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REVIEW

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Management of patients with multiple brain metastases

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Abstract

Metastases in the brain are a devastating and common cancer with a poor prognosis. Physicians, on the other hand, may help their patients by suspecting, recognizing, and treating them correctly. It is predicted that between 8 and 10% of cancer patients may develop brain metastases, resulting in roughly 200,000 new cases of brain metastases per year. Single and multiple metastases can share clinical, diagnostic, and therapeutic features. In the majority of brain metastasis, cancer cells move through the blood to the brain. The cerebellum is responsible for 15% of instances; whereas, the brainstem is responsible for 5%. The severity and speed with which the symptoms appear might vary substantially. In addition to the history and physical examination, CT and MRI with contrast give a safe, more sensitive diagnosis. The treatment is primarily palliative, although vigorous therapy in carefully selected patients can prolong the median survival time to about a year. Generally, the prognosis is guarded. Medical treatment includes corticosteroids and antiepileptic. Whole-brain irradiation, SRS, and chemotherapeutic agents are the most common adjuvant therapies. The neurosurgical approach to the management of such lesions has been greatly improved over the last few decades. Hereby, an updated review for the management of multiple brain metastasis.

Keywords Brain metastasis, Chemotherapy, Multiple metastases, Radiotherapy, Outcome

Background

A new form of headache or neurologic symptoms in a cancer patient might indicate brain metastasis. Despite the guarded prognosis, quick diagnosis and treatment can help the patient live longer and enjoy the final days of their life [1, 2].

In this review, we briefly highlight the essential diagnostic features of brain metastases, address the updated role of different diagnostic tools, and evaluate the efficacy and prognostic implications of currently available therapeutic approaches.

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Single and multiple metastases can share clinical, diagnostic, and therapeutic features. That is why in this review all characteristics are presented for both with the same integrity. However, the neurosurgical approach may be different, and diverse therapeutic modalities for those with multiple brain metastases are well discussed in depth [3–5].

Epidemiology

In the United States, it is estimated that between 8 and 10% of cancer patients may develop brain metastases, resulting in around 200,000 new instances of brain metastases per year. The occurrence of brain metastases at the time of initial diagnosis varies substantially depending on the histology of the tumor. For example, the incidence proportion of patients with brain metastases at diagnosis is estimated to be more than 25% in metastatic melanoma and metastatic lung adenocarcinoma, almost 10% in metastatic renal cell cancer, about 7% in metastatic breast cancer, 5% in metastatic head

and neck cancer or esophageal cancer, and at least 2% in nonesophageal metastatic gastrointestinal cancers [6].

After the initial diagnosis, many individuals may develop brain metastases. Those with lung cancer have 20% chance of developing brain metastases within a year; whereas, patients with breast cancer, renal cell carcinoma, and melanoma have 5 to 7% chance [7].

Origin

Malignancies that start in any organ can spread to the brain. Some tumor forms, on the other hand, are more prone to spread to the brain. Melanoma has the greatest rate of brain metastases in adults, followed by lung, breast, and kidney malignancies. Lung cancer and breast cancer, on the other hand, are more frequent than melanoma and so produce more occurrences of brain metastasis (Fig. 1). Prostate and gastric cancers, for example, do not typically metastasize to the brain, but they are so common that they generate a significant number of brain metastases each year. The most prevalent causes of brain metastases in children include osteogenic sarcoma, rhabdomyosarcoma, and testicular germ cell cancers [8].

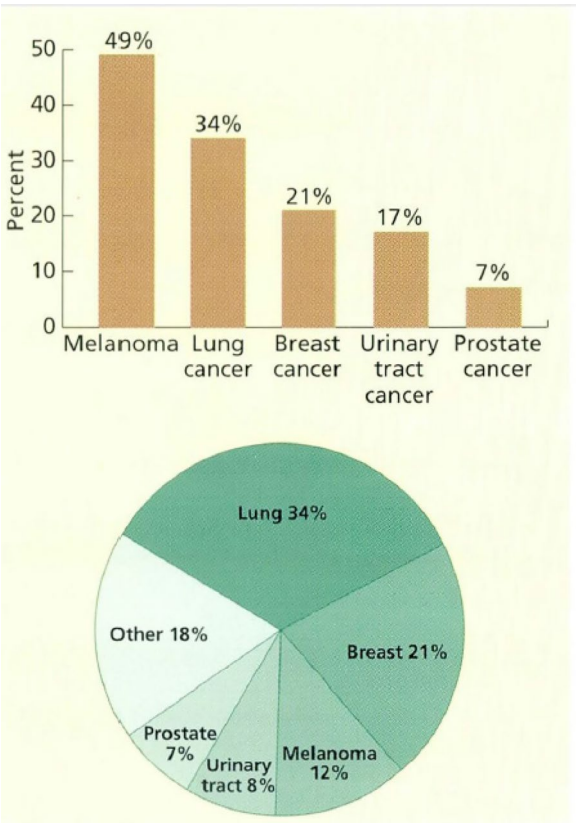

Fig. 1 Above illustration, of brain metastases in frequencies in relation to other malignancies. Below illustration is showing frequencies of different origins of brain metastases. Quoted from [30]

Spread

In the majority of brain metastasis, cancer cells move to the brain via the bloodstream. Typically, these cells come from a primary or metastatic lung tumor. Brain metastases, on the other hand, can occur without involving the lungs, adding support to the theory that some tumor cells preferentially move to specific organs (e.g., melanoma and small cell lung cancer spreading preferentially to the brain). Tumor cells enter the brain from the arterial blood, but they can also spread through the venous blood; vertebral venous system (Batson's plexus) [9].

Sites

The location of brain metastases is highly correlated with cerebral circulation. The cerebral hemispheres get the main bulk of blood flow and account for around 80% of all cranial metastases. Brain metastases tend to present in the most distal reach of the distal arterial tree. Capillaries trap the metastasizing cancer cells. The watershed zone in the gray–white matter junction represents up to 67% of them [30]. The cerebellum is responsible for 15% of instances; whereas, the brainstem is responsible for 5%. Metastases tend to arise in these locations at spots where the blood vessels' diameter rapidly decreases as well as in the arterial tree's distal reaches [10].

In some areas, blood arteries branch quickly into end capillaries, creating a "filter" that may operate as a trap for metastasizing cells. This occurs mostly in the gray matter–white matter interface, which has a high rate of metastasis [11].

Symptomatology

When the blood–brain barrier is disrupted, vasogenic edema occurs, which causes symptoms of brain metastasis. The surrounding brain tissue is compressed, and the edema may induce an increase in intracranial pressure. When pain-sensitive structures like the dura, dural sinuses, nervous system, and vasculature are disrupted, pain is felt [12].

The degree and speed with which symptoms arise can differ significantly. The brain occupies 70% of the intracranial volume, and cerebrospinal fluid and blood arteries account for the remaining 30%. When a slowly growing mass within the brain displaces cerebrospinal fluid and pressures the ventricular system, the intracranial pressure may remain near normal. In this scenario, symptoms may be minimal [13].

Autopsy investigations indicate a startling percentage of brain metastases that were previously undiagnosed clinically. Metastases, on the other hand, frequently cause a substantial quantity of edema in the surrounding area,

with a quickly growing mass impact. Symptoms might worsen quickly in this situation, necessitating an immediate assessment [12].

The most frequent symptom is headache, which affects around half of all patients. The headaches are generally stronger in the morning and gradually get worse in duration and severity. Regardless of the symptoms, every cancer patient who develops a new headache should be checked for brain metastases. Focal motor weakness, changes in mental state, gait abnormality, convulsions, and vision difficulties are some of the other symptoms [14].

Diagnostic features

A high degree of suspicion, as well as a thorough medical history and physical examination, are required. Because 80 percent of individuals with brain metastases have a history of cancer, a history of cancer should arouse suspicion. However, in 10% to 15% of individuals with brain metastases, the brain metastasis is the first sign of cancer, and a comprehensive examination reveals no identifiable original malignancy in the remaining 5% to 10% [15].

Clinical examination

Close attention to the patient's mental condition plus the neurologic evaluation during the physical examination. 75% of patients with brain metastases have cognitive impairments, and 66% have hemiparesis. Other clinical presentations include unilateral sensory loss, ataxia, aphasia, and papilledema. With a thorough history and physical examination, as well as an understanding of neuroanatomy, it is frequently possible to estimate where the single or multiple metastases are located [15].

Diagnostic tools

In addition to the history and physical examination, CT and MRI give a safe, more sensitive diagnosis. As a result, if brain metastases are suspected, a contrast-enhanced CT or better MRI is the gold standard diagnostic tool (Fig. 2) [16].

MRI and CT scans demonstrate that the majority of cases with brain metastases had numerous lesions. Multiple metastases are more common in lung cancer and melanoma; whereas, single metastases are more common in breast, kidney, and colorectal cancer. MRI is considered more sensitive than CT scan, especially when using high dosages of gadolinium contrast. For example, whereas CT, which is frequently the first imaging examination acquired, detects multiple metastases in 50% of patients, gadolinium-enhanced MRI reveals a prevalence of nearly 70% [17].

Before beginning treatment for a newly diagnosed cerebral tumor, the pathology must be determined. Differentials include Primary or metastatic neoplasm, ischemic or embolic infarction, infection, and hematoma. The clinical history as well as the appearance of the tumor on CT or MRI can help determine if it is a neoplasm or one of the other abnormalities. However, there is no way to tell the difference between a primary brain tumor and metastasis based on a single imaging feature. In the image, rounded semblance with a peripheral like "ring enhancement," placement inside the gray–white junction, and a substantial quantity of vasogenic edema are all characteristics of the lesion that raise the suspicion of metastasis or metastases when multiple. The existence of many lesions or a history of malignancy in a patient supports the diagnosis of metastasis [16].

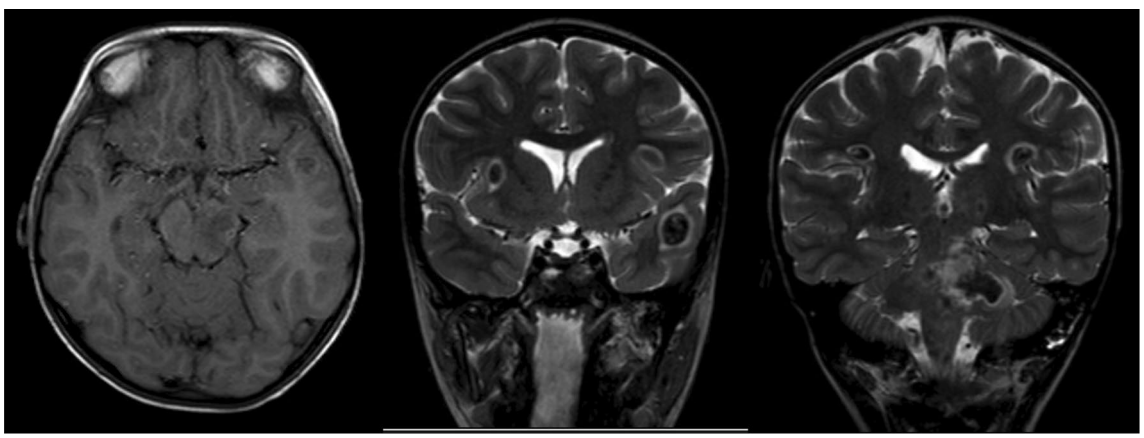

Fig. 2 Case of hemorrhagic multiple brain metastases. An 11-year-old kid with osteosarcoma and acute myeloid leukemia has been identified. This patient presented with sudden drop in conscious level and respiratory embracement. MRI brain T1WI axial and T2WI coronal cuts are showing multiple space-occupying lesions with hemorrhagic features. This is an example of multiple hemorrhagic BM

The detection of a single or several lesions in the brain should stimulate a search for other sites of lesions if the patient has no known cancer before. All patients should have chest radiography, and standard blood work, including hepatic and renal function testing. All males should have their prostate-specific antigen levels checked, and all women should get bilateral mammograms [17].

Further investigations include: a CT scan of the chest, abdomen, and pelvis as well as colonoscopy should not delay the acquisition of tissue for diagnosis, and if no other sites of illness are found, a brain mass biopsy is recommended. Other reasons for a surgical procedure will be mentioned later [16].

Prognostic factors

Prognosis is often guarded. Patients with brain metastases who are not treated have a steadily worsening course until they die approximately a month later, with the majority of fatalities resulting directly from the brain metastases [18].

The treatment is primarily palliative, even though aggressive therapy is used in a small minority of people and can prolong the median survival time by up to a year. The prognosis is influenced by several things [18].

Prognostic performance scale

Based on Karnofsky's performance status ratings (0 indicates no function, 100 shows normal function); the Radiation Therapy Oncology Group [19] lately categorized 1,200 patients treated with whole-brain irradiation into three prognosis groups:

- Any age with a Karnofsky score of less than 70 had the poorest prognosis (median survival of 2.3 months).
- Those with a Karnofsky score of 70 or above, age 65 or older, and an uncontrolled main tumor or testimony of other systems had a 4-month survival rate.
- The greatest prognosis was seen in patients less than 65 years old with a Karnofsky score of 70 or above, a managed main tumor, and no indication of additional metastases (median survival of 7.1 months) [20].

Single versus multiple brain metastases

The number of brain metastases was not elicited as a predictive factor in the Radiation Therapy Oncology Group trial. Patients with only single brain metastasis are thought to have a more favorable prognosis than those with multiple lesions, and those with "single" brain metastasis (i.e., one brain lesion without evidence of cancer elsewhere in the body) are thought to have a better prognosis than those with multiple lesions. Surgical access to the lesion/lesions and the period of disease are two characteristics associated with prolonged longevity [21].

Medical approach

The diagnosis of brain metastases is traumatic for sufferers and their families. Despite this, effective care can ease symptoms and prolong survival, and pharmacological therapy can play a vital role [22].

Corticosteroids

All symptomatic patients should get corticosteroids once the diagnosis has been confirmed, which can be decreased when the final therapy is finished. In about two-thirds of patients, this therapy improves their clinical condition and doubles their anticipated survival time. Treatment response is usually visible within a few hours, with the maximum impact occurring within a week. Although the exact mechanism through which steroids work is unknown, they appear to reduce symptoms by lowering vasogenic edema. The fact that symptoms of global cognitive impairment react quickly to steroids; whereas, specific neurologic abnormalities are more resistant, supports this idea [22].

Although corticosteroids are safe and effective, individuals with an intracranial lesion or lesions who have no known history of malignancy should be cautious [22].

Anti-seizure therapy

Patients having seizures should be treated with anticonvulsant medication. Seizures are generally controlled by a single medication. Prophylactic anticonvulsant medication has not been found to lessen the incidence of later seizures in individuals who come without seizures. Anticonvulsant treatment should not be used routinely in people who do not have seizures [22].

Whole-brain radiation

In the treatment of multiple brain metastases, radiotherapy is crucial. The standard approach is to treat the entire brain, and within three weeks, symptoms improve in over 80% of individuals [23].

After whole-brain irradiation, median survival increases to 4 to 5 months, Furthermore, the fatality rate from the neurologic disease is comparable to that of systemic disease. Whole-brain irradiation timing and doses are debatable. The normal duration is 2 to 3 weeks, and for the vast majority of patients, this regimen provides excellent symptom relief. However, for patients with a better prognosis, a lengthier treatment may result in fewer long-term adverse effects and should be explored [23].

Prophylactic cerebral irradiation is contentious, and treatment is only recommended for newly diagnosed

cancer patients who are at high risk of brain metastases, such as those with small cell pulmonary cancer or late-stage non-small cell lung cancer. Even though multiple studies have shown a considerable reduction in cerebral dissemination, no consistent evidence of a survival advantage has been found [24].

Surgical approach

Surgical excision for brain metastasis is indicated when there is no known cancer, solitary brain metastasis, persistent symptoms, or life-threatening edema following conservative therapy. The danger of craniotomy in patients with known malignancy has decreased as a result of developments in anesthetics, the widespread use of corticosteroids, and the introduction of stereotactic guidance [25].

The amount of systemic illness, as well as the location and quantity of brain metastases, are the primary contraindications of surgery. Resection of masses in important locations like the speech or motor areas might result in debilitating neurologic deficits, which are undesirable in the palliative scenario. Because of the existence of numerous metastases or broad systemic illnesses, surgical resection is not an option for most patients, even when theoretically possible [25].

Survival appears to be higher following surgical excision for a single rather than multiple brain metastases than after radiotherapy alone; nonetheless, metastases return in more than two-thirds of patients without cranial irradiation [26].

Combination of surgical excision and irradiation

Generally, healthy individuals had a median survival time of nearly a year after surgical removal of the tumor and whole-brain irradiation. This combination strategy improves median survival, disease-free survival, the mortality rate from brain metastases, and functional independence when compared to less aggressive care. For any patient with single brain metastasis and a good Karnofsky score combined surgical resection and brain irradiation should be attempted, further research is warranted [25].

Radiosurgery

Because it is designed to provide a high dose of radiation to a small target, stereotactic radiosurgery is particularly well suited for treating brain metastases. Small size; usually less than 4 cm, easy detection on contrast-enhanced MRI, rounded form, and no deep penetration into brain tissue are all characteristics of brain metastasis that make it appropriate for stereotactic radiosurgery therapy [27].

Stereotactic radiosurgery has two key advantages: it is less invasive, and it just targets the lesion, unlike whole-brain irradiation. The typical surrounding brain tissue is not irradiated. Because stereotactic radiosurgery is a localized treatment, whole-brain irradiation is commonly used with it to prevent metastases from spreading to other parts of the brain. This therapy technique has been the subject of several investigations [27].

Apart from resection, stereotactic radiosurgery is a viable alternative for patients who are not surgical candidates or who are opposed to craniotomy. Although the exact purpose of stereotactic radiosurgery is still being researched, it is a viable alternative for patients who are not surgical candidates. Proponents claim that stereotactic radiosurgery should be used instead of resection for single brain metastases since it is a non-invasive outpatient procedure that does not require general anesthesia [28].

Chemotherapeutic agents

In the treatment of brain metastases, intravenous chemotherapy has a limited role. The bulk of the agents fails to cross the blood–brain barrier in sufficient quantities to be effective. Intrathecal chemotherapy may help people with diffuse meningeal studding (meningeal carcinomatosis), but it fails to treat parenchymal metastases because of inadequate tissue penetration [29].

Diagnosis and treatment tips

- When a patient has indications and symptoms that point to an intracranial mass, a contrast-enhanced CT or MRI is recommended. If there are several lesions or if the patient has a history of malignancy, following a positive imaging study, the possibility of brain metastasis should be elevated.
- If the patient has no known history of cancer or has a distant history, the workup should include a comprehensive history and physical examination, chest radiographic exams, blood workup, and either mammography or a prostate-specific antigen assay, depending on the gender [30].
- If no accessible lesions are detected following these examinations, further CT scans should not be used to postpone craniotomy or stereotactic brain biopsy in establishing a diagnosis. After the diagnosis is established, all symptomatic individuals should be placed on corticosteroids, which may be reduced after treatment is finished. Whole-brain irradiation over 2 to 3 weeks is suitable for the majority of patients and provides good symptom relief. In certain individuals, however, adding craniotomy alternatively stereotactic radiosurgery together can result in longer survival and functional independence [31].

Discussion

In research including questions from doctors at Zurich's University Hospital for multiple brain metastases (BM), the poll included particular clinical circumstances of individuals with BM, as well as a sample of BM dissemination. The first example included a 55-year-old woman who had eight newly diagnosed BM from NSCLC (non-small cell lung cancer). All of the BM were less than 5 mm^3 in size and were found in non-eloquent areas in relation to eloquent centers of brain, such as the optic chiasm or brainstem [32].

In the event of median survival of more than 6 months, 32% of doctors would opt for a stereotactic technique, such as SRS (stereotactic radiosurgery) or fSRT (Fractionated stereotactic radiation therapy), whereas 68 percent would opt for WBRT (Whole-brain radiation therapy). Academic and non-academic centers had different treatment policies (p value 0.001), as did high-volume and low-volume centers (p value = 0.007). When the median survival time is shorter than 6 months, 15% of people choose a stereotactic technique, whereas the rest opt for a non-stereotactic method [33].

The second instance was a 45-year-old woman who had fifteen newly identified BM of NSCLC origins; all of which were less than 5 mm^3 in size and located in non-eloquent areas. In the event of median survival of more than 6 months, 16% of responders would choose stereotactic radiotherapy. Academic and non-academic centers (p value = 0,009), as well as high- and low-volume centers (p value = 0,001), had statistically distinct treatment policies, with both academic and high-volume facilities being more amenable to a stereotactic radiation strategy. More than 95% of responders would select a WBRT strategy if their expected survival was less than 6 months, and no statistical difference could be found [34].

Another European survey, which received over 200 responses, provides the first data on general treatment and care practices in patients with multiple BM in Germany. Other BM management surveys were not unique to multiple BM and were largely conducted among centers in English-speaking nations and Japan. Only this European survey concentrating on the management of non-small cell lung cancer brain metastases exists to the knowledge of the authors [35].

Surprisingly, even in patients with strong prognostic characteristics, the great majority of radiation oncologists would choose standard WBRT as the primary treatment option for patients with multiple BM. Only a small percentage of patients with more than four BM considered SRS, especially when they had strong prognostic characteristics. Their findings highlight the complexity of national and international recommendations when it comes to selecting patients for stereotactic radiotherapy [35].

The recommendations provide a wide range of options for selecting an effective treatment for numerous brain metastases. In terms of stereotactic radiation, the majority of participants appear to follow the guidelines' explicit instructions and do not treat stereotactically beyond the cut-off of four metastases on a regular basis. Their research also demonstrated that hippocampus sparing WBRT is only effective in a small number of cases [34].

The utility of stereotactic radiation or hippocampus sparing procedures has recently been strengthened by the findings of phase 3 studies. When comparing SRS to WBRT in 4 to 15 brain metastases, a randomized controlled phase 3 study done by the MD Anderson Cancer Center found equal survival and much less cognitive deterioration. With a randomized comparison of WBRT + memantine, the NRG-CC001 study provided the most data to date for hippocampus sparing [24, 36].

Because the MD Anderson trial omitted melanoma patients, who frequently present with multiple brain metastases, the question of whether histology is suitable for SRS in multiple brain metastases remains unsolved. As a result, there is currently a scarcity of high-quality clinical data for treating numerous brain metastases. More ongoing randomized studies comparing WBRT and SRS for patients with multiple BM are scheduled to be out soon, and the results will hopefully help to better define the function of different therapeutic methods in this situation. In patients with 5 to 15 brain metastases, a phase III trial (NCT03550391) will directly compare SRS to hippocampal-sparing WBRT with memantine. In general, traditional WBRT is becoming increasingly challenging as the pattern evolves [27, 37].

Academic and non-academic facilities, as well as high- and low-volume centers, had significantly different treatment regimens for multiple brain metastases, according to this study's statistical analysis. Academic and high-volume facilities appear to have already adjusted to the growing evidence of stereotactic radiotherapy in the event of multiple metastases, opting for a hippocampus sparing method over whole-brain irradiation more frequently [27].

In summary, the findings of such a study show that prognostic ratings be used with caution before treating brain metastases. According to the findings of this survey, prognostic scores are used more frequently in academic centers than in non-academic centers. Furthermore, treatment recommendations for cerebral irradiation in academic centers appear to be more frequently based on multidisciplinary tumor boards, which is also visible in high-volume centers compared to low-volume centers. The oncological therapy

landscape has diversified dramatically in recent years, thanks to an increase in therapeutic options for patients with oncological diseases, continued development of existing treatments, and the introduction of new systemic substances, particularly monoclonal antibodies and other targeted substances. Multidisciplinary tumor boards have grown more and more as oncological illnesses have become more complicated and there are more available options [33].

In the aforementioned study, in unique patient instances, it was addressed the issue of how to best integrate the promising cerebral systemic treatment. In newly diagnosed driver-mutated NSCLC with numerous brain metastases, over one-third of responders would delay cerebral irradiation in favor of systemic treatment with TKI (Tyrosine Kinase Inhibitor) alone. Several retrospective investigations looked at the subject of integrating systemic treatment in driver-mutated NSCLC. Although prospective data on this open topic is still lacking, deferring radiation was linked to a poorer OS (overall survival) result, and several meta-analyses of retrospective studies bolstered the idea of enhanced OS by up-front SRS. There hasn't been a randomized trial comparing TKI therapy alone against TKI therapy followed by cranial irradiation [38–40].

Uniqueness is demonstrated by the patient instances. While some participants utilize WBRT for many metastases regularly, the traditional cut-off for stereotactic radiation appears to be wrong in others, and stereotactic radiotherapy is used for far more than ten metastases [39].

It was recognized that the previous study has significant limitations: given the rapid advancement of radiation oncology technology and the creation of systemic medicines with increased brain activity for many tumor types, a tumor agnostic approach to BM must be approached with caution [33].

Treatment for brain metastases: ASCO-SNO-ASTRO guideline [41].

The population to be targeted is Patients having cancer-related brain metastases from non-hematologic solid tumors. The guideline does not include secondary CNS lymphoma.

Audiences are surgeons, oncologists, neurologists, and other doctors who work with the target population of multiple BM.

Guidelines are based on a comprehensive evaluation of the medical literature; an Expert Panel was organized to generate clinical practice guideline recommendations.

Summary of ASCO-SNO-ASTRO guideline recommendations:[41].

* Patients with brain metastases may be offered surgery if the following conditions are met:

- Patients with suspected brain metastases who will have surgery to diagnose and remove a tumor in an initial cancer diagnosis may be beneficial.
- Surgery is likely to assist patients with big tumors that have a mass impact.
- Patients with a large number of brain metastases and/or uncontrolled systemic sickness are less likely to benefit from surgery unless the residual disease can be treated without it.

* When surgery is indicated, no advice can be made about the resection approach (piecemeal vs. en bloc) [42].

* There is no way to say if laser interstitial thermal treatment is beneficial or not.

* Regardless of the systemic therapy utilized for the systemic illness, patients with symptomatic brain metastases should receive local therapy (radiosurgery, radiation therapy, and/or surgery) as specified in this guideline.

* Local treatment should not be delayed in patients with asymptomatic brain metastases. A multidisciplinary discussion (neurology, neurosurgery, medical oncology, and radiation oncology) of the possible advantages and risks the patient may encounter should be used to choose to delay local treatment [42].

* Patients with asymptomatic brain metastases from EGFR (epidermal growth factor receptor) mutant non–small cell lung cancer (NSCLC) may be prescribed osimertinib or icotinib. Local treatment may be postponed if these medicines are utilized until there is evidence of intracranial progression. Icotinib has not been licensed by the US Food and Drug Administration or the European Medicines Agency as of this publication.

* Patients with asymptomatic brain metastases from ALK (Anaplastic lymphoma kinase)-rearranged NSCLC may be treated with alectinib, brigatinib, or ceritinib. Local treatment may be postponed if these medicines are utilized until there is evidence of intracranial progression [43].

* Patients with asymptomatic brain metastases from immunotherapy-naive, programmed death-ligand 1–NSCLC who are also taking pemetrexed and a platinum drug may be given pembrolizumab.

* Patients with asymptomatic melanoma brain metastases may be treated with ipilimumab plus nivolumab (for all patients regardless of BRAF status) (gene found on chromosome seven that encodes a protein also called BRAF) or dabrafenib with trametinib (for patients with the BRAF-V600E mutation). Local treatment may be postponed if these medicines are administered until evidence of intracranial advancement is found.

* Patients with human epidermal growth factor receptor 2–positive metastatic breast cancer who have asymptomatic brain metastases and have progressed on prior

trastuzumab, pertuzumab, and/or trastuzumab emtansine–based treatment may be given a combination of tucatinib, trastuzumab, and capecitabine. Local treatment may be postponed if these medicines are utilized until evidence of intracranial advancement is found [44].

* Patients with asymptomatic brain metastases who have: • Karnofsky Performance Status (KPS) 50 or below, or • Performance status KPS 70 and no systemic therapeutic choices should not receive radiation therapy [45].

* Patients with one to four unresected brain metastases, excluding small cell carcinoma, should be provided SRS alone (rather than WBRT or a combination of WBRT and SRS).

* If the surgical area can be safely treated and the level of residual intracranial illness allows, SRS alone should be provided to patients with one to two removed brain metastases. can be safely treated and the intracranial residual mass allows, SRS alone should be provided to patients with one to two excised brain metastases [45].

* Patients with more than four unresected or more than two resected brain metastases with a superior performance status (e.g., KPS more than 70) should consider SRS, WBRT, or a combination of SRS and WBRT. For individuals with a better prognosis or who have access to systemic medication that is known to be active in the CNS, SRS may be recommended.

* Patients who will undergo WBRT and have no hippocampal lesions and estimated survival of 4 months or more should be administered memantine and hippocampal preservation.

* There can be no suggestion for the precise sequence of therapy for patients who will get both radiation therapy and surgery [41].

Neurosurgical perspective for multiple brain metastases

Multiple brain metastases are found in more than half of individuals with brain metastases. While the significance of surgical resection in the treatment of single brain metastasis is well understood, the indications for surgery in the treatment of several brain metastases are less clear. There are no randomized or prospective trials that show that surgery improves survival in patients with numerous brain metastases. Regardless, as treatment options for systemic cancer improve and more patients survive with better functional status, extensive surgical resection is becoming more common [46].

Resection may be effective for symptomatic alleviation in individuals with numerous brain metastases, especially in patients with a big dominant lesion. Furthermore, the greatest outcome is attained when all lesions can be removed, if technically feasible. Of course, this is true [47].

Because of practical limitations, early SRS treatments were often confined to 1–3 brain lesions. GKRS (gamma knife radiosurgery) for many lesions needed helmet changes and manual collimator plugging until the mid-2000s; while, linear accelerator-based SRS required cone-based collimation with particular quality assurance for each target lesion until the mid-2000s. Technology advancements have made it possible to treat a higher number of lesions in each patient. Multiple retrospective studies on individuals with more than 8–10 brain metastases treated with GKRS alone revealed that this was possible without compromising local control or survival. Yamamoto et al. published the findings of a Japanese multicenter prospective study (JLGK0901) involving 1,194 patients with 1–10 brain metastases who were treated with GKRS alone in 2014. The total tumor volume was 15 cc, with the biggest tumor being 10 cc [48, 49].

There was no difference in the rate of occurrence of new lesions, local recurrence, leptomeningeal spread, or the need for salvage SRS or WBRT across the three groups. The median OS for patients with a single brain lesion was 13.9 months, which was considerably better than the median OS for those with 2–4 lesions ($P = 0.0001$). Regardless of the number of lesions, the neurocognitive function was maintained. The size and volume of the brain lesions, in addition to the number of BM, determine the feasibility of SRS [50, 51].

Laser interstitial thermal therapy (LITT) is a minimally invasive procedure that can be used to treat a range of intracranial diseases. If the cells are not instantly destroyed by thermal exposure, laser energy causes a localized rise in temperature, which causes degradation of cell membranes and DNA, activation of particular heat-sensitive proteins, and rupture of the microvasculature. The implanted probe delivers focused laser energy into a specific lesion under MRI guidance, triggering heat-induced necrosis. A computer software application keeps track of the treatment temperature, duration of heat exposure, and probe placement [52].

Novel systemic therapies and future perspectives for multiple brain metastases

Traditional cytotoxic chemotherapy has a limited function in the treatment of intracranial illness due to the blood–brain barrier. The identification of targetable molecular alterations in subsets of cancer patients has resulted in the development of targeted therapies with improved blood–brain barrier penetration and efficacy in the treatment of brain metastases, which is why these alterations are included in the most recent DS-GPAs [53] Up to 35% of NSCLC patients include EGFR mutations, and osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), has been demonstrated to have good

intracranial response rates. The use of osimertinib with and without SRS for asymptomatic brain metastases is now being investigated in clinical studies (NCT03535363, NCT03769103). Alectinib and brigatinib, two new ALK inhibitors, have also shown some promise [54].

Immune-checkpoint inhibitors (ICIs), such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, have significantly altered the therapy paradigm for a variety of cancers, and these drugs are now considered standard of care for NSCLC, RCC, and melanoma in particular. Immunotherapy has shown potential in the treatment of asymptomatic brain metastases, particularly in the cases of NSCLC and melanoma. In comparison with SRS alone or sequential administration of ICIs and SRS, data from retrospective studies show that concurrent ICIs and SRS can increase intracranial tumor response, response persistence, and OS. The abscopal effect, or increased systemic anti-tumor immune activity, is thought to be responsible for this. The potential advantages of concurrent immunotherapy and SRS must, however, be weighed against the risks [54, 55].

In selected individuals, ***targeted treatments*** and ***immunotherapy*** may become conventional adjunct therapies to focused radiotherapy for brain metastases. If SRS is used to treat macroscopic illness, these innovative systemic medicines might be utilized to treat possible microscopic disease elsewhere in the brain and postpone distant intracranial development, functioning as a replacement for WBRT. After systemic therapy, a patient with significant brain metastases may be converted to a little disease, making him or her a candidate for SRS without WBRT [57].

Conclusions

Management of multiple brain metastases is challenging because of poor prognosis and involvement of other body organs other than the brain. In selected individuals, targeted treatments and immunotherapy may become conventional adjunct therapies to focused radiotherapy for brain metastases. While the significance of surgical resection in the treatment of single brain metastasis is well understood, the indications for surgery in the treatment of several brain metastases are less clear. We recommend randomized or prospective trials that investigate the role of surgery in the survival of patients with multiple brain metastases.

Abbreviations

ALK	Anaplastic lymphoma kinase
BM	Brain metastases
CNS	Central nervous system
CT	Computed tomography
DS-GPA	Diagnosis-specific graded prognostic assessment
EGFR	Epidermal growth factor receptor
fSRT	Fractionated stereotactic radiation therapy
GKRS	Gamma knife radiosurgery
ICIs	Immune checkpoint inhibitors
KPS	Karnofsky performance status
LITT	Laser interstitial thermal therapy
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
RCC	Renal cell carcinoma
OS	Overall survival
SRS	Stereotactic radiosurgery
TKI	Tyrosine kinase inhibitor
T1WI	T1-weighted image
T2WI	T2-weighted image
WBRT	Whole-brain radiation therapy

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Author contributions

Mohamed Arnaout contributed to conceptualization, data collection, methodology, writing—review & editing, and approval of the final manuscript. Samer Hoz contributed to conceptualization, revising final original draft preparation, and approval of the final manuscript. Angel Lee contributed to conceptualization, revising original draft preparation, and approval of the final manuscript. Mahmoud Taha contributed to conceptualization, writing—original draft preparation, supervision, and approval of the final manuscript.

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Declarations

Ethics approval and consent to participate

Not applicable.

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Competing interest

Authors certify that they have no conflict of interest.

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