in roughly 10% of SRS treated tumors with no plateauing overtime, which is especially concerning for long term survivors [119, 162, 163]. Risk factors associated with an increased risk of RN include lesion size, with larger lesions being associated with higher risk, radiation dose and prior SRS or WBRT to the same lesion [164, 165]. With respect to lesion size, studies also report that the use of single-fraction SRS in lesions >2 cm may be associated with a higher risk of RN than the use of fractionated SRS in lesions of this size [166, 167]. Data is limited and inconsistent with respect to the risk of RN in the setting of concurrent SRS and immunotherapy. Several retrospective studies suggest an increased risk of symptomatic RN associated with the use of this combination, whereas a recent retrospective analysis suggests otherwise [168-170]. Fortunately, there are several treatment options that can be utilized for the management of patients with symptomatic RN, including corticosteroids [171], the VEGF inhibitor, bevacizumab [165, 172-176], hyperbaric oxygen therapy (HBOT) [171, 173, 177], surgical resection and laser interstitial thermal therapy [171, 178, 179]. Owing to their low cost, ease of use and efficacy, corticosteroids are considered the first-line treatment for patients who present with worsening symptoms secondary to RN-induced cerebral edema [171].
Post-operative SRS is associated with an increased risk of leptomeningeal dissemination (LMD) compared to both post-operative WBRT and SRS for intact lesions not previously resected [180-185]. Several factors have been suggested to predict risk of developing LMD following post-operative SRS including, (1) a breast cancer histology, (2) infratentorial location, (3) the presence of multiple BM and (4) distant intracranial failure [180-185]. The suggested pathophysiology of LMD is the dissemination and seeding of viable tumor cells in the leptomeninges and CSF via hematologic dissemination or direct extension from a metastatic lesion/resection bed [186]. A proposed approach to minimizing the risk of LMD is the use of pre-operative SRS in an attempt to decrease the number of viable tumor cells capable of dissemination and seeding upon their “spillage” during surgical resection [187]. To the best of our knowledge, the only data available supporting the use of pre-operative SRS are two retrospective analyses, and both studies suggest that pre-operative SRS is associated with a decreased risk of symptomatic radiation necrosis (RN) and LMD compared to post-operative SRS [111, 184]. Furthermore, pre-operative SRS appears to confer rates of local/distant recurrence and overall survival (OS) comparable to those of post-operative SRS [184]. Additional data will be needed to further support the use of pre-operative SRS and as previously mentioned, several clinical trials are currently evaluating the benefits associated with this therapeutic strategy. For patients who develop LMD following surgery or SRS prognosis is poor and treatment is usually palliative, involving WBRT, intrathecal or systemic chemotherapy and supportive care [53].

*Whole Brain Radiotherapy*

The use of WBRT alone has historically been the standard for patients with multiple metastatic lesions and despite the development of SRS, WBRT continues to play a role in several treatment settings, including as an adjuvant following radiosurgery and surgical resection [162,
188-190]. Support for the use of adjuvant WBRT following radiosurgery came from several studies which found that adjuvant WBRT was associated with increased local control and decreased risk of development of new BM [188-190]. However, multiple studies have also found that adjuvant WBRT does not result in an increased duration of functional independence, nor does it improve overall survival [115, 162, 191]. In fact, the use of adjuvant WBRT was found to be associated with worse quality of life and deterioration in learning and memory functions [108, 149, 192]. While it is important to consider that the lack of survival benefit may be a result of extracranial disease progression rather than a failure of WBRT, the lack of survival benefit in conjunction with WBRT-associated neurocognitive deterioration support the use of SRS over WBRT in patients with limited metastatic lesions. The risk of local recurrence following surgical resection is proposed to be roughly 50%, even in the setting of MRI-confirmed gross total resection [108, 109, 193]. As with the use of adjuvant WBRT following radiosurgery, the use of adjuvant WBRT following gross total surgical resection is not associated with an improvement in overall survival, despite reduced risk of recurrence of local and development of distant metastases [162, 193, 194]. As a result of recent data from multiple clinical trials supporting the use of SRS in patients with limited intracranial tumor burden (e.g. ≤4 lesions that are <3 cm in diameter), SRS is beginning to replace WBRT in this setting [114, 149, 162, 190, 195]. One such non-randomized prospective study showed no difference in overall survival, neurologic deterioration, and local recurrence between patients with 2-4 lesions and 5-10 lesions when treated with SRS [114]. Randomized controlled studies evaluating the efficacy of SRS vs. WBRT for multiple BM are currently being conducted at MD Anderson (NCT01592968) and Brigham and Women’s Hospital/Dana-Farber Cancer Institute (NCT03075072). An additional phase 3 trial is currently investigating the use of Tumor Treating Fields (TTFields), which previously demonstrated a
benefit in glioblastoma patients [196], in conjunction with SRS for the treatment of patients with multiple metastatic brain lesions (NCT02831959).

The Quality of Life after Treatment for Brain Metastases (QUARTZ) study, which aimed to evaluate the possibility of omitting WBRT in the treatment of patients with BM arising from NSCLC, suggests that while WBRT may not improve survival or add any quality life years overall in the setting of multiple BM [42], there is a potential survival benefit demonstrated in patients under the age of 60 who have a good performance status [197]. Attempts to improve the efficacy of WBRT, which typically utilizes a conventional regimen of 30 Gy in 10 fractions [198], through the use of ultra-rapid high dose irradiation schedules [199], dose escalation protocols in patients with favorable prognosis [200] accelerated hyperfractionated regimens to 54.4 Gy [198] and the use of radiosensitizers such as misonidazole and bromodeoxyuridine [201, 202] have failed to demonstrate any benefit over the administration of conventional WBRT.

When WBRT is to be used, memantine or hippocampal-avoidance IMRT should be considered to minimize adverse neurocognitive effects [203, 204]. The RTOG 0614 trial aimed to evaluate the potential neuroprotective effects of memantine, a noncompetitive antagonist of the NMDA receptor, with respect to neurocognitive function in patients receiving WBRT [203]. Results of this trial suggest that memantine increased the time to cognitive decline and reduced decline in executive function, processing speed and delayed recognition compared to placebo [203]. Similarly, the RTOG 0933 phase II clinical trial evaluated the administration of cranial radiation while sparing the hippocampal neural stem cell compartment, which is thought to be crucial in the development of cranial radiation-induced neurocognitive deficits secondary to the increased sensitivity of these cells to therapeutic doses of radiation [204]. These exquisitely sensitive neural progenitor cells conveniently appear to be located in clusters within the dentate
gyrus, which allows for the use of intensity-modulated radiotherapy technologies (IMRT) such as helical tomotherapy and linear accelerator (LINAC)-based IMRT [204]. This study suggests that the use of helical tomotherapy and LINAC-IMRT is effectively able to spare the hippocampus and results in a significant decrease in the amount of radiation delivered to this exquisitely sensitive region. The use of hippocampal avoidance IMRT, results in approximately a 3-fold decrease in the dose delivered to the dentate gyrus, with the median and maximum dose received by the hippocampus being 5.5 Gy/12.8 Gy for helical tomotherapy and 7.8 Gy/15.3 Gy for LINAC-based IMRT [204]. A recent single-institution single-arm phase II trial evaluated cognitive performance and intracranial control with the use of hippocampal-sparing whole brain irradiation with simultaneous integrated boost (HSIB-WBRT) [205]. Radiation therapy in this trial consisted of 20 Gy in 10 fractions over 2-2.5 weeks delivered to the whole brain with a simultaneous integrated boost of 40 Gy in 10 fractions delivered to metastatic lesions [205]. The dose delivered to the hippocampus was limited to 16 Gy and all the metastatic lesions were at least 3mm away from the hippocampus [205]. This study found that performance on the Hopkins Verbal Learning Test-Revised delayed recall (HVLT-R DR) was significantly improved compared to that of patients treated with conventional WBRT and that the intracranial control achieved was comparable to that of WBRT plus SRS [205]. More recently, the NRG Oncology CC001 phase III trial aimed to compare the use of combination HA-WBRT and memantine verses the use of conventional WBRT with memantine [206]. Results of this study found that the combination of HA-WBRT plus memantine provided superior preservation of cognitive function and patient-reported symptoms. No difference in progression free (PFS) or overall survival (OS) were reported between the two groups [206]. Taken together, the results of these studies suggest that the use of HA-WBRT plus memantine confers superior preservation of neurocognitive function and should be strongly
considered for use in patients with good performance scores who are to receive WBRT for the treatment of metastatic lesions located outside of the hippocampus.

**Systemic Therapy**

Traditional, systemic chemotherapeutic agents have limited utility in the treatment of BM due to poor blood-brain barrier penetration, the presence of efflux pumps and impaired distribution through the blood-tumor barrier [207, 208]. While chemotherapy can be considered for the treatment of certain patients with multiple metastatic brain lesions, its efficacy reflects the sensitivity of the primary tumor, with the highest extracranial response rates seen in SCLC (30%-80%) and lowest in melanoma (10-15%) [92]. However, the intracranial response does not always correlate with the systemic response due to new mutations acquired by metastatic lesions. For these reasons, traditional cytotoxic drugs are limited in their utility as first line therapy for the treatment of BM, but can be considered in certain situations where they play a critical role in controlling extracranial disease [209].

Targeted therapy and immunotherapy for multiple intracranial metastatic lesions is rapidly evolving and should be considered in certain patients [92]. Previous studies have demonstrated the efficacy of targeted therapy in patients with intracranial lesions arising from NSCLC primary tumors harboring EGFR mutations or ALK rearrangements [92, 210], HER2-positive breast cancer [211] and BRAF-mutant melanoma [212, 213]. Multiple studies have provided positive results supporting the use of targeted therapies in patients with EGFR-mutant or ALK-rearranged NSCLC. One such study evaluating intracranial tumor burden and outcomes in patients with EGFR-mutant or ALK-rearranged lung cancer with cerebral metastasis found that most patients who were treated with tyrosine kinase inhibitors achieved an early and sustained volumetric
intracranial response regardless of presenting intracranial tumor burden or presence of neurological symptoms[214].

In patients with EGFR-mutant BM, the use of first generation EGFR inhibitors, such as gefitinib and erlotinib, has been shown to be associated with improved response rates, progression free survival (PFS) and overall survival (OS) [215, 216], but studies evaluating the combined use of these agents plus radiotherapy have failed to produce consistent results [217-219]. The development of second- and third-generation inhibitors, afatinib and osimertinib, which target the EGFR<sup>T790M</sup> mutation, has led to even more promising results. A phase III clinical trial found that osimertinib was associated with improved intracranial PFS and reduced CNS progression compared to other EGFR inhibitors [220, 221]. Several clinical trials are also currently evaluating the efficacy of osimertinib plus SRS (NCT03535363, NCT03497767, NCT03769103). Based on the above data, osimertinib is now considered first-line for the treatment of patients with EGFR-mutant NSCLC who have brain metastases.

For patients with ALK-rearranged NSCLC with brain metastases ALK inhibitors such as alectinib, ceritinib, brigatinib and lorlatinib should be considered [222]. These agents have been shown to have superior BBB penetration and increased levels of intracranial activity compared to the first-generation ALK inhibitor, crizotinib, and can also be used in patients currently on crizotinib [222]. While both alectinib and brigatinib have been shown to be superior to crizotinib with respect to improved PFS, rate and duration of intracranial and intracranial disease progression in ALK-inhibitor naïve patients, alectinib has also demonstrated efficacy in the setting of disease progression in patients previously treated with both crizotinib and ceritinib [223-226]. In the setting of crizotinib-resistance, brigatinib, ceritinib and alectinib are appropriate choices, however, given the highly promising results of alectinib, it is often the preferred agent [226]. The third-generation
agent, lorlatinib, which is a combined ALK/ROS1 inhibitor, has shown efficacy in patients who have progressed despite the use of first- and/or second-generation agents [227-229].

For patients with HER2-positive breast cancer with new or progressive intracranial disease who do not have a local control option (i.e. surgery, WBRT, SRS), systemic therapies may be considered. For patients who progress on the standard therapy of trastuzamab, taxane with or without pertuzumab, the use of trastuzumab-emtansine (T-DM1) has been proposed to confer a survival benefit [230]. Furthermore, additional agents that target the HER2 pathway including lapatinib, neratinib, tucatinib and tesevatinib, have shown early promise in the treatment of patients with HER2-positive breast cancer who brain metastases [231-235]. Studies have found that, when used in combination with capecitabine, both lapatinib and neratinib, have demonstrated intracranial activity and may be efficacious in this patient population [231-234]. The combination of tucatinib, capecitabine and trastuzumab has also demonstrated improved PFS and OS compared to the use of combination trastuzumab and capecitabine alone [235]. It is important to note, however, that the response rates of these agents may be dependent on previous radiotherapy as is evident by the decreased response rate associated with previous radiation as demonstrated in the LANDSCAPE trial evaluating lapatinib [211]. Fortunately, a trial evaluating the use of tucatinib in combination with trastuzumab-emtansine (T-DM1), suggests that this combination has anti-tumor activity in heavily pretreated patients [236].

Several studies have also found targeted therapies to have intracranial activity in patients with BRAF-mutation brain-metastatic melanoma [212, 237, 238]. In a multicenter, phase II trial dabrafenib, a BRAF inhibitor, was found to have intracranial activity in both patients who had progressed despite previous treatment as well as those who received no previous treatment [212]. An additional phase 2 trial comparing the use of another BRAF inhibitor, vemurafenib, in the
setting of previously untreated BM, demonstrated an intracranial response in this patient cohort [238]. Similar to the results seen in HER2-positive brain-metastatic breast cancer, patients who have not previously undergone treatment with radiotherapy for BM are more likely to respond to these targeted therapies [237, 238]. While both of these BRAF-inhibitors demonstrated intracranial responses, the response rates were less than 50% for both agents [212, 238]. More promising results, however, have come from a phase II trial evaluating the combination of the BRAF and MEK inhibitors, dabrafenib plus trametinib, which demonstrated response rates of 58% in patients without prior CNS treatment, 56% in patients with asymptomatic BM who had undergone previous local CNS treatment and 59% in those with symptomatic BM [239]. Additional BRAF/MEK inhibitor combinations such as ecoradenib plus binimetinib or vemurafenib plus cobimetinib have also been evaluated, but data is limited with respect to these combinations [240, 241]. It is important to note that the use of BRAF inhibitors has been associated with radiosensitization of normal tissues in patients treated with radiation prior to, during or after the treatment with these agents [242-245]. Lastly, with respect to leptomeningeal melanomatosis, the prognosis is unfortunately very poor and there is limited data regarding the use of targeted therapies in this population [246].

**Immunotherapy**

The field of immunotherapy has exploded over the last decade and the development of immune-checkpoint inhibitors has provided hope for more efficacious therapeutic strategies, especially with respect to the treatment of intracranial neoplasms.

The use of combination ipilimumab (CTLA-4 inhibitor) plus nivolumab (PD-1 inhibitor) in patients with brain-metastatic melanoma (MBM) who had not previously undergone local CNS
therapy has demonstrated superior intracranial response rates (46-56%) compared to the use of nivolumab alone (20%) [247, 248]. While the duration of the intracranial response seen in this patient cohort was improved compared to the previously discussed targeted therapies, the use of combination immunotherapy is associated with a high rate of grade ≥ 3 treatment-related adverse effects [247, 248]. It is also important to note that these studies were conducted in patients with asymptomatic brain metastases, which involved the use of no or very low dose steroids. This is an important consideration as previous studies have demonstrated that the use of steroids greatly alters the response to immunotherapy (25% vs. 10%) and as such, steroids must be stopped in order to achieve the full benefit from these agents [249, 250].

The use of single agent immunotherapy has also been evaluated in patients with MBM, however response rates were not as promising as those seen with combination immunotherapy (<30%) [251, 252]. Lastly, while most of the data regarding the use of immunotherapy in the treatment of patients with BM stems from work done in the setting of MBM, there is also support the use of immunotherapy in patients with NSCLC who lack oncogenic drivers [253-256] as well as those who have brain-metastatic renal cell carcinoma [257].

With respect to immunotherapy in combination with radiation therapy, multiple studies suggest that the concurrent use of SRS and immunotherapy is associated with improved OS as well as superior intracranial response rates and duration of response [258-260]. Additional studies have further supported a potential survival benefit of this combination [261, 262], and a very recent study found that nivolumab plus ipilimumab in combination with SRS improves OS in patients with MBM [263]. Furthermore, a study evaluating the use of a single agent immunotherapy (i.e. ipilimumab) in combination with SRS, suggests that the survival of patients treated with this strategy may be comparable to that of melanoma patients without brain metastases [264]. The
efficacy of combination immunotherapy and SRS has been found to be highly dependent on the timing of administration of these therapies, with multiple studies demonstrating superior benefit when these therapies are used concurrently [259, 260]. Multiple clinical trials are currently evaluating the use of combination immunotherapy and radiation therapy in the treatment of patients with BM (NCT02858869, NCT02978404, NCT02696993, NCT03955198, NCT03340129).

Additional data will be needed to determine the appropriate use and most effective combination of the above therapies for the treatment of patients with BM. To date, there are currently over 250 clinical trials currently enrolling patients and an additional 100 active trials tasked with further investigating the optimal therapeutic strategy for the treatment of patients with BM.

Recurrent

Salvage or repeated SRS is increasingly being use in the setting of recurrent BM and factors that influence efficacy of repeat SRS in achieving local control are similar to those previously discussed with respect to initial SRS treatment [265-268]. The use of surgery in the setting of recurrent BM may be considered in select patients, and factors that have been found to negatively influence the efficacy of reoperation include (1) the status of systemic disease, (2) KPS score ≤ 70 (3) time to recurrence ≤ 4 months (4) age ≥ 40 years and (5) primary tumor type of breast cancer or melanoma [269, 270]. The findings reported by Bindal et al., suggest that patients who meet ≤ 1 of these criteria have roughly a 57%, 5-year survival rate, whereas those who met ≥ 2 criteria experienced a 5-year survival rate of less than 11% [270]. Irrespective of these proposed negative predictive factors, reoperation may also be considered for symptom relief and for the improvement
of quality of life. Furthermore, the use of salvage WBRT may also be considered in select patients for whom SRS and surgery are not possible [271].

Symptomatic Treatment and Palliative Care

Glucocorticoids, such as dexamethasone, have been used for decades in the treatment of peritumoral edema and high intracranial pressure. Dexamethasone doses of 4-8 mg twice a day improves neurological symptoms caused by cerebral edema in up to 75% of patients, whereas lower doses (2-4 mg) can be used prophylactically to reduce the risk of acute radiation toxicity [197, 209]. However, the use of systemic steroids is associated with a large number of potentially serious side effects. To reduce the risk of gastric ulcers and hemorrhage, most patients receiving corticosteroids are routinely treated with histamine H2 antagonists or proton pump inhibitors to reduce the risk of gastric ulcers and hemorrhage [197]. If used, steroids should be tapered within 1 week of initiation and fully discontinued by 2 weeks to avoid chronic use symptoms [40]. As previously noted, with respect to immunotherapy, steroids should be used with caution due to their immunosuppressive nature and negative effect on OS and PFS in patients treated with immune checkpoint inhibitors [272].

Short-term anticonvulsants, such as levetiracetam, oxcarbazepine, or topiramate monotherapy, are indicated in patients experiencing seizures [273]. Effective seizure control can be achieved with minimal side effects [273]. Prophylactic anticonvulsants do not prevent the occurrence of future seizures, but the use of short-term agents, like levetiracetam, prior to surgical resection of tumor until postoperative day 7 reduces the incidence of seizures during this period [209]. Rare, but potential adverse effects of these agents include headache, nausea, restlessness, rash, and somnolence [273].
WBRT is the treatment of choice for palliative care in BM patients. By helping manage neurological symptoms and local disease, WBRT was shown to improve both survival time and health-related quality of life in patients [274].

Prognosis

Despite the progress made in both diagnostic and therapeutic modalities, the prognosis for patients with brain metastasis remains relatively poor. The recent Surveillance, Epidemiology, and End Results Program (SEER) population study representing around 28% of US population shows median survival ranging from 6-12 months depending on the type of primary tumor [6]. Patients with brain metastases arising from prostate primary tumors displayed the longest survival at 12 months, while breast, NSCLC, and melanoma exhibited a median survival of 10, 6, and 6 months respectively (Figure 1C) [6].

Determining prognosis is important in guiding the clinical management and therapeutic strategy in patients with BM. Several prognostic classification schemes have been developed, including the RTOG RPA Classification for Brain Metastasis (RTOG RPA) and the Graded Prognostic Assessment (GPA) [5, 275]. While both the RTOG RPA and the GPA consider age, KPS, extracranial metastases, in the determination of prognosis, the RTOG RPA relies on the subjective measure of primary tumor control [5, 275]. As such, the GPA, which establishes a cumulative score based on the four weighted factors of age, KPS, presence of extracranial metastatic lesions and number of cerebral metastatic lesions in lieu of primary tumor control, is the preferred prognostic index. However, as previously discussed, metastatic behavior and potential vary depending, not only on the broad type of primary tumor, but also with respect to molecular subtypes [93]. In an attempt to at least consider primary tumor type, a disease specific GPA (DS-GPA) was introduced (Table 2) [276]. Continuous efforts to refine the DS-GPA are
frequently being made, with the recent update being the inclusion of Cumulative Intracranial Tumor Volume (CITV) [11, 277-279]. In addition to the DS-GPA, it is important to also consider the specific molecular subtypes of primary tumors, which may affect survival or response to treatment in the setting of BM. For example, EGFR mutations and ALK rearrangement status should be considered in the prognostic evaluation of patients with NSCLC. Similarly, the HER2 and hormone receptor status should be considered in patients with metastatic breast cancer, as should BRAF mutation status in melanoma. It is important to note, however, that genomic alterations may be different in metastatic lesions compared to primary tumors [280]. A whole-exome sequencing study of matched primary tumor with brain metastases found that 53% of cases demonstrated genomic alterations in metastatic lesions that were not present in primary tumors [280]. This phenomenon will be important to consider as the incorporation of molecular alterations into prognostic classification schemes evolves.

Conclusions

Despite advances in the treatment of primary malignancies, the incidence of brain metastasis continues to rise and remains a therapeutic challenge. Current treatment options, which include a combination of surgical resection, SRS, WBRT, and systemic therapy are often inadequate, and prognosis remains poor. As new treatment options become available, the optimal therapeutic regimen for patients with cerebral metastasis should be based on an integrated multi-disciplinary approach combining surgery, radiation and systemic therapy as well as the patient’s overall performance status, type of primary tumor and its molecular subtype, as well as the number, location, and size of lesion(s). A team of experts from diverse field of medical oncology, radiation oncology, neurosurgery and precision genomic medicine in collaboration can make the highest impact in the management of this difficult clinical problem.
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References


Figure Legends:

Figure 1: Current epidemiology of brain metastasis by cancer type among patients from the Surveillance, Epidemiology, and End Results (SEER) program described at the time of diagnosis of systemic malignancy [6]. Patients were all diagnosed with non-hematologic malignancies originating outside the CNS between 2010-2013. Only the top six cancer types with highest incidence of brain metastasis were included in this summary. Data includes (A) incidence of BM within the cohort, (B) likelihood of BM if diagnosed with metastatic disease, and (C) median survival of these BM patients in months (Figure adapted from the SEER data [6]) (D) summary of top symptoms and (E) key molecular prognostic factors [41, 43, 281]. GI = gastrointestinal; NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer; IQR = Interquartile range; EGFR = Epidermal growth factor receptor; ALK = Anaplastic lymphoma kinase; BRAF = B-Raf proto-oncogene; ER = Estrogen receptor; PR = Progesterone receptor; HER-2 = human epidermal growth factor receptor 2.
Figure 2: Brain metastasis pathophysiology. (A) Metastasis is a complex, multistage process that begins when cancer cells acquire genetic mutations resulting in invasion, intravasation, circulation, intracranial arrest, and colonization [14]. Once a primary tumor metastasizes, cancer cells spread hematogenously and thus distribute similarly to regional blood flow of the brain – 80% hemispheres, 15% cerebellum, and 5% brainstem. Among 16 major cancer types studied, lung, breast, and melanoma were the most likely to metastasize to the brain and carried a relative risk >1 [15]. In order to arrest in the central nervous system, metastatic cells must penetrate the blood brain barrier (BBB), which is a neurovascular unit formed by unique cerebral endothelial cells joined together by intercellular tight junctions. Along with pericytes, astrocytes, neurons, and
microglia, it controls the exchange of substances between the CNS and periphery to maintain the delicate environment required for neuronal function [16]. (B) Cancers with a high propensity to metastasize to the brain have developed mechanisms to increase BBB permeability and disrupt endothelial function [17-21]. Within the tumor microenvironment, glial cells such as astrocytes and microglia boost tumor survival and proliferation through immune suppression [22-27].

![Figure 3. Treatment algorithm for symptomatic cancer patients with potential brain metastasis.](image-url)
Tables:

Table 1: Treatment options for brain metastasis, their general indications, adverse effects, need for adjuvant therapy, and alternative/future treatment methods.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
<th>Treatment Specific Effects</th>
<th>Adverse Effects</th>
<th>Adjuvant Therapy</th>
<th>Alternatives &amp; Future Directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical Resection</td>
<td>Limited number of lesions (1-4) Lesion causing significant cerebral edema/mass effect</td>
<td>General surgical adverse outcomes such as epidural/cavity hematoma, CSF leak, cerebral infarction,</td>
<td>Use of adjuvant SRS recommended for better local control</td>
<td>SRS if patient is a poor surgical candidate</td>
<td></td>
</tr>
<tr>
<td><strong>SRS</strong></td>
<td><strong>WBRT</strong></td>
<td><strong>Systemic Therapy</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large dominant lesion (&gt;2-4cm), especially in eloquent areas. Pathological diagnosis needed.</td>
<td>Limited number of lesions (1-4), Evolving to include &gt;5. Adjuvant therapy after surgical resection.</td>
<td>BM for chemo-sensitive primary tumor (e.g. SCLC or breast cancer). Generally, not first line therapy. If other treatment options are needed. Tumor with targetable molecular markers or sensitive to immunotherapy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus well as DVT and delirium among others.</td>
<td>Radiation Toxicity observed in around 9% of patients. Close observation only recommended.</td>
<td>Colitis, pneumonitis, thyroiditis, vitiligo, and other immune related adverse events in up to 25% of patients. Neurological side effects with Immunotherapy (1% of patients): hypophysitis, encephalitis, demyelinating polyneuropathy, and encephalomyelitis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractionated SRS for large lesions or those near eloquent area.</td>
<td>Multiple lesions (&gt;4). Prophylactic for patients with SCLC. Need complete response to chemotherapy prior to WBRT. Salvage therapy for recurrence.</td>
<td>Various drug combinations and doses currently under investigation. Combination of immunotherapy and radiotherapy currently under investigation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Close observation. SRS use for multiple lesions.</td>
<td>Multiple clinical trials ongoing.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: **SRS** = Stereotactic radiosurgery; **WBRT** = Whole Brain Radiotherapy; **SCLC** = Small Cell Lung Cancer; **TTField** = Tumor Treating Field.

**Table 2: Disease-specific graded prognostic assessment (DS-GPA) worksheet.**

<table>
<thead>
<tr>
<th>Lung Cancer</th>
<th>GPA Scoring Criteria</th>
<th>Total Score</th>
<th>Median Survival Time in Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognostic Factor</strong></td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>&gt; 60</td>
<td>50-60</td>
<td>0-1.0</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>70-80</td>
<td>&lt; 50</td>
</tr>
<tr>
<td><strong>KPS</strong></td>
<td>&lt; 70</td>
<td>90-100</td>
<td>2.5-3.0</td>
</tr>
<tr>
<td><strong>ECM</strong></td>
<td>Present</td>
<td>-</td>
<td>2.5-3.0</td>
</tr>
<tr>
<td><strong># BM</strong></td>
<td>&gt; 3</td>
<td>2-3</td>
<td>3.5-4.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grand Total</strong> =</td>
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</table>

<table>
<thead>
<tr>
<th>Melanoma</th>
<th>GPA Scoring Criteria</th>
<th>Total Score</th>
<th>Median Survival Time in Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognostic Factor</strong></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>KPS</strong></td>
<td>&lt; 70</td>
<td>70-80</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td><strong># BM</strong></td>
<td>&gt; 3</td>
<td>2-3</td>
<td>2.5-3.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>3.5-4.0</td>
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</table>
### Breast Cancer GPA Scoring Criteria

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Total Score</th>
<th>Median Survival Time in Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-1.0</td>
<td>3.35 (3.13-3.78)</td>
</tr>
<tr>
<td>0.5</td>
<td>1.5-2.0</td>
<td>7.70 (5.62-8.74)</td>
</tr>
<tr>
<td>1</td>
<td>2.5-3.0</td>
<td>15.0 (12.94-15.87)</td>
</tr>
<tr>
<td>1.5</td>
<td>3.5-4.0</td>
<td>25.3 (23.10-26.51)</td>
</tr>
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<td></td>
</tr>
</tbody>
</table>

### Renal Cell Carcinoma GPA Scoring Criteria

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Total Score</th>
<th>Median Survival Time in Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-1.0</td>
<td>3.27 (2.04-5.10)</td>
</tr>
<tr>
<td>1</td>
<td>1.5-2.0</td>
<td>7.29 (3.73-10.91)</td>
</tr>
<tr>
<td>2</td>
<td>2.5-3.0</td>
<td>11.2 (8.80-14.80)</td>
</tr>
<tr>
<td>2.5</td>
<td>3.5-4.0</td>
<td>14.7 (9.73-19.79)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### GI Cancer GPA Scoring Criteria

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Total Score</th>
<th>Median Survival Time in Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-1.0</td>
<td>3.13 (2.37-4.57)</td>
</tr>
<tr>
<td>1</td>
<td>1.5-2.0</td>
<td>4.40 (3.37-6.53)</td>
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<tr>
<td>2</td>
<td>2.5-3.0</td>
<td>6.87 (4.86-11.63)</td>
</tr>
<tr>
<td>3</td>
<td>3.5-4.0</td>
<td>13.5 (9.76-27.12)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: **Basal** = triple negative; **LumA** = luminal A (estrogen & progesterone receptor positive); **LumB** = luminal B (triple positive); **HER2** = HER2 positive only. **ECM** = extracranial metastases; **KPS** = Karnofsky performance status.