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Diagnosis and Treatment Options for Brain Metastasis of Melanoma

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1. Introduction

Metastasis to the brain is a devastating and common consequence for patients with malignant melanoma. A significant number of patients with melanoma eventually develop brain metastasis at the time of death. Patients are often symptomatic from their lesions and a large percentage of those with neurological deficits eventually die from the brain metastasis. Diagnosis does not typically occur until late in the disease course, which can preclude many treatment options. Additionally, rapid progression of the disease state and worsening health status magnifies the difficulties of treatment. Currently, contrast-enhanced computer tomography (CT) and magnetic resonance imaging (MRI) remain the main diagnostic modalities. Confirmation is usually achieved with surgical biopsy or resection. After diagnosis, treatment options are somewhat limited - surgical management, radiation therapy, and chemotherapy are most commonly used either alone or in combination.

This chapter provides a description of the common presenting symptoms, diagnostic modalities, and treatment options for patients with metastatic melanoma to the brain. This chapter will also discuss emerging technologies which may have notable impacts on the future of disease management. Ultimately, prompt diagnosis and treatment for patients with brain metastases may have important implications for the duration and quality of life of these patients.

2. Epidemiology and demographics

In general, patients with intracranial metastases significantly outnumber those with primary brain tumors. However, there are a small number of population-based epidemiological studies that address the true incidence of intracranial metastases, and studies devoted primarily to intracranial melanoma metastases are even less common [1]. Along with the limitations inherent to most surveys, such as sampling size and variability, there are several other limiting factors. This includes inadequate reporting, difficulty attaining ante-mortem diagnosis, and greater emphasis cancer databases place on the incidence of primary tumors rather than metastasis [2]. As a result, it is quite likely that current population-based epidemiological studies underestimate the true incidence of cancer metastasizing to the brain [2]. A significant amount of the reported data now originates from clinical, neurosurgical, and autopsy series which are subject to their own limitations as well.

However, as methods of diagnosis and treatment continue to improve, a more accurate picture can be portrayed.

Malignant melanoma is one of the most common systemic cancers to metastasize to the central nervous system (CNS). Following lung and breast carcinoma, melanoma historically has the third highest incidence of metastasis to the brain [3]. One recent study has indicated it may now surpass that of breast carcinoma, most likely a result of increasing rates over time [1]. Of cases with metastasis to the brain, melanoma is the primary tumor for about 5 to 21 percent of these patients [4]. CNS involvement or deficits are the first manifestation of melanoma in 9 to 12 percent of patients [5]. For those that carry a diagnosis of melanoma, between 12 to 60 percent can expect to develop metastases to the brain [6, 7]. However, because it only accounts for 5% of metastatic cancers [8], the total number of cases or individuals is often erroneous [1]. Although melanoma is a less common cancer, it has the highest propensity for metastasis to the brain [1, 9]. An estimated 49 to 73 percent of patients who die from melanoma will have developed brain metastases by the time of death and are found on autopsy [10, 11]. It is responsible for the deaths in an estimated 20 to 55 percent of affected patients, and contributes to death in up to 95 percent of all cases [11-13]. Thus, the impact and consequences of metastatic melanoma are quite detrimental in medicine.

Anyone with a diagnosis of melanoma is at risk for developing CNS metastases. Previous studies have tried to elucidate these factors that increase the risk of CNS metastases. Among the demographic aspects intrinsic to patient demographics, only male gender was found to show greater predominance in patients with brain metastases [14]. Of the characteristics of the primary lesion, melanomas appearing wide, thick, or ulcerated or with acral lentiginous or nodular histological findings were more frequently found in patients who developed brain metastases[14]. Also, primary lesions arising from the mucosal surfaces, skin of the head and neck, or skin of the trunk were more frequently found in this group [14, 15]. Patients with involvement of the lymph nodes or visceral organs, especially the lungs or multiple visceral organs, showed an increased likelihood of metastasizing to the brain [14, 16]. These factors are also associated with shortened overall survival time survival times [14, 16]. Interestingly, with the exception of primary lesions of the head and neck region, these factors did not affect survival after a diagnosis of a brain metastasis [14]. Other factors that were evaluated, such as the patient's race, pigmentation of the primary tumor, and pregnancy at the time of melanoma diagnosis, were not significantly correlated with the development of brain metastases[14]. The average age of presentation of patients with brain metastases is 48 to 53 years old, which is similar to that of patients with extracranial metastases[14, 17].

3. Pathophysiology

Metastases to the brain requires a complex series of steps, each mediated by a combination of intricate molecular mechanisms that are not completely understood. Each of these steps typically involves overcoming various physiological barriers including the blood-brain barrier [2]. Similar to other systemic cancers, as the primary melanoma matures, the process of angiogenesis increases the vascular supply to sustain the metabolic needs of the cancer cells and allows the tumor to grow. It progressively invades the surrounding host tissue and eventually spread hematogenously by invading local venules or lymph channels, which drain into the venous circulation [2]. Because venous circulation returns to the right side of the heart, the first capillary beds the circulating tumor cells encounter are typically found in

the lungs. These tumor cells are generally larger than the capillary vessels and may arrest in these pulmonary capillary beds. As a result, patients typically have lung metastases earlier in the time course of melanoma. They may often be identified at the time intracranial metastases are diagnosed. Between about 27 to 68 percent of affected patients may have concurrent lung metastases, which further shortens the survival time [14, 18, 19]. In order to reach arterial circulation and thus the cerebral vasculature, these melanoma cells must reach the left side of the heart either by: (1) metastasizing to the lung and invading the pulmonary venous circulation, (2) traversing the lung capillary bed to the pulmonary venous circulation, or (3) crossing through a patent foramen ovale thus bypassing the pulmonary circulation [2].

When tumor cells reach the left side of the heart and systemic circulation, the most important factors involved in promoting intracranial metastasis are the blood supply and greater preference for brain tissue [2]. The cerebral vasculature receives approximately 15 to 20 percent of the cardiac output in the resting state, which increases the likelihood that circulating tumor cells will reach the brai n[2]. It would be expected to receive a proportional amount as well, however the distribution of metastases based on blood flow, or the mechanical hypothesis, does not account for the high propensity of melanoma to metastasize to the brain compared to other cancers [20]. Instead, the seed and soil hypothesis likely contributes to the metastasis and plays an important role in explaining this phenomenon. This hypothesis postulates that certain genetic alterations in the tumor cells (the seed) influences them to show preference for the brain and find its microenvironment a more favorable place (the soil) to support their growth [20]. These alterations may include increased expression of adhesion molecules that show preferential adhesion to brain endothelial cells [21, 22] and increased production of degradative enzymes enabling tumor cells to penetrate the endothelium and the basement membrane [23]. Locally produced growth factors in the brain may also stimulate growth of the metastatic cells [24].

When tumor cells reach the cerebral vasculature, they may arrest in the capillary beds due to their greater size. In order to form metastases, they must extravasate across the microvasculature of the blood-brain barrier into the brain parenchyma [2]. The blood-brain barrier is a continuous, non-fenestrated endothelium composed of tight junctions and protects against the invasion of microorganisms and also the interaction of most drugs, including chemotherapeutic drugs [25]. However, it provides little protection against the invasion of metastatic cells into the brain parenchyma and may even be altered to a leakier barrier in primary tumors and metastases [26]. The cells adhere to and penetrate the basement membrane and astrocytic foot processes, eventually reaching the parenchyma.

In the end, only about 0.1 percent of the initial circulating tumor cells survive the protective mechanisms of the body to form distant metastases [7]. Additionally, metastasis typically occurs relatively late in the disease course for most patients with malignant melanoma. This may be explained by CNS involvement occurring as a result of a late metastatic event from another distant metastatic site, such as the lungs [7]. It may also be possible that metastasis is actually an early event in the disease course, but relatively slow metastatic growth results in delayed neurological effects and delayed detection [7].

4. Pathology

The histopathology of intracranial metastases mimics that of the primary melanoma. Melanoma can metastasize to virtually any portion of the intracranial cavity. The most

common site is the parenchyma, but involvement of any anatomic structure in the CNS can occur, including the dura, leptomeninges, choroid plexus, pituitary, and pineal glands. As with other systemic cancers that metastasize to the brain, the distribution reflects the size and volume of the region and its vasculature. Thus, a significant majority are supratentorial, the most common location being the cerebral hemispheres along the vascular distribution of the border zones (water-shed areas) between the anterior and middle cerebral arteries as well as the middle and posterior cerebral arteries [6, 14]. In total, the parietal lobe is involved in about 26 to 45%, frontal love in 21 to 36%, temporal lobe in 19%, occipital lobe in 11%, cerebellum in 7%, and cerebellum in <1%. The spinal cord is rarely involved [6, 14]. About 75 percent of metastases are found in the gray-white junction, where supplying cerebral vessels are slightly constricted, resulting in reduction of blood flow and thus increased risk of tumor cells arrest [6]. Melanoma is also known to have an increased likelihood of developing multiple metastases. Approximately 16 to 61% of patients will have more than one intracranial lesion at the time of diagnosis [14, 17, 18]. Individual lesions are usually relatively small with the largest typically measuring between 1 to 4 cm in diameter, while few are rarely greater than 4 cm. Larger intracranial lesions are noticeably less common and will most often be solitary [6, 14, 18]. Similar to other systemic cancers, the metastases from melanoma tend to expand as roughly spherical masses and establish well-defined interfaces with the surrounding brain parenchyma. Thus, expansion pushes the normal surrounding tissue aside rather than invading it. This contrasts from most primary brain tumors which often show diffusely infiltrated margins [27].

Metastases from melanoma have the highest risk of hemorrhage as compared to other systemic metastases to the brain. Hemorrhage is found on neuroimaging in 27 to 40% of patients with intracranial lesions, while histopathological evaluation has indicated that 62 to 71% of patients have evidence of a prior hemorrhage [6, 18]. The bleeding may be confined to the intracranial lesion itself, extend into the area surrounding it, or expand into an intracerebral hematoma. When multiple metastases are present, simultaneous hemorrhage usually occurs rather than isolated hemorrhage of individual lesions [28]. This most often results in subacute progression which is characteristic of non-hemorrhagic brain metastases. Occasionally, it can cause significant complications such as hematomas and hydrocephalus from obstruction of cerebrospinal fluid flow [18]. Vasogenic edema surrounding brain metastases is also common and can cause similar effects as hemorrhage.

5. Clinical findings

The clinical presentation of melanoma metastases to the brain does not significantly differ from that of other intracranial metastases or primary brain tumors. The presenting signs and symptoms are dependent on the number and location of the lesions as well as the rate of growth. Regardless of etiology, most CNS lesions produce clinical effects either through compression of surrounding neurological tissue or destruction of neurons. For intracranial metastases, the primary mechanism of action is compression from the local mass effect of tumor expansion or secondary effects from raised intracranial pressure or impediment of cerebrospinal fluid circulation. Most patients present with nonfocal complaints secondary to increased intracranial pressure[19]. Common symptoms of increased intracranial pressure include headaches, mental change, somnolence, and nausea and vomiting. Focal or generalized seizures resulting from irritation of neurons are also common in patients with brain metastases[6]. Patients with a single metastasis often present with additional focal

signs and symptoms. This can include such neurological deficits as cranial nerve palsies, visual deficits, hemiparesis, and hemisensory loss[6]. Generally, these nonfocal or focal complaints can present in up 75 percent of patients with brain metastases, whereas the incidence of seizures in patients may be as high 50 percent [6, 14, 29]. Although patients with metastases of melanoma to the brain can present with a range of signs and symptoms, there are still a number of patients who may have few or no obvious indications of an underlying pathology[14, 29]. This may be due insufficient mass effect, however their growth rate compared to primary brain tumors is notably faster. Clinical effects may then be subacute in onset, presenting over weeks rather than months. An acute onset may also occur in such instances as hemorrhagic transformation, dubbed a "tumor TIA". Thus, it is important for physicians to have a high index of suspicion when dealing with patients at risk of developing brain metastases. It is a strong possibility and should be high on the list of differential diagnosis in any patient with a history of melanoma that presents with new neurological signs or symptoms [6].

6. Diagnosis

When there is a high clinical suspicion for metastatic melanoma to the brain based on the history and neurological exam of a patient, neuroimaging is the most important diagnostic modality. Currently, computed tomography (CT) and magnetic resonance imaging (MRI) provide the most beneficial imaging of the CNS. Between these two modalities, MRI with and without gadolinium contrast enhancement is the preferred choice for all systemic metastases. MRI is known to increase the conspicuity of lesions and have increased sensitivity in detecting the presence of additional and smaller metastases to the brain [30, 31]. However, because CT is more readily available in emergent situations, it is often used to image large lesions, hemorrhage, and significant edema, but will be insufficient to definitively rule out intracranial disease [6]. If a single metastasis is found on CT or the scan appears within normal limits, MRI with administration of contrast is warranted because of its improved abilities for detection of lesions [30, 31]. Other radiographic imaging modalities, such as positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose, generally are not useful in the diagnosis or imaging metastatic melanoma of the brain[32].

In the majority of patients, MRI is often the only necessary diagnostic test. However, neuroimaging cannot unequivocally differentiate metastases from other intracranial pathologies. The presence of a lesion on a CT or MRI scan in patient with melanoma or other progressive systemic cancer is not always diagnostic for metastatic spread. The differential diagnosis often includes primary intracranial tumors, cerebral abscess, demyelinating disease, and cerebral infarction or hemorrhage. Each of these etiologies will likely need to be carefully ruled out, however certain characteristics provide for strong evidence of metastases. Brain metastases from melanoma frequently appear bright on T1-weighted images and dark on T2-weighted images. This appearance may be attributed to the production of melanin in the tumor [33, 34]. If hemorrhage occurs, the presence of blood breakdown products can alter the T1-weighted or T2 weighted signal[34, 35]. On CT, brain metastases from melanoma are typically slightly hyperdense compared to the surrounding nervous tissue and exhibit moderate contrast enhancement [6]. Increasing the volume of contrast material injected as well as delaying imaging after the injection of intravenous contrast material may improve detection and conspicuity of lesions on CT examination [36]. When the metastases are small, uniform contrast enhancement is typical, but when larger,

peripheral ring enhancement may occur. This ring is usually thicker in comparison to an abscess and more regular than a primary tumor. As noted previously, metastases are usually found at the gray-white junction in the watershed areas of the brain and are typically spherical in shape with more regular margins and a substantial amount of vasogenic edema surrounding a small tumor nidus [6, 14, 27].

After neuroimaging, confirmatory diagnosis can be accomplished through surgical biopsy or, preferably, excision of the entire mass. This allows for definitive differentiation of metastases originating from melanoma versus metastases from possible systemic cancers and other suspected etiologies. If more than one lesion exists, the largest or most symptomatic one should be addressed first for biopsy or resection. Once a brain metastasis has been discovered either through imaging or biopsy, screening for the primary systemic cancer is necessary if one has not already been diagnosed. In contrast, for those patients who have been diagnosed with malignant melanoma but their neurological exam is within normal limits, routine screening of the CNS with neuroimaging rarely identifies metastases and is thus generally not recommended [37].

7. Survival

The prognosis of patients with disseminated melanoma is particularly poor if the CNS is involved. Currently, no reliably curative treatments are available for patients and most therapeutic trials for melanoma exclude patients with brain metastases [38]. For those with documented brain metastases, the overall median survival time is between 3.8 and 5.2 months, a notably shorter survival time in comparison to patients with other sites of distant metastases. The survival percentages are inversely proportional to the length of time after diagnosis [39-43]. Additionally, the median time between the diagnosis of primary melanoma and the diagnosis of metastatic melanoma to brain is about 3.1 to 3.7 years [13, 14, 41]. Among a number of clinical and pathologic factors that have been analyzed, the disease free-interval (DFI) is one of a few that independently predicts survival after diagnosis of AJCC stage IV melanoma. Significant survival benefit occurs when the DFI is greater than 12 months. The anatomical site of the primary melanoma has also been shown to have predictive value. There is an almost fourfold difference between sites associated with highest survival and lowest survival rate. Melanomas with primary metastasis from the skin and lymph nodes have a median survival of about 15 months, whereas those from the brain and liver have a median survival of about 4 months. The third factor that independently predicts survival is the preceding stage of disease before the patient is diagnosed with stage IV melanoma. Patients experience significant survival benefit if they develop stage IV melanoma without progressing through stage III and have a DFI greater than or equal to 72 months, or if they progress through stage III to stage IV and have a DFI greater than or equal to 18 months. Other factors such as gender, age, Breslow depth, Clark level, year of diagnosis, and number of metastatic sites have not shown predictive value[39].

8. Supportive therapy

Several approaches can be taken to provide patients with supportive measures until more definitive treatment can be considered and administered. This primarily involves the medical management of cerebral edema and the resulting increased intracranial pressure, the control of seizures, and the prevention of other associated complications and conditions.

These are generally the most common medical problems in patients with metastasis of melanoma to the brain as well as most other brain tumor. The overall survival in patients with brain metastases treated with only supportive care is approximately 1 to 2 months[14].

8.1 Steroids

The vasogenic edema that is characteristic of metastases is a significant factor in the morbidity of patients. It occurs as a result of BBB break down, allowing sodium and water to leak into and accumulate in the extracellular space of the brain parenchyma[44, 45]. Corticosteroids have been shown to adequately manage this vasogenic edema and can dramatically improve a patient's condition[46, 47]. The beneficial effects are often noticeable within 6 to 24 hours after the first dose and reach maximum effect within 3 to 7 days[48]. Its mechanism of action is quite complex and not completely understood. The antiedema effect may be contributed to stabilization and reduction of the permeability of tumor capillaries through endothelial cell interactions[44, 45]. Corticosteroids are usually indicated in any patient who is symptomatic from the metastatic edema and during the course of definitive treatment with radiation or surgery, but it is typically not necessary in asymptomatic patients with small metastases unless treatment with radiation or surgery is expected[49, 50]. Dexamethasone is administered most commonly because it has minimal mineralocorticoid activity and may have a lower risk of complications compared to other corticosteroids[47]. Long-term use of corticosteroids can result in such significant adverse effects as myopathy, osteoporosis and avascular bone necrosis, diabetes mellitus, cognitive dysfunction, gastrointestinal (GI) hemorrhage, bowel perforation, and opportunistic infections, such as Pneumocystis jirovecci pneumonitis and oropharyngeal candidiasis[51].
In instances of significant mass effect or acute decompensation of brain metastases, the onset of effects of corticosteroids is not quick enough and thus the approach to medical management changes[45]. Acute decompensation can be due to a number of causes such as intratumoral hemorrhage, obstructive hydrocephalus, seizures, or hyponatremia. The resulting acutely increased intracranial pressure should be addressed immediately in order to minimize the risk of herniation or worse[47]. This involves stabilization of the BBB, minimization of the vasogenic edema, and emergent intervention with surgical debulking or irradiation. Elevation of the head of the bed, hyperventilation, mannitol, diuretics and are all rapid onset measures that can provide support until steroids take effect and should precede any neuroimaging[49, 52].

8.2 Antiepileptics

Seizures are a common occurrence in patients with brain metastases. The likelihood of seizures is highest in patients with melanoma compared to other cancers including lung and breast carcinoma[51]. Those who present with seizures should generally be treated with antiepileptic drugs (AED)[49]. The use of prophylaxis is often based on individual preference of the treating physician rather than supporting clinical evidence[45]. No significant benefit has been shown with anticonvulsant prophylaxis using phenobarbital, phenytoin, or valproic acid in patients who had no history of seizures[45]. In addition to the lack of efficacy, the risk of potential side effects has been shown to be increased in patients with brain tumors[53]. Overall, almost 25 percent of patients diagnosed with either a primary or metastatic brain tumor and are taking AEDs experience side effects severe enough to warrant a change in or discontinuation of therapy [53]. Thus, it is recommended

that prophylactic anticonvulsants should not be routinely used in patients with newly diagnosed brain tumors[53]. However, because there is a high risk of recurrence, long-term treatment with AEDs is indicated after a patient with melanoma metastases to the brain has suffered their first seizure[51]. Phenytoin has historically been the mainstay of anticonvulsant therapy because it is generally effective and well tolerated. Selection of the particular AEDs to administer requires careful consideration of the treatment the patient is receiving. This is because important interactions can occur with other drugs commonly used in treatment for brain metastases, such as antineoplastic agents and dexamethasone, often from activation of hepatic metabolism through the cytochrome P450 enzyme system[49]. Newer AEDs, including levetiracetam and topiramate, typically do not affect cytochrome P450 and have shown greater reduced seizure frequency and fewer side effects[54].

Anticonvulsant prophylaxis after supratentorial surgery is generally recommended for patients, including those undergoing resection of brain metastases. AEDs have been shown to be beneficial in preventing early seizures postoperatively[45]. However, there is not strong evidence to support the use of long-term treatment to reduce the incidence of late seizures after supratentorial surgery. Thus, in those patients with brain metastases from melanoma who have not had a seizure, the recommended plan for antiepileptic therapy is to gradually taper and discontinue AEDs after the first postoperative week. This is especially appropriate for patients who are medically stable and are experiencing notable side effects from their anticonvulsant medication[53].

8.3 Anticoagulants

Patients with any systemic cancer are known to be in a hypercoagulable state, increasing their risk for deep venous thrombosis (DVTs) and venous thromboembolisms (VTEs). This is especially true for brain metastases for which thromboembolic disease contributes significantly to morbidity and mortality[55]. The risk is often greatest in hemiplegic patients and in the postoperative period since patients are often immobile. In order to prevent DVTs and VTEs from occurring after craniotomy, adequate prophylaxis is often necessary. However, this can be difficult due to the possibility of intratumoral hemorrhage and intracranial bleeding with anticoagulation therapy. Current methods of prophylaxis include mechanical and/or pharmacological interventions, however no optimal one has been identified and current recommendations remain controversial[56]. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are the main pharmacological anticoagulants which inhibit formation of thrombi. Mechanical methods attempt to minimize venous stasis and enhance fibrinolysis. This includes early ambulation, compression stocking, intermittent external pneumatic compression devices, and electrical calf muscle stimulation. In general, both approaches are effective in preventing DVTs and VTEs[57], but heparin may be more effective although at a greater risk of intracranial hemorrhage[45]. Mechanical prophylaxis with concomitant anticoagulation therapy during the postoperative period is not only safe but also protects patients more so than either approach does alone[57].

In patients that have developed a DVT, treatment is necessary to prevent a pulmonary embolism (PE), restore lower limb circulation, and resolve other associated problems. Pharmacological treatment with UFH and LMWH are the mainstays of therapy, with LMWH showing better outcomes including fewer bleeding complications. Patients who have strict contraindications against anticoagulation can be treated with placement of an

inferior vena cava (IVC) filter[49]. However, these should generally not be the first line of treatment because it has a higher complication rate and are less effective in prevent PE in comparison to anticoagulation. One retrospective study of IVC filter complications occurring in patients with brain tumors and DVT found that there was a complication rate of 62 percent and PE still occurred in 12 percent of cases despite proper placement of the IVC filter[58]. Thus, IVC filters should be reserved for patients that have had recent craniotomy, are at increased risk for intracranial hemorrhage, are poorly compliant with medications, or will have prolonged thrombocytopenia from chemotherapy.

9. Definitive treatment

After receiving supportive measures, patients diagnosed with melanoma that has metastasized to the central nervous system must be evaluated for the possibility and type of definitive treatment. Current options available to physicians include whole brain radiation therapy (WBRT), stereotactic surgery, conventional surgical resection, or chemotherapy. These can frequently be used alone or in combination with one other. However, for the majority of patients, these are largely palliative measures. Determining the optimal modality is dependent on a number of factors including the size, number, location, and sensitivity of the lesion, the overall status of the malignant melanoma, the neurological status as measured by the Karnofsky Performance Scale (KPS), general condition of the patient, and the preferences of the patient and his or her family. It can thus be difficult to decide on a course of treatment given the number of issues that need to be considered.

9.1 Whole brain radiation therapy

The first use of external beam WBRT for treatment of brain metastases was reported in 1954 by Chao et al[59] and again later in 1961 by Chu et al[60]. It has since become an important treatment modality for brain metastases. One of the fundamental benefits of WBRT is that it is a noninvasive means in which to treat the entire brain and provide palliation of symptoms. Thus, it allows for relatively simple targeting of any and all lesions in the brain with radiation including microscopic ones, micrometastases, which are not detected on neuroimaging. This has been demonstrated in studies which showed that prophylactic and postoperative irradiation of the brain decreases subsequent development of intracranial metastases. This effect is most likely due to elimination of micrometastases that were present at the time[61, 62]. External WBRT is thus advantageous and typically considered the mainstay of treatment for most patients with multiple metastatic deposits from melanoma in the brain[38, 63, 64]. More localized treatment modalities would be less beneficial in such situations because it would require targeting of each lesion individually. However, solitary metastases that are too large for either surgical resection or stereotactic surgery or those that impinge on sensitive areas of the brain are often treated with WBRT[63, 65].

The broad application of radiation to the brain can also be an important disadvantage. This is because it not only affects the malignant tissue, but the normal tissue is also exposed to the harmful effects of ionizing radiation. Side effects are typically dependent on the total dosage, dosing interval, and fraction size. Acute side effects of external WBRT include memory loss, fatigue, headaches, temporary hair loss, scalp rash or desquamation, hyperpigmentation, otitis media, and cerebral edema[63, 66]. Somnolence syndrome is a set of symptoms, often seen in children, involving lethargy, anorexia, and irritability that

present 1 to 4 months after treatment. There are generally no focal neurological deficits with this syndrome[66-68]. If the patient survives long-term, late side effects may occur which include cerebral edema, atrophy, focal radiation necrosis, white matter demyelination, leukoencephalopathy, endocrinopathy, and progressive cognitive dysfunction[69-71]. A recent randomized controlled trial found that patients suffered significantly greater decline in learning and memory functions after receiving WBRT compared to patients only receiving stereotactic radiosurgery[72]. These consequences should be considered if the patient has the potential to survive for a prolonged amount of time following radiation treatment. Another issue that is important when considering external WBRT for treatment of metastatic melanoma to the brain is the significant resistance melanoma has to this mode of radiation therapy. Of all the primary tumor types, malignant melanoma is considered to be one of the most radioresistant to WBRT[73]. Larger fractions may be necessary in order to achieve desired effect, increasing the likelihood for negative side effects[74]. However, because there are few other effective modalities for treatment of multiple metastases in the brain, it is still commonly used in these patients.

The Radiation Therapy Oncology Group (RTOG) conducted several extensive phase III randomized trials to evaluate the efficacy of various treatment schedules. The results of which indicated that 30 Gy administered in 10 fractions of 3 Gy over a period of 2 weeks results in palliative results and survival time equivalent to more protracted and higher-dose schedules[75, 76]. This has since become the most commonly used external WBRT schedule in the United States for brain metastases in general. Although this is often inadequate for long-term tumor control except in the most radiosensitive histologies, it allows for minimization of toxicity and negative side effects of irradiation. The median survival after administration of WBRT to patients with brain metastases is typically improved to about 3 to 6 months but is dependent on the number of lesions, the radiosensitivity of the metastases, and the status of the underlying cancer. Despite its known general resistance to radiation therapy, studies have shown local tumor response of melanoma metastases to the brain after administration of WBRT[77, 78]. Many fractionation schemes have been devised with larger doses per fraction in an attempt to enhance this tumor response. However, a review of several retrospective series has revealed that no scheme is better than the current standard of 30 Gy in 10 fractions[38]. Improved clinical outcomes may occur after WBRT, showing mildly increased median survival times to about 2.0 to 6.1 months[79-82]. When patients are stratified according to the RTOG recursive partitioning analysis (RPA), the effect of WBRT can be better extrapolated. The RPA separates patients into three prognostic groups according to their KPS, extracranial disease, and patient age. Those in RPA class 1 frequently have the best prognosis due to younger age (<65 years) and higher KPS scores (>70) whereas RPA class 3 often have the worst prognosis due to lower KPS scores (<70). The survival times after WBRT expectedly correlate with RPA class. Those with brain metastases originating from melanoma had median survival times of about 7.1 to 10.5 for patients in class 1, 4.2 to 5.9 for patients in class 2, and 1.8 to 2.3 for patients in class 3[82, 83]. Despite only having minimal effects on the survival time, using external WBRT and supportive management in patients with metastatic melanoma of the brain has demonstrated palliation of symptoms[79]. Symptomatic improvement is an important effect that can enhance the quality of life given the bleak prognosis despite all treatment modalities. Patients often have improvement of headaches, weakness, and mental status. There are some who question its ability to reverse neurological symptoms and suggest omitting WRBT melanoma metastases are fewer than four[72]. However, WBRT still

currently remains the mainstay of treatment for patients with multiple brain metastases but is not typically first-line in solitary metastases [65]. It is a viable adjuvant therapy in addition to serving as an option for primary therapy. In cases of single brain metastases, surgical resection or stereotactic radiosurgery are usually the preferable option for primary therapy unless both are contraindicated. Patients that additionally have advanced systemic disease or conditions that preclude surgery or radiosurgery in addition to a solitary lesion would likely be better suited for WBRT.

9.2 Surgical resection

Surgical resection was first reported for use in the treatment of brain metastases in 1926 by Grant[84]. As noted earlier, metastatic brain tumors characteristically form well-circumscribed and rounded masses at the junction of the gray and white matter. This renders them highly amenable to surgical resection. Additionally, with modern neurosurgical techniques and the available new technologies such as functional mapping, intraoperative ultrasonography, and computer assisted stereotaxy, surgical resection can be accomplished with increased precision and control. It has become a mainstay of treatment despite the development of newer methods including WBRT or stereotactic radiosurgery. This is because it offers several advantages over both. Surgery **(Figure 1)** provides immediate palliative action and relief of symptoms with removal of the lesion, which decreases the intracranial pressure, alleviates compression and mass effect on the surrounding parenchyma, prevents or stops hemorrhage and edema into the intracranial space, and restores CSF flow if obstruction has occurred. No other treatment modality can provide this immediate effect which is critical in emergent situations such as impending herniation or posterior fossa tumors. Removal of the tumor with surgical resection additionally provides diagnostic advantages. It is the only modality that allows for physical extraction of the mass in order to determine a histological and pathological diagnosis. This is important in patients in which the etiology of the lesion is uncertain or the primary cancer has not been identified. Studies have demonstrated that up to approximately 11 percent of suspected cranial metastases are actually found to be nonmetastatic lesions, such as cerebral abscesses or primary tumors, on pathological evaluation[85]. Surgical resection also avoids some of the prominent drawbacks of WBRT, most notably the resistance of melanoma metastases to radiation therapy and the negative effects of diffuse radiation on normal neurological tissue. Instead, it circumvents the use of radiation and surgically localizes the area of the metastases, minimizing damage to the rest of the unaffected brain parenchyma and avoiding the acute and long-term side effects depicted in WBRT. Surgical resection is thus most advantageous for solitary or a limited number of metastases to brain where diffuse involvement does not occur. However, there is still significant morbidity and mortality associated with surgical resection given its invasive nature. These risks continue to gradually improve with the advancement of available procedures and tools, as was seen with the utilization of CT and MRI neuroimaging. Several recent studies have shown the risk of mortality to be between 0 to 14.2 percent during the postoperative period [14, 18, 86, 87] which is compared to earlier reports of mortality in up to 22 percent of patients[87].

Given the limited survival time of patients harboring metastatic melanoma of the brain, postoperative neurological deficits and prolonged recovery times are best avoided if possible. Patient selection is important in minimizing poor outcomes and maximizing the response to treatment. In general, surgical resection is most appropriate for patients with a

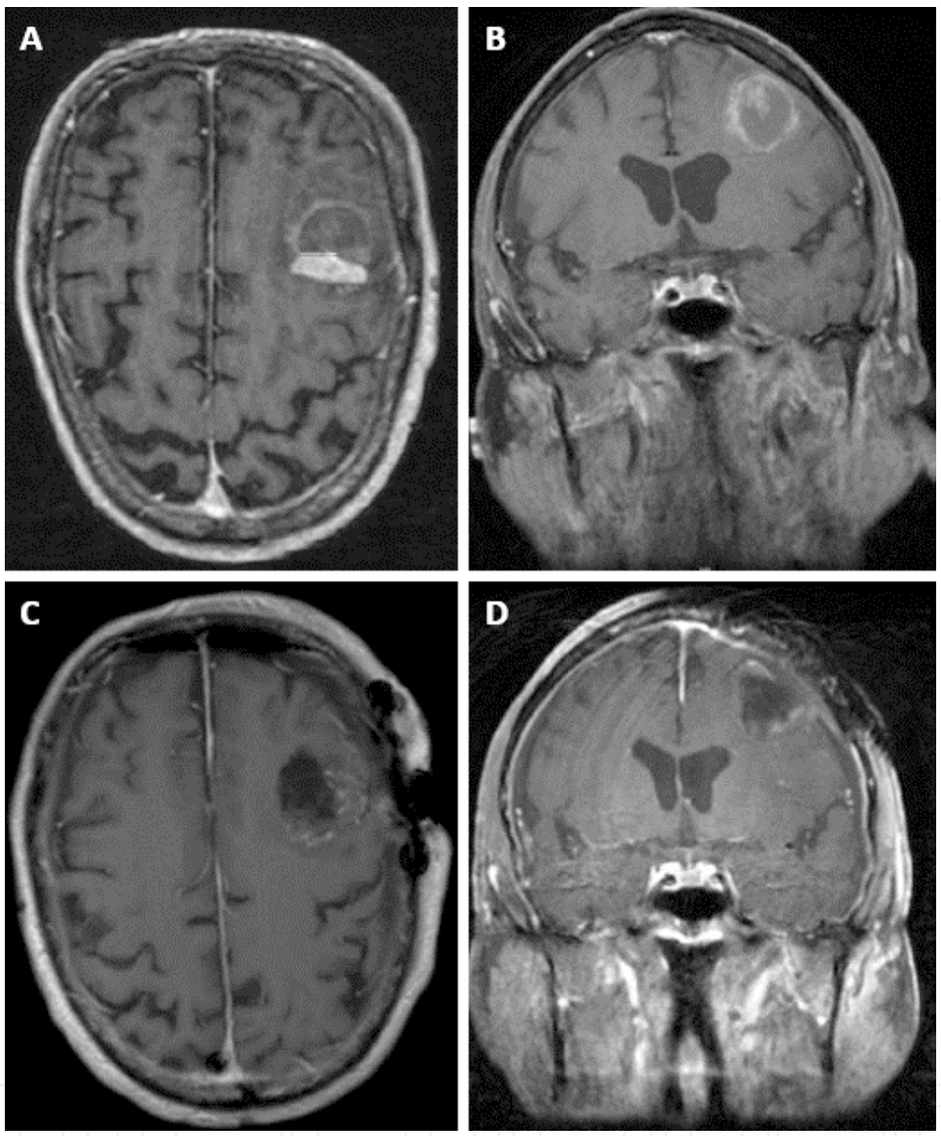

Fig. 1. Representative patient with intracranial metastatic melanoma who underwent surgical resection. **A,** pre-operative contrast-enhanced axial and **B,** coronal T1 magnetic resonance image (MRI) demonstrating left frontal metastasis with intratumoral hemorrhage. **C,** post-operative contrast-enhanced axial and **D,** coronal T1 MRI demonstrating gross total resection of the metastasis.

single brain metastasis, limited systemic disease, and favorable KPS score (>70). Metastases greater than 3 cm in diameter should be preferentially treated with surgery because large tumors typically have minimal response to the other modalities[88]. Selection of patients with multiple metastases to the brain remains somewhat controversial. Several retrospective studies have examined the efficacy of surgical resection alone in the treatment of brain

metastases from melanoma. It is clear that surgical resection of a single melanoma metastases greater extends the survival time in comparison WBRT alone or supportive therapy alone. In these studies, the median survival time after surgery varies between 5 and 22 months with the more recent ones showing a median survival time between 8 and 16 months[87-89]. In contrast to solitary metastasis, the role of surgical intervention in cases of multiple brain metastases remains controversial due to lack of randomized control trials[63]. Previously, this was typically a contraindication, but one retrospective study challenged this notion. Bindel et al[90] compared patients with single and multiple brain metastases that were treated with surgical resection. Patients that underwent partial resection of multiple metastases, complete resection of multiple metastases, and resection of a single metastasis all had similar rates of surgical morbidity and mortality of approximately 8 to 9 percent and 0 to 4 percent, respectively. However, those patients that underwent only a partial resection demonstrated a median survival time of about 6 months, whereas those that were treated with complete resection were found to have a longer median survival time of about 14 months. This provided evidence that total surgical resection of multiple metastases was comparable to resection of a solitary metastasis in efficacy. Several ensuing studies showed similar support for the use of surgical resection in the presence of multiple metastases[91, 92]. Thus, surgical resection of multiple metastases can be supported, although the general recommendation limits the number to less than 3 lesions in patients that have limited or controlled systemic disease.

A regimen that has been frequently discussed in the treatment of brain metastases is the combination of surgery plus external WBRT. Several studies have been conducted to compare the value of surgical resection followed by WBRT to that of either modality alone. Patchell et al[85] and Vecht et al[93] both demonstrated that those patients who were treated with the combination regimen had longer median survival times that those patients who received only WBRT. In contrast, Mintz et al[94] found that there was no survival advantage or improved quality of life with the administration of WBRT after surgery. This finding may be due to the overall lower patient performance status and greater prevalence of patients with more severe extracranial disease in their study. Patchell et al[85] actually demonstrated that patients with active systemic disease had a poorer prognosis when treated with surgical resection and WBRT. Studies comparing surgery alone with the adjunctive WBRT have also shown mixed results. Dosoretz et al[95] found that WBRT at a total dose of 30 Gy showed no survival advantages after surgical resection of a solitary metastasis. DeAngelis et al[70] and Hagen et al[96] also reported no effect on survival time, but noted WBRT postoperatively may reduce the risk of recurrence and thus recommend its use in patients after surgical resection for a single metastasis. Patchell et al has also further investigated the advantages of this combination regimen. In this prospective trial, patients were randomized to treatment with external WBRT or observation after surgery for a solitary brain metastasis. The results showed that patients who received the WBRT postoperatively had improved tumor control as seen by lower recurrence of metastases anywhere in the brain as well as at the site of resection. As with DeAngelis et al[70] and Hagen et al[96], this trial did not demonstrate prolonged survival time in patients receiving the adjunctive WBRT and did not slow the functional decline of patients, as measured by their KPS scores. Other studies have specifically addressed its use in melanoma metastases and have shown similar nonsignificant affect on prolonging survival times.

9.3 Stereotactic radiosurgery

Stereotactic surgery (SRS), also known as Gamma Knife, was first introduced in 1951 by Leksell[97]. Since then, it has developed into a sophisticated system that has the ability to accurately target an intracranial lesion and administer focal, collimated beams of ionizing radiation produced from a linear accelerator (linacs) or cobalt-60 sources. The radiation dose is administered in a single fraction via numerous crossfiring of beams of radiation that converge onto the targeted sight. The crossfiring of these beams from numerous directions allows for rapid radiation falloff in the surrounding tissue and thus minimize extraneous exposure. The advantage of SRS lies in its ability to administer localized treatment while sparing the rest of the normal brain parenchyma from the diffuse irradiation that occurs in WBRT. Moreover, the mechanism of action of SRS is thought to be different than WBRT and may instead affect the tumor vasculature, which would increase its effectiveness against the typically radioresistant cancers including malignant melanoma[98]. The advantage of SRS **(Figure 2)** over surgical resection is attributed to its ability to reach small, deep metastases in the brain without significant disruption to the rest of the brain parenchyma. Thus, it avoids the prolonged recovery time, increased length of hospital stay, and high costs that occur with an invasive surgery and instead only requires the administration of a single-fraction of radiation. Although it generally avoids these immediate side effects of surgical resection, delayed complications from SRS can occur which typically resemble other radiation-induced side effects such as radiation necrosis. This occurs in less than 10 percent of patients and is dependent on the volume treated and dose administered.

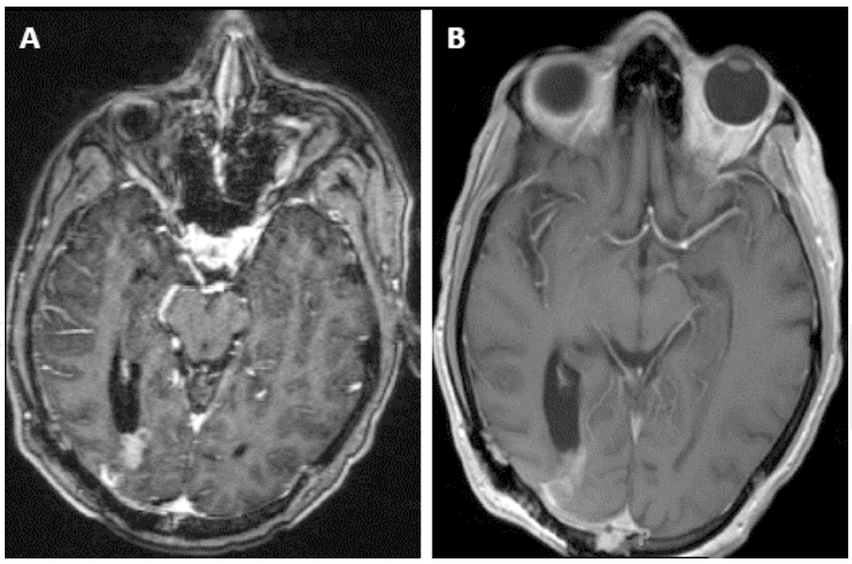

Fig. 2. Representative patient with intracranial metastatic melanoma who underwent stereotactic radiosurgery. **A,** pre-radiation contrast-enhanced axial T1 magnetic resonance image (MRI) demonstrating right occipital lobe metastatic melanoma. **B,** post-radiation contrast-enhanced axial T1 MRI.

There are a few disadvantages of SRS in comparison to the other treatment modalities. In comparison to surgery, its minimally invasive approach cannot provide immediate

treatment effects which are often important in critical or life-threatening situations such as impending herniation. The inability to remove metastases also prevents a definitive histological diagnosis, and given the chance a suspected cranial metastases may actually be a nonmetastatic lesions, pathological diagnosis can be of great importance[85]. Also, increased risks in treating large metastases have hindered its use for those tumors that are larger than 3 cm in diameter. This is due to the limited conformity that can be achieved for large tumors, resulting in decreased response with increasing tumor size and increased radiation doses to the surrounding brain parenchyma[99]. Mehta et al[100] noted that tumors less than 2 cm^3 in volume showed a total response rate of 78 percent whereas as tumors greater than 10 cm^3 in volume demonstrated a total response rate less than 50 percent. Thus, SRS is typically recommended for patients with lesions less than 3 cm on neuroimaging, patients with lesions that are surgically inaccessible, patients that are asymptomatic, or patients that cannot tolerate surgery.

Multiple studies examining the efficacy of SRS have shown generally positive results. For all types of metastatic histologies, the local control rate after treatment with SRS ranges between 85 and 90 percent at one year[101-103]. For metastatic melanoma to the brain, the local control rate was shown to be approximately 90 to 97 percent[103-105]. Clinically, stabilization or improvement of neurological symptoms after treatment was noted in about 78 to 100 percent of patients[104, 106]. Patients also demonstrated a median survival time comparable to that of surgical resection which was found to be about 5 to 14 months[106-110]. However, as with the other treatment modalities, patient factors and selection affects outcome. Those with minimal extracranial disease typically fared better than their counterparts more extrcranial disease. This is also true for patients with overall better performance status, as measured by the KPS, compared to those with lower performance status. Patients with solitary brain lesions additionally demonstrated longer survival times than those patients with multiple brain lesions. However, an increased number of metastases should not be a reason to withhold SRS treatment[106-110].

Combination therapy has been studied and utilized in the treatment of metastatic melanoma to the brain. A landmark RTOG-sponsored study[111] compared the treatment of brain metastases using WBRT alone and SRS plus WBRT. Patients were first stratified according to the number of brain metastases and the extent of their extracranial disease and then randomized to treatment with WBRT only and SRS plus WBRT. There was a significant survival advantage for those harboring a solitary lesion treated with the combination therapy. There was no survival advantage for patients with multiple metastases treated with the combination approach. However, patients treated with WBRT and SRS were more likely to have improved or stable performance status and also decreased need for steroid use after therapy. There was no difference in mental status change and no increase in toxicity with the SRS and WBRT administration. The authors thus concluded that the combination approach of SRS plus WBRT should be the standard treatment for patients with a single unresectable brain metastasis. For patients with two to three bran metastases, despite the survival advantage the combination treatment should be considered because it results in improvement in the overall performance status.

To date, there are no prospective, randomized control trials comparing SRS with surgical resection. However, a few retrospective studies have provided insight into a comparison between the two treatment modalities. Auchter et al[112] designed a multi-institutional

retrospective analysis comparing the outcome of patients treated with surgery and SRS and found no difference in the overall survival, functional independence, or recurrence rate. O'Neill et al[113] conducted a similar comparison and found no difference in median survival time after treatment with either approach. However, there was a significant difference in local tumor control, with no recurrence occurring after administration of SRS and about 58 percent recurrence after surgical resection. Bindel et al[114] conducted a smaller study in which patients undergoing SRS or surgical resection were matched on the basis of age, sex, primary tumor histology, extent of systemic disease, pretreatment KPS score, time to diagnosis of brain metastases, and number of brain metastases. The results demonstrated an overall survival advantage for surgical resection with a median survival time of 16.4 months compared to 7.5 months in the SRS treated group. Surgical resection also showed superiority to SRS in terms of local recurrence and morbidity. Thus, they favored the use of surgery over SRS for the treatment of solitary brain metastases. Cho et al[115] conducted a more encompassing study analyzing the treatment of solitary brain metastases with WBRT only, surgery plus WBRT, or SRS plus WBRT. The results demonstrated that the actuarial survival time was the same for the combination surgery group and the SRS surgery group, and both had longer survival times than patients receiving WBRT alone. Cho et al thus concluded that SRS is a reasonable and potentially more attractive alternative than surgical resection for single brain metastases. There are still several ongoing trials that include SRS in the treatment plan for brain metastases.

9.4 Chemotherapy

The use of chemotherapy for the treatment of extracranial melanoma has generally shown a poor response. Thus, it is not surprising that the response of melanoma metastases to the brain is also poor. The effect of cisplatin and etoposide has been shown to have a 0 percent response rate while other common metastatic cancers such as NSCLC and breast carcinoma have shown up to a 39 percent response. A significant obstacle for chemotherapeutic action on intracranial metastases is the BBB which limits the passage of large molecules into the brain parenchyma. Even after penetrating the BBB, some agents are rapidly eliminated and only have a transient effect. Attempts have been made to identify agents that can adequately cross the BBB to have tumorcidal effects. Fotemustine, a nitrosurea with high penetrations, has been shown to have response rates ranging from 12 to 25 percent in phase II European trials but is not available in the United States[116, 117]. Temozolamide, a dacarbazine analogue with high penetration, was approved for use by the FDA for use in primary brain tumors and was found to have a modest response rate of 7 percent for metastatic melanoma[118]. Combination chemotherapy has also been explored for increased effectiveness. A combination regimen of temozolomide and thalidomide, an antiangiogenic agent, has been explored because of its action against the vascularization of the tumor. Although the response was slightly better, this was at the expense of increased toxicity. A combination of chemotherapy and external WBRT is also being actively explored. Mornex et al[119] compared fotemustine alone versus fotemustine and WBRT and found that the response rates and survival times were not significantly different. Similarly, a phase III trial comparing WBRT alone and temozolomide plus WBRT demonstrated improved response rate but no prolonged survival time[120]. In general, current evidence does not support routinely administering chemotherapeutic agents for the treatment of cerebral metastases from melanoma.

9.5 Immunotherapy

Melanoma is a highly immunogenic tumor and treatment with immunotherapy has been attempted to halt the metastatic process. Predominantly from case studies, the overall response has not been optimal. Traditionally, the diagnosis of brain metastases has been an exclusionary criterion for receiving immunotherapy in patients with melanoma. However, biological response modifiers (BRMs) and cellular immunotherapy have been able to induce infrequent responses from brain metastases. One case report noted the near complete response in a patient with brain metastases after a treatment regimen of interleukin-2 (IL-2), interferon (IFN), and 5-fluorouracil[121]. Anecdotal cases of partial or complete responses have also been reported after ipilimumab therapy for metastatic melanoma to the brain which was treated earlier by surgery or SRS[122]. Another case report identified a patient with brain metastasis refractory to IL-2 and chemotherapy was responsive to lymphodepletion followed by infusion with autologous MART-reactive tumor infiltrating lymphocytes (TILs) and high doses of IL-2[123]. Hong et al[124] investigated the response rate and response duration of melanoma brain metastases to adoptive cell therapy (ACT) with autologous antitumor lymphocytes plus IL-2 following a lymphodepleting preparative regimen. They found that greater than 50 percent of patients had complete or partial response to the treatment regimen with rare occurrence of negative side effects. Majer et al[125] conducted a study of 70 patients with or without brain metastases treated with temozolomide or DTIC plus the BRMs IL-2 and IFN-α 2B. They demonstrated that patients with brain metastases who were treated previously with SRS had a prolonged median survival time of 15.8 months versus 11.1 months in patients without brain involvement. Overall, there have been limited studies and trials into the use of immunotherapy and additional investigation into its efficacy is needed.

10. Conclusions

Metastasis to the brain is a devastating and common consequence for patients with malignant melanoma. A significant number of patients with melanoma eventually develop brain metastasis at the time of death. Current treatment options typically include surgery and radiation therapy for brain metastases but the number of options is increasing. Prolonged survival depends on prompt diagnosis and treatment for patients harboring these lesions.

11. References

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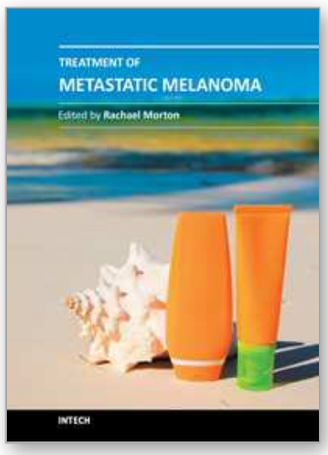

Treatment of Metastatic Melanoma

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Surgery continues to be the mainstay treatment for melanoma localized to the primary tumor and/or lymph nodes. Results from randomized controlled trials indicate that sentinel node biopsy for the treatment of cutaneous melanoma of intermediate thickness has a beneficial effect on recurrence rates, and adjuvant radiotherapy to regional lymph node fields following surgical resection reduces loco-regional recurrence in patients at high risk of relapse. Isolated limb perfusion, electrochemotherapy, and photodynamic therapy continue to be evaluated for treatment of stage IV disease. However, the greatest excitement in new treatment has been with targeted therapies for genetic mutations. In particular, the promising results of partial and complete tumor response in stage IV disease from early phase trials of the B-RAF kinase inhibitors. This book provides a contemporary insight into the therapeutic treatment options for patients with metastatic melanoma and is relevant to clinicians and researchers worldwide. In addition, an update on current clinical trials for melanoma treatment has been included, and two chapters have been reserved to discuss the treatment of oral and uveal melanoma.

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