Brain and Spinal Cord Tumors

Chapter 2

Brain Metastasis

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1. Introduction

Brain metastases originate from tissues outside the central nervous system (CNS) and spread secondarily to the brain. They are 10 times more common than primary brain tumors, and account for more than half of all clinically diagnosed brain tumors in adults [1]. The incidence of brain metastases seems to be rising as the control of systemic cancer has improved and patient survival has subsequently increased. This chapter looks at the epidemiology of these tumors and their prognostic assessment, with a focus on strategies for treating both the tumors and their associated symptoms through surgery, radiosurgery, radiation therapy, and future treatment modalities.

1.1. Epidemiology and incidence

In patients with systemic malignancies, brain metastases occur in 20–40% of adults, with 60-75% being symptomatic during life and the remainder being discovered incidentally on computed tomography (CT)/magnetic resonance imaging (MRI) or at autopsy [2,3]. Older studies on the epidemiology of brain metastases grossly underestimated their actual incidence, because neurosurgeons were hesitant to operate on patients with known systemic cancer. Similarly, major ascertainment bias and underreporting problems are limiting factors in obtaining accurate epidemiologic data from large patient populations. Recent clinical series and autopsy studies demonstrate an increasing incidence of brain metastases, but the true incidence of brain metastasis is difficult to ascertain. In the United States, it is estimated that between 6% and 14% of all newly diagnosed cancers will ultimately metastasize to the brain [4,5]; based on the

1.7 billion new cancer diagnoses expected in 2016 [6], between 100,000 and 240,000 cases are expected to eventually lead to brain metastases. The apparent increase in the incidence of cerebral metastases may be due to a variety of factors. Increases in the length of survival of cancer patients, an aging patient population, advances in neuroimaging techniques, and routine staging that assesses the CNS may be associated with increased incidence of brain metastases.

Although virtually any malignant cancer can metastasize to the brain, the incidence of brain metastases varies dramatically between cancer types [7]. The histology and epidemiology of the primary cancer are the principal determinants of the frequency of brain metastasis. In adults, the most common primary tumors responsible for brain metastases are carcinomas, and include lung (30-60%), breast (10-30%), skin (melanoma) (5-20%), kidney, and colorectal cancers. Less frequent are metastases from prostate, esophageal, and oropharyngeal cancers, non-melanoma skin cancers, and sarcomas. Brain metastases from an unknown primary site account for up to 15% of patients. In these situations, histopathology of biopsy specimens, including immunohistochemistry, can often help identify the primary origin [8]. For patients with biopsy-proven brain metastases from an unknown primary tumor, the lung should be the primary focus of evaluation. Lung cancer is the most common primary cancer type in patients with unknown primary origin, and over 60% of such patients have a primary lung cancer or pulmonary metastasis from a primary tumor located elsewhere [9,10]. Positron emission tomography may also be useful in these patients, either by identifying the primary tumor or finding other sites of metastatic disease that can be more readily biopsied [11].

For all types of cancer, brain metastases diagnosed during life are relatively uncommon. According to two large series, the incidence of brain metastases in each type of cancer is as follows: lung (16-20%), melanoma (7%), renal cell carcinoma (7–10%), breast cancer (5%), and colorectal cancer (1–2%) [12,13]. The propensity of primary tumors to spread to the brain parenchyma (neurotropism) differs, being high in melanoma, small-cell lung cancer, choriocarcinoma, and other germ cell tumors; intermediate in breast cancer, non-small cell lung cancer (being more frequent in adenocarcinomas than in squamous tumors), and renal cancer; low in cancers of the prostate, gastrointestinal tract, ovary, and thyroid, and sarcomas.

1.2. Pathogenesis

The most common mechanism of metastasis to the brain is hematogenous spread [14]. The majority of brain metastases arise from embolization of tumor cells through the arterial circulation. Metastatic lesions are located in the cerebral hemisphere in about 80% of patients, in the cerebellum in 15%, and in the brainstem in 5%, with metastases in the basal ganglia, pineal gland, and hypophysis being very rare. Metastases are generally located at the junction of the gray matter and white matter where blood vessels decrease in diameter and act as a trap for clumps of tumor cells. Brain metastases also tend to be more common at the terminal

"watershed areas" of arterial circulation [15]. However, different primary tumors may have a predilection for metastasis to different areas within the brain. For example, melanoma is unusual in its predilection to metastasize to the cerebral cortex and basal ganglia rather than the gray-white matter junction [16]. Pelvic, gastrointestinal, and breast cancers more frequently metastasize to the posterior fossa [15,17]. These phenomena may be due to the cell surface properties of metastatic cells and the endothelium within the CNS vasculature, but the exact reasons are unclear.

The less-recognized mechanism is the "soil and seed" hypothesis [18]. Specific molecular factors may be expressed on tumor cells, and tumor cells may also respond to brain-derived growth factors, and be able to invade, proliferate, and induce angiogenesis [19,20].

1.3. Demographics

The incidence of brain metastases is dependent on age, similar to that of primary systemic cancers. The highest incidence of brain metastasis is observed in the fifth to seventh decades [21]. The age group most at risk for brain metastasis varies by primary cancer type [22,23]. In children, the most common sources of brain metastasis are sarcomas, neuroblastoma, and germ cell tumors [24,25].

The overall incidence of brain metastasis is not affected by sex. However, there are some differences in the two sexes in the types of primary cancer associated with brain metastases. For example, lung cancer is the most common source of brain metastases in men, whereas breast cancer is the most common source in women [26].

1.4. Advanced imaging study

In the CT era, about 50% of brain metastases were diagnosed as single metastases, whereas MRI has revealed that two-thirds to three-fourths of brain metastases are multiple lesions [27,28]. Contrast-enhanced MRI is the preferred imaging modality for the diagnosis of brain metastases, and is more sensitive than either nonenhanced MRI or CT scanning in detecting lesions in patients suspected of having cerebral metastases and in differentiating metastases from other CNS lesions. Davis PC et al. reported that contrast-enhanced MRI demonstrated more than 67 definite or typical parenchymal metastases, compared with more than 40 using T2-weighted MRI and 37 using double-dose contrast-enhanced CT in their study on 23 patients [29]. Moreover, various techniques, such as magnetization transfer, three-dimensional, magnetization-prepared rapid gradient-echo and triple dose gadolinium imaging studies may further improve metastatic lesion detection with MRI [30-33].

2. Prognosis Assessment

Historically, patients with brain metastasis had such poor prognosis that little thought

was given to determining an individual's prognosis or optimal treatment. For untreated patients with brain metastases, the median survival is approximately 1 to 2 months. With advances in medical and surgical treatment of brain metastases, it is sometimes difficult to predict the life expectancy of these patients.

2.1 Recursive partitioning analysis (RPA)

Several studies have been performed to identify factors associated with a favorable prognosis. The following factors have been revealed to be associated with good prognosis of patients with brain metastases: a high Karnofsky performance status (KPS) score, a single brain metastasis, an absence of systemic disease, a controlled primary tumor, and a younger age (< 60–65 years) [34]. The first effort came in the late 1990s, when the Radiation Therapy Oncology Group (RTOG) performed an RPA. The RTOG has a large database using which Gaspar et al. performed an RPA on 1200 patients with brain metastases [35]. Based on univariate analysis, the KPS was the most important factor and the first node of a prognostic tree. Among patients with a KPS of 70 or greater, the status of the primary tumor was the second most important prognostic factor. Age was the third factor and the status of systemic metastases the fourth. Three prognostic classes were then constructed (**Table 1**). Using this approach, median survival ranged from 7.1 months in patients with the best prognostic score (RPA class 1) to 2.3 months in those with the worst (RPA class 3). In this RTOG analysis, approximately 20%, 65%, and 15% of the patients were in classes 1, 2, and 3, respectively. Furthermore, these three prognostic classes were identified and the outcome correlated with median survival. These results were subsequently validated in another RTOG trial that included 445 patients with brain metastases [36]. The median survival was 6.2 months for class 1 patients and 3.8 months for those in class 2. In conclusion, RPA classes present significant information that can be used to select patients for intensive local treatment.

2.2. Diagnosis-Specific Graded Prognostic Assessment (DS-GPA)

While the RPA classification can be applied to any patient with brain metastases, the survival results following treatment for brain metastases are highly heterogeneous and depend in part upon the primary tumor. This observation led to a proposal for the DS-GPA [37,38]. The DS-GPA is based upon an analysis of nearly 4000 patients with newly diagnosed brain metastases treated between 1985 and 2007. Multivariate analysis using the same criteria as the RPA analysis as well as the primary diagnosis led to the establishment of separate criteria for patients with non-small cell lung cancer, small cell lung cancer, melanoma, renal cell carcinoma, breast cancer, and gastrointestinal cancer (**Table 2**). The significant prognostic factors for each type of cancer differ in this model. The factors for lung cancer are KPS, presence of extracranial metastases, and number of brain metastases; the factors for melanoma and renal cell carcinoma are KPS and number of brain metastases; the factors for breast cancer are KPS,

subtype (based upon estrogen receptor/progesterone receptor and HER2 status), and age; the sole factor for gastrointestinal cancer is KPS. For each of these disease categories, the DS-GPA provides a higher level of refinement, where the median survival ranges from 2.79 to 25.30 months, and there is a statistically significant survival gradient with improvement in overall survival with a better DS-GPA score. These criteria account for primary tumor type and unique features applicable to each primary tumor, making the system relevant to daily clinical practice and improved prognostic information that may be useful for patient management as well as clinical trials.

2.3. Other factors associated with prognosis

Although the Mini-Mental Status Examination (MMSE) does not provide additional prognostic significance to the RPA, a poor MMSE has been shown to be prognostically important in a study on 445 patients in the RTOG group [39]. There are a few additional controversies, as some factors, such as primary breast tumor, metachronous presentation, a time interval of 12 months or greater between the diagnosis of the primary tumor and the appearance of brain metastasis, the number of brain metastases, and the response to steroids, are recognized as favorable prognostic factors [40-43]. The prognosis is not different for brain metastases with unknown primary tumors and those from known primary tumors [44].

There are some prognosis assessment tools for brain metastases associated with stereotactic radiosurgery (SRS) [45,46]. Seriazwa et al. reported that the Score Index for Radiosurgery in Brain Metastases (modified BSBM) was found to be excellent for predicting neurological outcomes, independently of life expectancy, in SRS-treated brain metastases in their study on 2838 patients (**Table 3**).

For patients with brain metastases of melanoma, favorable prognostic signs include the delayed onset of a single brain metastasis without other visceral metastatic disease and a normal serum lactate dehydrogenase (LDH) level, or initial presentation with an unknown primary tumor presenting as a solitary melanoma brain metastasis. In contrast, multiple brain lesions, extensive visceral metastases, high serum LDH, or a primary lesion of the head and neck region historically carry an unfavorable prognosis [47-49].

3. Clinical Manifestation

Brain metastases have highly variable clinical features and should be suspected in any cancer patient who develops neurologic symptoms or behavioral abnormalities. Up to two-thirds of all brain metastases are symptomatic at some time in living patients [50]. Although modern screening protocols using brain MRI more frequently detect asymptomatic brain metastases, clinical evidence of neurologic signs and symptoms is the first indicator of brain metastases in most patients. The etiology of symptoms lies with elevated intracranial pressure,

focal irritation, or destruction of neurons secondary to the mass itself or the surrounding edema [7]. Less commonly, intratumoral hemorrhage, obstructive hydrocephalus, or embolization by tumor cells result in symptoms.

Headache: Headache is a common presenting symptom and becomes more common with multiple metastases or posterior fossa lesions. Headaches occur in approximately 40–50% of patients with brain metastases [35,51]. Although the classic early morning headache is uncommon, it is highly suggestive when present. In a study on 111 patients [52], headache was present in 48% and equally affected those with primary and metastatic brain lesions. The headaches were similar to tension type in 77% of patients, migraine in 9%, and other types in 14%. The typical headache was bifrontal but worse ipsilaterally; it was the worst symptom in about one-half of patients. In contrast to tension type headaches, brain tumor headaches were worse with bending over in 32% of patients, and nausea or vomiting was present in 40%. Worsening headache may also follow maneuvers that raise intrathoracic pressure, such as coughing, sneezing, or the Valsalva maneuver.

Focal neurologic dysfunction: Twenty to forty percent of patients present with focal neurologic dysfunction. Focal irritation or destruction of surrounding brain tissue and edema often result in focal neurologic symptoms that have very important localizing value, including hemiparesis, visual field defect, and aphasia [53]. Hemiparesis is the most common complaint, but its manifestations depend upon the location of the metastases.

Cognitive dysfunction: Cognitive dysfunction, including memory problems and mood or personality changes, is the presenting problem in 30-35% of patients. However, metabolic encephalopathy is a much more common cause of cognitive dysfunction than metastatic disease in cancer patients who develop an altered mental status [54].

Seizures: Seizures in patients with brain metastases are almost exclusively associated with supratentorial lesions [55]. Approximately 25% of patients with brain metastases have seizures, and 10% of these patients complain of seizures as the presenting symptom [56].

Stroke: Although most patients with brain metastases tend to have subacute progressive symptoms, another 5–10% present acutely because of stroke caused by hemorrhage into a metastasis, hypercoagulability, invasion or compression of an artery by the tumor, or embolization of tumor cells [57,58]. Melanoma, choriocarcinoma, and thyroid and renal carcinoma have a particular propensity to bleed [53].

4. Treatment

Longer survival, improved quality of life, and stabilization of neurocognitive function for patients with brain metastasis are the goals of treatment. Treatment must be directed not

only at the brain metastasis but also at a multitude of other symptoms that plague patients with cancer and brain metastases [59].

4.1. Symptomatic management

The symptomatic management of patients with brain metastases is similar to the approach used in those with primary brain tumors. The key components include the control of peritumoral edema with corticosteroids, the treatment of seizures, and the management of venous thromboembolic disease.

Peritumoral edema: Most patients with peritumoral edema and brain metastases can be adequately managed with glucocorticoids. Symptomatic brain metastases show marked clinical improvement within 24–48 hours after dexamethasone administration [60]. Dexamethasone is the standard agent because its relative lack of mineralocorticoid activity reduces the potential for fluid retention. In addition, dexamethasone may be associated with a lower risk of infection and cognitive impairment compared to other glucocorticoids [61,62]. The guidelines recommend a dose of dexamethasone of 16 mg per day or more for patients with severe symptoms due to increased intracranial pressure and edema because of brain metastases. For patients with milder symptoms, a starting dose of 4–8 mg of dexamethasone daily is recommended; steroids are not recommended for asymptomatic patients. Based upon this review, the drug should be tapered slowly over a 2-week period or longer in symptomatic patients [63].

Seizure: The need for anticonvulsant therapy in patients who experience a seizure because of a brain tumor is clear. These patients should be treated with monotherapy with a standard first-line antiepileptic drug because of the high risk of recurrence [34]. The initial use of multidrug regimens should be avoided whenever possible. Monotherapy increases the likelihood of compliance, provides a wider therapeutic window, and is more cost-effective than combination drug therapy [64]. If patients experience recurrent seizures after initiation of therapy, doses of the initial agent should be escalated and adequate serum concentrations should be verified before switching drugs or adding a second agent. If adequate seizure control cannot be obtained, an alternative antiepileptic drug should be prescribed or a second antiepileptic drug added [65]. Prophylactic antiepileptic drugs are generally not recommended for patients with brain metastases without a history of seizure [66]. An exception might be those with metastatic melanoma, hemorrhagic lesions, and multiple metastases [34,67]. For this subgroup of patients who have a higher risk of developing seizures, the role of prophylaxis remains to be addressed. Generally, seizure related to brain metastases is difficult to control with antiepileptic drugs; perhaps there are some underlying pathophysiologic mechanisms and interaction with other drugs [68]. Newer antiepileptic drugs, such as levetiracetam, pregabalin, lamotrigine, lacosamide, and topiramate, are generally preferred for seizure treatment in this setting, as these agents have a more favorable safety profile compared with older agents and avoid potential

drug-drug interactions [69–72].

Vascular complication: Although intracranial hemorrhage associated with brain metastases is less common, it can still be fatal. Brain metastases from melanoma, choriocarcinoma, thyroid carcinoma, and renal cell carcinoma have particularly high propensities for spontaneous hemorrhage [73,74]. Treatment strategies in patients with brain metastases that have a high risk of spontaneous hemorrhage must be individualized, as there are no prospective studies in this patient population to inform the balance of risks and benefits. Patients with brain metastases have a latent hypercoagulable state that predisposes to thromboembolism, particularly in the postoperative period [75]. The incidence of venous thromboembolism ranges between 1.03% and 20% [34]. The management of venous thromboembolism requires a balance between the effectiveness of the treatment and the risk of intracranial hemorrhage or limited life expectancy.

4.2. Surgical treatment

When considering surgical resection, some factors must be addressed, including the extent of systemic disease and the size, location, and multiplicity of the tumors. The extent of systemic disease is the single most important factor that determines treatment outcome. Progression of systemic disease accounts for up to 70% of deaths among patients undergoing surgical resection for brain metastases [76]. Although there are some controversies, patients that are expected to survive for at least 3 months are generally surgical candidates. Kim et al. reported the clinical factors of patients who survived for less than 3 months after surgical resection of brain metastases [77]. In their study on 83 patients with a single brain metastasis, 25 patients (30.1%) died within 3 months of craniotomy. In their multivariate analysis, a poorly-controlled primary cancer, a KPS score < 70, and adjuvant therapy had a significant influence on poor prognosis. In another study on 1953 patients, factors associated with worse overall survival included sex (male, hazard ratio (HR) 1.2), multiple brain metastases (HR 1.3), no surgery (HR 1.8), and no SRS (HR 1.8). In contrast, 23 patients (1.2%) survived ≥ 10 years, and the median survival for ≥ 10-year survivors was 18.5 years. This study found that patients with favorable prognostic features should undergo multimodality treatment for solitary lesions [78]. Brain metastases can be effectively palliated with aggressive local treatment in selected patients. As life expectancy of patients with brain metastases is often limited by extracranial disease, aggressive therapy is generally reserved for those who are expected to survive long enough to benefit from aggressive treatment of their brain metastases.

Tumor location is another important factor when considering surgical resection. The depth of the tumor and its location in the eloquent areas of the brain are generally main points when considering surgery. Tumor size is also an important factor when physicians decide between treating brain metastases with surgical resection or SRS. Larger lesions are more likely

to produce mass effect and be symptomatic. Surgical resection is more readily performed than SRS in tumors greater than 3cm in maximum diameter.

Advances in neuro-anesthesia and neurosurgery have significantly improved the safety of surgical resection of brain metastases, making this approach applicable to a larger number of patients [79]. Furthermore, the surgical resection of brain metastases is one key element in multimodal treatment. However, standard surgery alone is often not sufficient to achieve local control, because most brain metastases are not sharply delineated but have an irregular tumor-brain interface or even an infiltrative growth pattern. An infiltrative growth pattern of cerebral metastases might be one reason for their extraordinary high local recurrence rate and may influence overall survival. Intraoperative detection of any residual tumor and development of more radical surgical techniques is therefore an important neurooncological challenge and might result in better tumor control [80]. To achieve these goals, some authors have studied the usefulness of pathologically confirmed clean surgical margins during surgical resection for better local control of single brain metastasis in non-eloquent areas. After gross total resection, they resected additional surrounding brain tissue to a depth of at least 5 mm until a pathological free margin was confirmed. In two studies on 94 and 90 patients, respectively, they concluded that a wide surgical resection of brain metastases, including tumor cells infiltrating the adjacent brain parenchyma with confirmed clean surgical margin provides better local control [81,82].

For patients with a single, surgically accessible lesion that is large or associated with significant edema and mass effect, surgical resection achieves rapid symptom relief and local control. In addition, patients with solitary brain metastases who have limited systemic disease are generally good surgical candidates. In carefully selected patients, resection has been shown to improve survival and decrease the risk of neurologic death compared with a radiation-alone approach. There have been three randomized controlled trials comparing surgical resection combined with whole brain radiation therapy (WBRT) with WBRT alone in patients with single brain metastases. In the first trial, 48 patients with a single brain metastasis were treated with either surgical resection followed by WBRT or WBRT alone [83]. The group treated with surgical resection combined with WBRT had significantly fewer local recurrences (20% versus 52%), significantly improved survival (40 weeks versus 15 weeks), and a better quality of life. Factors that correlated significantly with increased survival in addition to surgical treatment were the absence of extracranial disease, longer time to development of brain metastasis, and younger age. In the second trial of 63 patients with a single brain metastasis, the overall survival of patients who underwent surgical resection and WBRT was significantly longer than patients who received WBRT alone (10 months versus 6 months), and patients remained functionally independent for a longer period [84,85]. The benefit from surgical resection was seen primarily in patients with stable extracranial disease (median survival, 12 months). Pa-

tients with active extracranial disease and those older than 60 years did not appear to benefit from surgical resection. However, the third trial did not show improved survival outcomes in the surgical resection combined with WBRT group, because patients with a lower KPS score at baseline were included, and a higher proportion of cases had extracranial disease [86,87].

Surgical resection is more often reserved for patients with controlled systemic disease at the time of diagnosis of brain metastases, and survival outcomes are better for these patients. However, if the systemic disease was controllable, such as bone metastases from breast cancer, or if the primary cancer is radio-resistant, such as renal cancer and melanoma, even patients with disseminated systemic disease could benefit from surgical resection, especially in consideration of quality of life [34]. In the past, most neurosurgeons were hesitant to operate on patients with multiple brain metastases [76]. Bindal and coworkers studied surgical resection in patients with multiple brain metastases [88]. In their study, all patients had two or three brain metastases, and most received WBRT after surgical resection. Group A included 30 patients with multiple tumors who underwent resection of some, but not all the lesions, and group B included 26 patients in whom all the lesions were resected. These two groups were compared with a control group (group C, who had single brain metastases that were completely resected). There was no difference in surgical mortality (3%, 4%, and 0% for groups A, B, and C, respectively) or morbidity (8%, 9%, and 8%, respectively). Patients with multiple metastases that were all resected (group B) had a significantly longer survival time (median, 14 months) than patients with multiple metastases in whom some lesions were not resected (group A; median survival, 6 months). The survival of patients in group B was similar to that of patients with resected single metastases (group C; median survival, 14 months). Hence, the authors concluded that resecting multiple brain metastases (typically two to four) is as effective as resecting a single brain metastasis as long as all the lesions are resected.

Stereotactic biopsy should be performed when the diagnosis of brain metastasis is in doubt. The clinical situations which require stereotactic biopsy include the following: 1) the primary tumor is not known to be metastatic or rarely metastasizes to the brain; 2) the history of cancer is remote; 3) patients with a single lesion; 4) brain MRI showing prominent diffusion restriction raising suspicion for abscess or heterogenous, irregularly shaped centrally necrotic mass lesion suggestive of malignant glioma.

The major risks associated with surgical resection include infection, postoperative neurologic worsening, intracranial hemorrhage, and cerebral infarction in the perioperative period [79]. The risk of permanent neurologic deficit associated with surgical resection is estimated to be about 8–9% [89].

4.3. Whole brain radiation therapy

Patients who undergo surgical resection of a single brain metastasis have a 50–60% risk

of local recurrence at the resection site within the next 6–12 months [90,91]. Some studies are there on the role of adjuvant WBRT after SRS or surgical resection. In the largest meta-analysis, including five randomized trials of 663 patients, WBRT adjuvant to SRS or surgical resection decreased the relative risk of intracranial disease progression at 1 year by 53% (relative risk 0.47, 95% confidence interval (CI) 0.34–0.66), but did not improve overall survival (HR 1.11, 95% CI 0.83–1.48) [92]. Moreover, in the largest individual trial on 359 patients (either SRS (n = 199) or surgery (n = 160)) with one to three brain metastases, the results included the following [90]: 1) administration of WBRT following SRS or surgical resection significantly decreased the rate of local recurrence at 2 years compared with control (59% versus 27% in those initially treated with surgical resection, and 31% versus 19% in those initially managed with SRS). WBRT also decreased the rate of recurrence at new sites (42% versus 23% following initial surgery and 48% versus 33% following SRS); 2) global health-related quality of life scores [93] and scores in physical functioning and fatigue were better in the observation arm at early time points but similar at 1 year; 3) there was no significant difference in overall survival (median 10.9 months and 10.7 months in the WBRT and observation groups, respectively).

WBRT is associated with an increased risk of neurocognitive impairment that may reduce quality of life. There are some randomized trials that found that combining WBRT with SRS increased the likelihood of a decline in learning and memory function compared with treatment with SRS alone [94,95]. Furthermore, SRS to the post-resection cavity has become the alternative to postoperative WBRT because of concerns about cognitive impairment due to WBRT. There are some randomized trials suggesting that postoperative SRS decreases the risk of neurocognitive decline compared with WBRT, and improves local control compared with observation. In a multicenter trial of 194 patients, patients were randomly assigned to postoperative SRS (12 to 20 Gy in a single fraction, depending on cavity volume) or WBRT (30 Gy in 10 fractions or 37.5 Gy in 15 fractions) [96]. At 6 months, patients treated with postoperative SRS had a lower risk of cognitive deterioration (52% versus 85%) and similar median overall survival (12.2 months versus 11.6 months) compared to those who received WBRT. However, the postoperative SRS group showed a worse local control rate (80% versus 87% at 6 months and 61% versus 81% at 12 months) as well as a worse overall intracranial control rate (55% versus 81% at 6 months) compared to the WBRT group.

WBRT alone is the treatment of choice for patients with single brain metastasis not amenable to surgery or radiosurgery, especially those with active and disseminated systemic disease [85]. The treatment effect would be greater in radiosensitive tumors, such as breast cancer than in radio-resistant tumors. In addition, WBRT has for a long time been the sole treatment for multiple brain metastases, with a median survival of 2–6 months [34]. The most commonly used schedule is 30 Gy in 10 daily fractions. Other randomized controlled trials studied altered WBRT dose fractionation schedules (40 Gy in 20 fractions given twice daily

or 20 Gy in 4 or 5 daily fractions), and they concluded that altered WBRT dose-fractionation schemes as compared to standard (30 Gy in 10 daily fractions) had a benefit in terms of overall survival, neurologic function, and symptom control [97].

4.4. Stereotactic radiosurgery

Recently, an increasing number of patients with brain metastases have been treated using SRS. This procedure delivers a single high dose of radiation, using multiple cobalt sources (gamma-knife) or a linear accelerator through the stereotactic method [34]. SRS is a reasonable alternative to surgery or WBRT for small tumors that are not surgically accessible. Of note, neurotoxicity and local failure after SRS increase with increasing lesion size, and thus consideration of SRS rather than surgery should generally be limited to lesions with a diameter of 3 cm or less [98]. For patients with newly diagnosed brain metastases, a series of reports examining SRS reported a rapid decrease in symptoms, a local control rate of 80–90%, and a median survival of 7–12 months [99–103]. Another advantage of SRS is that it can be used in metastases from highly radio-resistant tumors, like melanoma and renal cell carcinoma, which respond very poorly to conventional radiation therapy [34].

For patients with multiple brain metastases, some randomized trials were performed examining the use of SRS as an initial therapy for up to four brain metastases that were appropriate targets (< 3 cm in diameter) [92,104]. Although there are controversies about the number of treatable tumors, prospective nonrandomized data in patients with newly diagnosed brain metastases suggest that up to 10 tumors with a total cumulative volume ≤ 15 mL may be treated in a single session with similar efficacy and no increase in toxicity [98,105]. A multivariate analysis of 80 patients with 126 lesions revealed that radiation dose was an important factor for local control (local control rates for ≥ 14 Gy and those < 14 Gy were 90% and < 50%, respectively) [106]. Lesion phenotype was an additional factor that independently influenced local control, with cystic and necrotic tumors being more likely to recur than solid tumors in a large retrospective study [107].

Acute symptoms after SRS can include mild nausea, dizziness or vertigo, seizures, or new headaches. Neurologic symptoms may arise from transient swelling that begins 12–48 hours after SRS. Acute SRS-related symptoms can be prevented or controlled by a short course of steroids around the time of SRS [108]. Radiation necrosis is the most common delayed complication after SRS for the treatment of brain metastases. Radiation necrosis is not a neoplasm, but the lesion tends to progressively enlarge with a mass effect and cause diffuse peritumoral edema in a way that resembles neoplasia. Radiation necrosis can be mostly controlled by medical treatment, but, in cases refractory to medication, surgical intervention is required [109]. It can occur in approximately 10% of treated tumors anywhere from 6 months to several years after treatment [110–112]. The two most important risk factors for radiation necrosis in

patients with brain metastases are prior radiation (either SRS or WBRT) to the same lesion and lesion size (with larger tumor volumes associated with higher risk). Use of hypofractionated rather than single fraction SRS for tumors > 2 cm may decrease the risk of radiation necrosis [113].

4.5. Chemotherapy

Unlike surgical resection and SRS, systemic chemotherapy allows for the treatment of the entire brain and extracranial disease. In the past, chemotherapy has been considered ineffective because of the blood-brain barrier. However, it is now generally recognized that the blood-brain barrier is disrupted at the site of brain metastases. Chemosensitivity is the most important factor for the effectiveness of chemotherapeutic agents on brain metastases [114]. Brain metastases from chemosensitive tumors, such as small cell lung cancer, germ cell tumors, and breast cancer, are as responsive as primary systemic cancers. Chemotherapy alone in these types of metastases presents a relatively considerable response rate, approximately 20–60% [115-117]. Moreover, the addition of radiation therapy to chemotherapy may improve the response rate [118-120]. In clinical situations, chemotherapy is an initial treatment (or followed by WBRT) in patients with brain metastases from small cell lung cancer and germ cell tumors only, whereas WBRT remains the main treatment modality in patients with brain metastases from non-small cell lung cancer, breast cancer, and other solid tumors [34]. In addition, for patients with gynecologic brain metastases, Kim and coworkers performed a retrospective multi-institute analysis of overall survival [121]. They concluded that, in addition to traditional prognostic factors in brain metastases, multiple treatment methods, such as neurosurgery and combined chemoradiotherapy may play an important role in prolonging the survival of patients with brain metastases of gynecologic cancer.

4.6. Future prospective depending on histology

Although surgical treatment and radiation therapy remain the main treatment modalities for brain metastases, the management of brain metastases has become increasingly individualized for some types of cancers and genotypes [122,123]. For example, patients with brain metastases from melanoma, breast cancer, and non-small cell lung cancer are optimally treated by multimodal therapy, and clinical trials have been performed to prove the effectiveness of these systemic therapies.

For patients with brain metastasis of melanoma, immunotherapy and targeted therapy have provided dramatic advances in treatment. Immunotherapy significantly prolongs survival in patients with disseminated systemic melanoma and may have clinically useful activity against melanoma brain metastases. Established immunotherapy approaches for systemic disease include the anti-cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody (ipilimumab), monoclonal antibodies directed against programmed cell death 1 protein (pembroli-

zumab, nivolumab), and the combination of nivolumab and ipilimumab [124–126]. Advances in understanding the pathogenesis of melanoma have developed targeted therapy for treatment in patients with metastatic melanoma. Dabrafenib targets the BRAF V600E and BRAF V600K mutations, and vemurafenib is a small-molecule inhibitor of BRAF. These two agents proved effective in melanoma patients with brain metastases in a prospective phase II study [127,128]. For patients with brain metastases of HER2-positive breast cancer, prospective clinical trials were performed to evaluate the treatment results of lapatinib and trastuzumab-emtansine. However, the effectiveness of these agents has not yet been validated, and further studies are required [129,130]. For patients with brain metastasis of non-small cell lung cancer with an epidermal growth factor receptor (EGFR) mutation, the small molecule EGFR tyrosine kinase inhibitors erlotinib and gefitinib have antitumor activity [131,132]. Furthermore, some have reported that WBRT combined with gefitinib/erlotinib showed superior results to WBRT alone and was well tolerated in patients [133].

5. Recurrent Disease

Recurrent disease may be amenable to treatment with salvage SRS, surgery, or WBRT. SRS is increasingly used to treat new or recurrent tumors that arise after initial therapy in patients with a good performance status and stable extracranial disease [134]. Retreatment with WBRT or partial brain reirradiation may provide some benefit for carefully selected patients who are not candidates for surgery or SRS [135]. However, reirradiation is likely to exceed the brain's tolerance and may result in delayed toxicity if the patient survives long enough. Local control rates for previously untreated tumors are expected to be similar to those achieved with initial therapy. In selected patients with local recurrence of a single brain metastasis and good performance status, reoperation affords a neurological improvement and prolonged survival [136,137].

6. Conclusion and Future Directions

There is an increasing awareness of late cognitive dysfunctions following WBRT. Therefore, there has been an increased use of SRS, as well as new radiation approaches, such as hippocampus-sparing intensity modulated radiation therapy, to solve this problem. Cognitive dysfunction is an important problem in terms of quality of life for patients with brain metastases. Immunotherapy and targeted therapies have revolutionized the management of several solid tumor types or subtypes. Although it needs to be validated, the use of upfront immunotherapy and targeted therapies in small asymptomatic multiple brain metastases to delay or avoid WBRT is an interesting approach. Furthermore, the combination of SRS and targeted agents or immunotherapies has a rationale and is attractive; however, more data are needed on the timing and sequence of the different combinations to avoid unexpected toxicities. As the management of brain metastases has become increasingly individualized for some types of

cancers and genotypes, the prognosis assessment scale should be stratified. More data about the genetic and molecular factors associated with treatment results are needed to improve the prognosis scale.

Table 1: Recursive partitioning analysis (RPA) of prognostic factors in patients with brain metastases

RPA class	Criteria	Median survival time (months)
I	Karnofsky Performance Status≥ 70 < 65 years of age Controlled primarytumor No systemic metastases	7.1
II	Karnofsky Performance Status≥ 70 andat least one of the following: ≥ 65 years of age Uncontrolled primary tumor Presence of systemic metastases	4.2
III	Karnofsky Performance Status< 70	2.3

Table 2: Diagnosis-specific graded prognostic assessment

Non-small-cell and small-cell lung cancer				
Prognostic factor	Scoring criteria			Patient score
	0	0.5	1.0	
Age (years)	> 60	50-60	< 50	
KPS	< 70	70-80	90-100	
Extracranial metastases	Present	-	Absent	
Number of BM	> 3	2-3	1	
Total:				
Median survival (months) by score: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8				
Melanoma				
Prognostic factor	Scoring criteria			Patient score
	0	1.0	2.0	
KPS	< 70	70-80	90-100	
Number of BM	>3	2-3	1	
Total:				
Median survival (months) by score: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2				
Breast cancer				
Prognostic factor	Scoring criteria			Patient score
	0	0.5	1.0	1.5	2.0	
KPS	≤50	60	70-80	90-100	n/a	

Subtype*	Basal	n/a	Luminal A	HER2	Luminal B	
Age (years)	≥60	< 60	n/a	n/a	n/a	
Total:						
Median survival (months) by score: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3						
Renal cell carcinoma						
Prognostic factor	Scoring criteria					Patient score
	0		1.0		2.0	
KPS	< 70		70-80		90-100	
Number of BM	> 3		2-3		1	
Total:						
Median survival (months) by score: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8						
Gastrointestinal cancers						
Prognostic factor	Scoring score					Patient score
	0	1	2	3	4	
KPS	< 70	70	80	90	100	
Total:						
Median survival (months) by score: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5						

7. References

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