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Current Management of Brain Metastases: Overview and Teaching Cases

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Abstract

Over the past two decades, increased global incidence of malignancy, improved systemic disease treatment with prolonged survival, and increased central nervous system (CNS) surveillance in cancer patients have all contributed to a rise in cerebral metastatic disease. As many patients retain good neurologic function, the approach to their management has shifted markedly; a pre-terminal prognosis and palliative treatment have been replaced by individualized care plans to prolong functional survival. However, the rapid shifts in disease characteristics, treatment options and emerging evidence can be challenging to navigate, and a rational approach to brain metastases is needed. We discuss the changing epidemiology of brain metastases and consider approaches to prognostic classification. We review current treatment modalities and discuss the significant studies pertaining to each, with emphasis on Level 1 evidence when available and cooperative group trials, as well as studies on adverse effects. To integrate the information presented, we offer case scenarios that highlight pertinent decision-making factors. The shift in care goal for cerebral metastases from symptom palliation to prolongation of survival is not only feasible, but in many cases indicated. The appropriate application of various treatment modalities must be considered in the context of individual patients and their primary cancer.

Keywords: brain metastases, surgery, whole-brain radiation, stereotactic radiosurgery, targeted therapy

1. Introduction

Brain metastases are the most frequent intracranial neoplasm in adults, and the most common intracranial metastatic site is the brain parenchyma [1–3]. Historically, intracranial dissemination represented a poor prognosis for cancer patients, best supportive care leading to an over-

all survival around 1–2 months [4]. Advances in systemic cancer management, however, as well as in local treatments for cerebral disease, have greatly altered the prognosis and survival for patients. Brain metastasis management is therefore an emerging area of interest in organ-specific metastasis research addressing standard protocols for local management, including rational use of surgical resection, stereotactic radiosurgery (SRS), adjuvant or exclusive whole-brain radiotherapy (WBRT), and emerging systemic therapies. As survival increases, considerations for maintenance of neurocognitive function and quality of life gain greater importance. Decision-making for treatment of brain metastasis patients should be carried out in a multi-disciplinary setting, incorporating expertise from surgeons, oncologists, radiation oncologists, psychologists, and rehabilitation therapists.

2. Epidemiology of brain metastases

A *single* brain metastasis refers to the presence of only one parenchymal lesion in the context of an active primary cancer and possible extracranial metastases. In contrast, *solitary* brain metastasis describes the presence of only one parenchymal deposit with controlled primary tumour and no other metastatic disease. A synchronous brain metastasis is one that is identified at the time of presentation of the primary cancer, while a precocious one presents prior to the primary malignancy.

The accurate global incidence of brain metastasis based on population study is unknown, with estimates ranging around 7–14 per 100,000 [5]. Among cancer patients, estimates of prevalence range from 8.5 to 9.6% [6, 7]. These numbers are likely low, as they come from relatively old studies in which imaging or histology were often incomplete or which ignored cerebral disease in seriously ill patients with symptomatic advanced cancer [1]. Autopsy series report higher rates; a 1963 series found CNS metastases in up to 24% of patients [8], and in 1978, Posner and Chernick found that 15% of patients with cancer had parenchymal brain dissemination [9].

The incidence of brain metastases appears to be rising, with several contributing factors [2, 10]. First, the global incidence of cancer is climbing, but mortality rates are declining as a result of improved detection and treatment [1, 11]. New chemotherapeutic agents have led to a better prognosis and longer survival for many cancers, but fail to prevent central nervous system (CNS) spread due to low penetration of the blood–brain barrier, thus allowing greater opportunity for development of intracranial disease [1]. For example, the agent trastuzumab, a targeted therapy for HER2-positive breast cancer with presumed low CNS penetrance, has altered the natural history of this disease and may have unmasked the CNS as a sanctuary site [1]. In addition, improvement in surveillance, particularly due to greater diligence in following patients who have cancer and integrating brain MRI imaging into these follow-ups (64% today *vs*. 14% 20 years ago), has revealed more cerebral lesions prior to symptom development. For instance, patients with a new diagnosis of small cell and non-small cell lung carcinoma (NSCLC) typically undergo routine screening brain MRI, and inclusion into many clinical trials requires negative screening brain MRI [2].

The incidence and prevalence of brain metastases is also influenced by patient-specific factors, such as race or site of primary tumour. African-Americans with lung, melanoma, or breast cancer, but not renal cancer, appear at greater risk of developing brain metastases than Caucasians [6, 12]. However, confounders such as variability in healthcare access and awareness may account for some racial differences.

Although any neoplasm can potentially disseminate to the brain, certain primary histologies exhibit a higher propensity to do so; a population-based study from the Metropolitan Detroit Cancer Surveillance System found that 19.9% of lung, 6.9% of melanoma, 5.1% of breast, 6.5% of renal, and 1.8% of colorectal cancers develop brain metastases [6]. The prevalence of the primary tumour also affects the incidence of cerebral disease; thus 39–56% of brain metastases arise from lung, 13–30% from breast, 6–11% from melanoma, 2–6% from renal, and 3–4% from colorectal cancers [13–15]. Of note, in 10% of cases, no primary cancer can be identified [3]. The histology of the primary tumour is a key determinant in almost all epidemiological aspects of brain metastasis, including incidence, time interval from diagnosis of primary tumour to occurrence of intracranial spread, prognosis, and survival. In addition, the influence of molecular and genetic features is being increasingly recognised. For instance, the occurrence of cerebral dissemination varies according to the molecular subtype of breast cancer: the incidence for patients with triple-negative tumours [human epidermal growth factor receptor-2 (HER2) non-overexpressed, and oestrogen and progesterone receptor (PR) non-expressed] is 25–46%; whereas, it is 7.6% for patients with luminal tumour A (HER2 non-overexpressed, oestrogen and progesterone receptors expressed, and low proliferation index) [3].

Although a specific gender susceptibility might exist, the primary tumour type is thought to play an important role in the fact that the incidence of brain metastasis is higher in women than men. The increasing incidence of lung cancer in women and the propensity of breast tumours to metastasise to the brain have contributed to reverse the trend of 20 years ago, when more males were diagnosed with brain metastases [6, 16].

The median age at diagnosis has remained fairly stable for the past 20 years, ranging from 57 to 63 years [1]. Primary cancer influences the age at diagnosis: lung cancer, 40–49 years; melanoma, renal, and colorectal cancer, 50–59 years; breast cancer, 20–39 years. The higher frequency of cerebral metastases in younger and/or African-American women with breast cancer could be explained by the larger number of triple-negative tumours in this population, a subtype associated with a high risk of CNS progression [1].

Brain metastasis remains associated with advanced cancer, and over the past 20 years the proportion of patients with intracranial spread who also harbour extracranial metastases has increased (44 *vs*. 14%). [17]. The number of patients presenting with only one brain metastasis has fallen from 63 to 29%, while the proportion of patients with three or more lesions has increased from 17 to 36%. In addition, detection of synchronous brain metastases, at diagnosis of primary tumour, is also more frequent (from 18 to 30%) [17]. These changes are likely due to the increased use of brain MRI imaging. At the same time, the median time interval from diagnosis of primary tumour to detection of cerebral metastasis has increased from 3 to 8

months, depending on the site of primary tumour: 2.6–7 months for lung cancer as opposed to 39–47 months for breast cancer [1].

The increase in concurrent extracranial metastases directly impacts the assessment of prognosis; the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification correlates clinical factors with median survival [18]. The most favourable prognosis, with median survival of 7.1 months, is seen in Class 1 patients who have a Karnofsky performance score (KPS) of ≥70, age <65, and controlled primary tumour without extracranial metastases. Class 3 patients have KPS <70 and a median survival of 2.3 months and are considered poor prognosis. All other patients fall into Class 2, including those with KPS ≥70 but other unfavourable characteristics, such as uncontrolled primary tumour, extracranial metastases, or age ≥65; these have a median survival of 4.2 months. The past two decades have seen a shift in patients away from both the most favourable (19 to 7%) and most unfavourable (44 to 31%) classes to the intermediate class [17–19].

It is well-recognised that primary tumour type influences median survival, with ranges including 2.7–6.3 months for lung, 5.1–6 months for colorectal, and 4.8–10 months for melanoma. In addition, survival for breast cancer differs according to histological and molecular subtypes; median survival for inflammatory breast cancer is 2.9 months, triple-negative is 4.9 months, HER2 overexpressing receiving trastuzumab is 11.3–26.3 months, and hormone receptor-positive is 19–24 months [1]. The diagnosis-specific graded prognostic assessment (DS-GPA) further incorporates prognostic variables significant to particular primary tumours; for instance, while age, KPS, the presence of extracranial metastases and number of brain metastases are seen to influence survival in lung cancer, and age, KPS and receptor subtype affect breast cancer survival, only KPS and number of BM were significant factors in melanoma and renal cell cancer and only KPS in gastrointestinal cancer survival [20].

Accurate prognostic information is useful to optimise treatment for patients who may gain months to years of survival following intracranial progression and to avoid overtreating patients who will derive little benefit. A contemporary cohort of brain metastasis patients who received more local (surgical resection and stereotactic radiosurgery) and systemic (chemotherapy and targeted therapy) treatment compared with a historical cohort had minimal improvement in median survival (3.2 *vs*. 3.9 months). However, 1-year survival increased from 15 to 34%, increased survival was seen at all time points during follow-up, and some long-term survivors were observed [17]. Survival was dependent on presenting symptoms of brain metastasis and treatment received.

Improvements in local procedures, along with increasing availability of systemic therapies, have altered the prognosis for patients with brain metastases.

3. Overview of brain metastasis management

Brain metastasis is a devastating sequela of cancer and develops in 25–40% of that patient population [21–23]. It is associated with a high morbidity and mortality; without treatment, median survival after diagnosis is approximately 1 month [24]. Treatment options include whole-brain radiation therapy (WBRT), surgical resection, stereotactic radiosurgery (SRS),

and systemic therapies. With maximal management the overall survival rate increases to 10–12 months, although some patients demonstrate a remarkable response to treatment [21, 23, 24]. As a result, there is an ongoing debate regarding the most effective treatment regimen.

Not all brain metastases are equal, and there are many factors to consider when deciding on an appropriate treatment plan. Brain metastases can be categorised as solitary, single, or multiple. Furthermore, patients can be classified by type of primary tumour, status of systemic disease, functional status, and age to determine their prognosis, using such systems as the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA), or diagnosis-specific graded prognostic assessment (DS-GPA). Evaluation of these factors is important in identifying patients who will likely benefit most from aggressive treatment, as well as avoiding overtreatment of patients who are unlikely to benefit. In patients with a favourable prognosis (RPA class 1, some class 2), increasing overall and functional neurological survival are reasonable goals and thus focal therapies form a major component of treatment, and outcome assessment includes neurocognition and quality of life. In patients with an unfavourable prognosis, management focuses on symptom palliation as needed.

3.1. Whole-brain radiation therapy

WBRT was historically the treatment of choice for brain metastases, given that it was noninvasive and provided symptom relief and a modest survival benefit to a group of patients with few options. In most centres presently, it is used for patients with an unfavourable prognosis due to their extracranial disease or high burden of brain metastasis, or poor functional status. It is also used as adjuvant to focal treatment modalities (surgery or SRS), in order to reduce local recurrence and development of distant metastases, as well as salvage therapy on intracranial recurrence.

Over 70% of patients diagnosed with brain metastasis have multiple brain lesions at the time of diagnosis [21, 23]. The primary goals of treatment are to palliate symptoms and maintain neurologic function, and in some cases to increase survival, by treating the existing lesions and decreasing the volume of micro-metastases. The RTOG showed that approximately 50% of patients experienced neurological improvement by 2 weeks after initiation of WBRT. Median survival was 15–18 weeks, and 21 weeks in patients who were ambulatory [25]. Surprisingly, the dosing regimen did not affect survival [25, 26]. The typical radiation schedule involves a 7–15-day course of whole-brain radiation with 1.5–4 Gy per fraction. In some circumstances, a single fraction of 6–8 Gy or a bi-weekly fractionation regimen may be appropriate, such as when multiple treatment sessions may be impractical for a debilitated patient or unfeasible due to resource constraints. Such protocols may result in both inferior control rates and increased neurocognitive adverse effects, so should be applied with caution. Not all tumour histologies respond equally to radiation therapy; small cell lung cancer, germ cell tumours and hematologic malignancies are highly radiosensitive, while renal cell carcinoma, melanoma, and sarcoma are relatively radioresistant.

Acute adverse effects of WBRT include hair loss, nausea, vomiting and increased cerebral oedema with worsening of neurological symptoms. Concerns about long-term neurocognitive effects have been raised over the past two decades, especially as survival for patients with metastatic cancer is increasingly prolonged. A 1989 retrospective review found that

1.9–5.1% of patients who underwent WBRT developed progressive dementia, ataxia, and urinary incontinence causing significant morbidity [27]. Although most patients who developed these complications were given 5–6 Gy per fraction, a dose much higher than what is usually given today, a decline in memory and learning function is recognised in patients treated with typical fractionation protocols for WBRT, detectable between 6 and 12 months after treatment and not reversible [28]. Yet patients with brain metastases have detectable neurocognitive decline even prior to any treatment, indicating that cognitive changes may be attributable to the presence of tumour [29] and that failure to control metastatic brain disease also has a significant adverse impact on neurocognitive function [30]. Recent studies have explored strategies to reduce the toxicity of treatment, such as hippocampal-avoidance WBRT, which uses intensity-modulated radiotherapy (IMRT) to reduce the radiation exposure of the hippocampal neural stem cell niche important to memory function. A phase II study found reduced decline in Hopkins Verbal Learning Test-Revised Total Recall (HVLT-R TR), with low progression of disease within the hippocampal avoidance area, compared with historical controls [31]. Other approaches include use of the NMDA receptor antagonist memantine during and following WBRT administration; a small randomised controlled trial of memantine *vs.* placebo did not show a difference in the primary endpoint of memory decline (as measured by HVLT-R Delayed Recall), but did demonstrate longer time to cognitive decline [32]. The effectiveness of neuroprotective strategies and indeed the optimal modalities for neurocognitive testing remain areas of study.

3.2. Surgery

Surgical resection is considered for patients with a single symptomatic lesion in an accessible location, with the goal of reducing mass effect (e.g. to improve neurologic deficit or reduce seizures), decreasing tumour burden, and obtaining a tissue diagnosis when brain metastasis is in the differential diagnosis.

Level 1 evidence provides support for effectiveness of surgery in single metastatic brain lesions in patients with good functional status and controlled systemic disease. Patchell et al. randomised 48 patients into 2 groups (surgery + WBRT *vs.* needle biopsy + WBRT) and found that overall survival was higher in the surgical group, with a mean survival of 40 weeks compared to 15 weeks ($p < 0.01$). There was also a lower incidence of recurrence in the surgical site and longer functional independence [33]. This was supported by the results of Vecht et al., who also found improved overall and functionally independent survival with surgery + WBRT *vs.* WBRT alone in patients with good functional status and controlled extracranial disease; when there was active extracranial disease, the median survival was 5 months regardless of treatment [34]. In contrast, Mintz et al. found no significant difference in survival between the surgical and non-surgical groups [35]. However, the patient population in this study had a higher percentage of active systemic disease and lower functional status, compared to the other studies; these randomised controlled trials together emphasise the influence of these prognostic factors.

The surgical treatment of multiple brain metastases is more controversial. These patients tend to have greater systemic disease burden and are generally expected to have a short survival, so aside from the occurrence of a large lesion or one causing significant mass effect, they

are regarded as poor candidates for surgical resection. A case-controlled study by Bindal et al. showed that the mean survival of patients who had all of 2 or 3 lesions resected was significantly longer than that of patients who underwent incomplete resection and was similar to that of patients who had a single metastasis that was resected [36]. However, this study did not control for the number and locations of lesions. In contrast, Paek et al. did not identify a difference in survival among patients who underwent resection of one versus two or three metastases [37]. Iwadate et al. found that total residual tumour quantity, rather than lesion number, was a significant predictive factor; an improvement in survival from 4.5 to 12.4 months was seen when patients with multiple brain metastases underwent a total or subtotal resection with cumulative residual tumour <2 cm ($p < 0.05$) [38]. Taken together, these observational studies and conflicting results do not support resection of multiple metastases for the purpose of tumour control.

Following surgical resection, local recurrence is common and adjuvant radiotherapy aims to eliminate tumour cells remaining within the tumour bed, as well as to reduce micro-metastases in other locations throughout the brain. However, while multiple retrospective series have shown that WBRT does decrease distant recurrence, it confers no survival benefit [39–41]. In a randomised controlled trial comparing surgery *vs.* surgery + WBRT for a single metastasis, adjuvant WBRT reduced the local recurrence rate from 46 to 10% ($p < 0.001$), distant recurrence from 37 to 14% ($p < 0.01$), and decreased the likelihood of death from neurological causes. Remarkably, WBRT reduced the rate of total intracranial progression from 70 to 18% ($p < 0.001$), but there was no overall survival benefit or difference in duration of functional independence [42]. The EORTC 22952 randomised controlled trial evaluated adjuvant WBRT *vs.* observation following local treatment, either surgical resection or radiosurgery. The probability of local and distant relapse was significantly reduced in the WBRT arm, after both surgery and SRS. Survival with functional independence (WHO performance status > 2) and overall survival did not differ between the two arms, and initial treatment (surgery or SRS) was not a significant factor [43].

Radiosurgery to the resection cavity following surgical excision has become increasingly utilised in order to spare the use of WBRT. Multiple retrospective series showed improved local control with the addition of adjuvant SRS to surgery, with rates comparable to adjuvant WBRT [44–46]. The first prospective study included 50 resection cavities, of which 40 received SRS and 10 were observed, and found a significantly lower rate of local failure in the SRS group (15 *vs.* 50%, $p = 0.008$) [47]. An ongoing phase III study through the Alliance for Clinical Trials in Oncology aims to provide level 1 evidence on this issue, randomising to WBRT or SRS patients with ≤4 metastases who have had ≥1 tumour resected. The primary endpoints will include overall survival and neurocognitive progression. As it stands, the high rate of local recurrence following surgery warrants adjuvant radiation, and the low morbidity of SRS to the tumour bed favours this combination of treatments to improve local control.

3.3. Stereotactic radiosurgery

In recent years, more patients are being managed with stereotactic radiosurgery, a non-invasive option for focal treatment of metastatic brain tumours. This technique was originally developed by Lars Leksell and utilises multiple convergent radiation beams on a tumour to deliver

a highly focused and concentrated dose. It has the advantage of exhibiting a steep radiation dose drop-off outside the tumour border, thereby reducing radiation exposure to surrounding tissue. Metastatic brain tumours tend to be lesions with discrete borders and spherical shape, often less than 3 cm in size, making them ideal candidates for SRS. Its non-invasiveness allows SRS to treat lesions in surgically inaccessible locations, as well as multiple lesions in a single outpatient session. Additionally, its efficacy is similar among relatively radio-resistant histologies such as renal cell carcinoma and melanoma, compared to radiosensitive tumour types. A minimal marginal dose of 18 Gy is associated with improved local control [48], and dose prescriptions generally range 18–25 Gy, lower doses being favoured in the brainstem and other eloquent locations, and when combined with WBRT. It does not reduce mass effect, however, and toxicity and local failure increase with increasing tumour size. While the acute effects of SRS are generally well-tolerated, the most common delayed complication is radiation necrosis, which may occur in up to 10% of tumours, 6 months to several years after treatment. Radiation necrosis develops more frequently with higher radiation dose, following prior stereotactic or fractionated radiation treatment, in larger tumours, and possibly when SRS is combined with targeted or immune therapy [49]. Distinguishing treatment effect from tumour recurrence is necessary but challenging, as both can exhibit increased enhancement and peri-lesional oedema, and advanced imaging techniques such as perfusion MRI and amino acid PET are under investigation to increase diagnostic specificity. Treatment is largely symptomatic, with corticosteroids. Observational studies have explored treatment for severe cases including resection, laser interstitial thermal therapy, bevacizumab, or hyperbaric oxygenation [50].

The efficacy of SRS was demonstrated in a randomised controlled trial carried out by Kondziolka et al., which compared WBRT plus a single-dose radiosurgery boost to WBRT alone in patients with 2–4 brain metastases. At a planned interim analysis, the primary endpoint of local control so strongly favoured combination treatment that the study was stopped ($p = 0.0016$). This left it underpowered to demonstrate a difference in overall survival. At one-year follow-up, the rate of local failure was 100% in patients treated only with WBRT, compared to 18% in those who had received SRS boost ($p = 0.002$) [51]. The subsequent RTOG 9508 randomised controlled trial also comparing WBRT plus SRS to WBRT alone in patients with 1–3 tumours found that the primary endpoint of median survival was met in the combined treatment arm, but only in patients with a single lesion (6.5 $vs.$ 4.9 months, $p = 0.04$). The secondary endpoints of local control and improvement in performance status were met in the whole treatment cohort [52]. A secondary analysis of this data by Sperduto et al. that stratified patients by GPA found that WBRT + SRS conferred a survival benefit in good-prognosis patients (GPA 3.5-4) even with >1 lesion [53]. As with surgery, these studies emphasise the significant prognostic effect of good pre-treatment function and controlled systemic disease.

In comparing stereotactic radiosurgery with surgical resection, multiple retrospective studies have shown comparable survival, with some suggesting improved local control for SRS [54, 55], others favouring surgery [56], and still others suggesting a similar local control rate for the two modalities [57]. A single randomised controlled trial comparing surgery + WBRT with SRS was stopped prematurely due to poor accrual; the data acquired showed similar rates of local recurrence, overall survival and neurological death between the two arms [58]. Overall, the data suggest that SRS is at least as effective as surgery for tumour control and given the

collective experience with its safety and utility, in the absence of a specific surgical indication such as a large or symptomatic lesion or uncertain diagnosis, is appropriate as first-line treatment for 1–3 newly diagnosed brain metastases.

The use of adjuvant WBRT for SRS has been controversial, and several randomised controlled trials have compared SRS with adjuvant WBRT to SRS alone. Similarly to the EORTC 22952 results, the Japanese Radiation Oncology Study Group found no significant difference in the primary endpoint of overall survival, or in functional preservation, despite significant reduction in local and distant recurrence in the WBRT arm [59]. In a single-institution RCT, Chang et al. evaluated a primary endpoint of cognitive function as determined by HVLT-R TR. A planned interim analysis at 4 months found a higher rate of total recall deterioration in the SRS + WBRT arm, and the trial was therefore halted. At study conclusion, overall intracranial recurrence was reduced in the WBRT arm, but a survival benefit was seen in the SRS-alone arm, a difference from other studies that the authors attributed to salvage therapies [60]. A cognitive primary endpoint was evaluated in the multi-institutional study of Brown et al., deterioration defined as decline of >1 standard deviation on ≥1 of 7 instruments assessing a range of cognitive domains. Cognitive deterioration was significantly worse in the WBRT arm, as were quality of life measures. Intracranial relapse was significantly greater in the observation arm, but overall survival was not different [61]. The evidence supports consideration of close observation for intracranial progression following SRS for 1–3 metastases, with salvage therapy at that time, to avoid routine use of adjuvant WBRT.

Earlier series limited the use of SRS to ≤4 lesions, a restriction that was largely technical rather than biological, and currently multiple lesions can be easily treated in a single session. Yet the evidence that guides treatment of a few lesions cannot necessarily be extrapolated to the management of many tumours; for instance, although SRS is highly conformal, with increasing tumour number the intervening brain is exposed to more radiation. In addition, some series suggest that the number of tumours is less important than the total tumour volume. A prospective observational study in patients with 1 to 10 brain metastases treated with SRS found that patients with a single lesion experienced significantly longer survival, but showed no difference in survival between patients with 2–4 and 5–10 tumours [62]. These latter groups also showed no difference in local or distant failure, suggesting that up-front use of SRS may be as appropriate for ≥5 lesions as for ≤4. An ongoing trial through the North American Gamma Knife Consortium aims to shed light on the neurocognitive outcome of patients with multiple metastases randomised to either SRS or WBRT. Included are patients harbouring ≥5 lesions, with no maximum number but total tumour volume restricted to 15 mL. This study will additionally evaluate patient- and caregiver-assessed quality of life, and include a cost analysis.

At the time of intracranial progression, repeat SRS may be considered in patients who maintain a good functional status and controlled systemic disease. Imaging suggestion of local recurrence must be distinguished from treatment effect, and especially if minimally symptomatic, a conservative approach with serial imaging is generally warranted before repeat treatment. Risk factors for local recurrence may include larger tumours, lower marginal dose, and melanoma histology. Multiple retrospective series have shown efficacy for SRS in new or recurrent tumours, including after WBRT, with adjustment to lower fraction dose in the

setting of prior radiation exposure. These series suggest a local control rate comparable to first-time SRS [63–65].

3.4. Systemic therapy

The use of cytotoxic chemotherapy in treatment of brain metastases has historically been limited due to the perception that the blood–brain barrier isolates tumour cells from circulation agents. Furthermore, these patients usually have already been heavily pre-treated with conventional chemotherapy for their primary cancer, this prior exposure leading to tumour resistance against many agents. In addition, death from progression of systemic disease may preclude an assessment of the effect of the agent on intracranial disease. However, some phase II clinical trials have shown promising results for newer drugs in the treatment of certain subtypes of metastatic brain lesions [66]. The DNA-alkylating agent temozolomide has been widely studied for the treatment of brain metastases, in large part due to its high blood–brain barrier penetrability. It has modest efficacy in monotherapy, but in combination with radiotherapy or other chemotherapeutic agents has demonstrated encouraging results, with up to 40% disease control in brain metastases from various primary sources as well as minimal drug-related toxicity [67–69].

A meta-analysis of platinum-based chemotherapeutic agents (e.g. cisplatin) for small cell lung cancer demonstrated a 66% response rate for patients with brain metastases at initial diagnosis and 36% response rate for delayed brain metastases [70]. Unfortunately, most patients suffered from relapse of their disease or toxic side effects such as febrile neutropenia and sepsis [71]. In non-small cell lung cancer (NSCLC), these agents have shown a 28–45% response rate in chemotherapy-naïve patients [72]. Inhibitors of epidermal growth factor receptor (EGFR) have been approved for treatment of NSCLC due to the identification of frequent *EGFR* mutations in these tumours, and some retrospective series have demonstrated effect in brain metastases [73–76]. A phase II study of erlotinib in NSCLC patients with asymptomatic brain metastases showed a 58% complete or partial response rate, including in some tumours without *EGFR* mutation. The median progression-free survival was significantly longer in mutant *EGFR* tumours than in wild-type tumours (15.2 *vs.* 4.4 months, respectively; $p = 0.02$) [77]. Other NSCLC tumours bear an oncogenic *EMI4-ALK* translocation, and 30% of these patients develop brain metastases [78]. The ALK-targeted tyrosine kinase inhibitor (TKI) crizotinib has demonstrated CNS penetration and effect, although patients invariably relapse [79]. Second-generation inhibitors of ALK may exhibit greater activity and durability of effect [80]. Combination of targeted agents with radiotherapy may be synergistic and yield improved response and survival, at the cost of increased adverse effects [81].

Patients with intracranial breast cancer metastases have response rates of 43–59% to cyclophosphamide with various combinations of 5-fluorouracil, methotrexate, and vincristine [72]. The molecular subtypes of breast cancer demonstrate different tendencies for brain dissemination, with triple-negative and HER2-positive tumours carrying the highest risk [82]. Routine treatment of the latter group of patients with HER2-directed therapy has markedly improved the overall prognosis, but a number of studies have shown an increase in brain metastases in

patients treated with trastuzumab [83]. This effect may be secondary to increased survival of patients with this agent and low permeability of the antibody through the blood–brain barrier [71, 72]. There is increasing interest in the role of agents such as lapatinib, a dual EGFR- and HER2-specific TKI, which has shown modest intracranial anti-tumour activity in phase II trials [84, 85]. In addition, the phase II LANDSCAPE trial evaluating the combination of lapatinib and capecitabine, an inhibitor of DNA synthesis, demonstrated a 66% partial response and suggested that this systemic treatment may be an alternative to WBRT in HER2-positive patients [86]. Further randomised controlled trials are ongoing to explore the role for these and other systemic agents.

Cerebral metastases in melanoma historically carried a dismal prognosis. Cytotoxic chemotherapy is largely ineffective in management of metastatic melanoma, but new biologically active agents have dramatically altered the course of both intra- and extracranial disease for some patients. A phase II study of the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibody ipilimumab demonstrated a 24% tumour control rate in patients asymptomatic from brain metastases, and a 10% control rate in symptomatic patients on steroid therapy. The survival of patients with limited brain metastases on ipilimumab was similar to that of patients who did not have CNS disease [87]. In addition, occasional long-term responses have been observed with ipilimumab [88]. Dabrafenib, a small-molecule BRAF inhibitor, has shown efficacy in melanoma containing a *BRAF* mutation; in a phase II trial, among melanoma containing the *BRAF* V600E mutation, an intracranial response was demonstrated in 39% of patients who had not previously undergone treatment for brain metastasis, and in 31% of patients who had progressive brain metastases after local treatment [89]. Even with bulky disease, BRAF inhibitors can rapidly improve symptoms and control intracranial disease, although the response is generally short-lived. Investigations are ongoing into the optimal strategies for combining and incorporating these agents into management plans, as well as into other strategies.

4. Illustrative cases for evolving clinical considerations in brain metastases

Continued improvement in managing primary and systemic malignancy combined with greater sensitivity in detection of intracranial dissemination has increased the clinical burden of cerebral metastases. However, advances in therapy including refined surgical techniques and operative adjuncts, stereotactic radiation, and targeted systemic agents have shifted the goals of management from symptom palliation and modest survival increase to potentially long-term maintenance of neurologic function, cognitive independence, and quality of life. While progress is being made on many fronts, the array of treatment options also leads to many new areas of uncertainty. The cases below highlight some of the challenges currently faced by clinicians caring for patients with brain metastases.

Case 1: Whole-brain radiotherapy and neurotoxicity

A 47-year-old man develops headaches and clumsiness of his left arm. He has no significant medical history and is employed as an accountant. MRI of the brain demonstrates
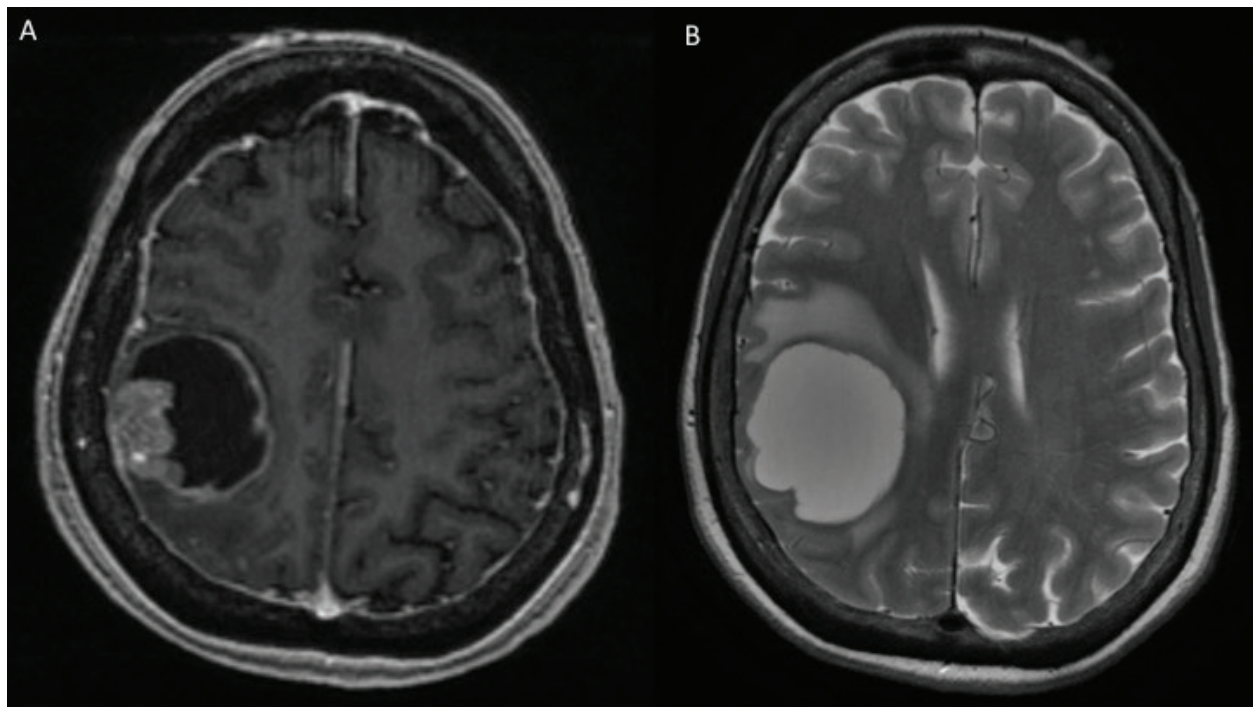
Figure 1. Pre-treatment (A) T1 with gadolinium contrast and (B) T2 MRI at initial presentation, showing a single large right-sided mass with oedema and mass effect.

a right frontoparietal enhancing 3 cm mass with associated cyst, with surrounding vaso-genic oedema (Figure 1A and B). CT scan of the body reveals a pulmonary nodule but no other lesions. Due to the neurologic symptoms, he undergoes craniotomy, and the intra-cerebral lesion is metastatic adenocarcinoma consistent with lung primary. He makes satisfactory recovery from surgery with improvement of neurologic function. He wishes to receive aggressive treatment for the brain metastasis but hopes to continue working as long as possible.

Randomised controlled trial data indicate that intracranial recurrence following surgical resection of a metastasis can be as high as 70%. This same study showed that adjuvant whole-brain radiotherapy (WBRT) following surgery improves local control and decreases distant intracranial recurrence as well as neurologic mortality. Overall survival is unchanged [42]. Adjuvant WBRT following surgery is therefore recommended as a standard of management. However, many patients and physicians are increasingly concerned about the neurocognitive sequelae of WBRT, and some may wish to defer adjuvant WBRT in a patient with favourable prognostic factors (e.g. oligo-metastatic brain disease, good functional status, limited systemic disease) [27]. Retrospective studies report local control rates for SRS given to the tumour bed of a resected lesion that are comparable to post-operative WBRT [45, 46]. Patients must be counselled that intracranial progression also carries risk of neurocognitive deterioration.

In this case, SRS to the resection cavity would improve the rate of local control while sparing the neurocognitive adverse effects of whole-brain radiation. This patient requires close monitoring for the development particularly of new intracranial lesions.

Case 2: Local treatment of multiple metastases

A 52-year-old man presents with a 2-week history of word-finding difficulties and right leg weakness. He has a history of non-small cell lung cancer (NSCLC), negative for driver mutations, stage II at diagnosis, and treated 2 years prior. Four months ago, he received treatment for a single pulmonary metastasis, and on cytotoxic chemotherapy has demonstrated no recurrence. At this time, MRI of the brain shows two enhancing masses, a 3-cm medial left frontal lesion and a 3.5-cm left temporal tumour. The lesions are associated with extensive vasogenic oedema, and early uncal herniation is visible (Figure 2A and B).

Stereotactic radiosurgery is an acceptable first-line treatment for a limited number of cerebral metastases in patients with good function and controlled systemic disease. However, SRS does not reduce mass effect and may transiently worsen oedema, leading to increased neurologic deficits.

Symptomatic mass effect is rapidly and effectively decreased with surgical tumour excision, but patients with multiple cerebral metastases are generally expected to have a short survival, so are considered poor candidates for surgery. Only retrospective series are available to address the issue, and the data are unclear as to whether the number of lesions or the total volume has a greater impact on outcome. Nevertheless, consideration of surgery may be made
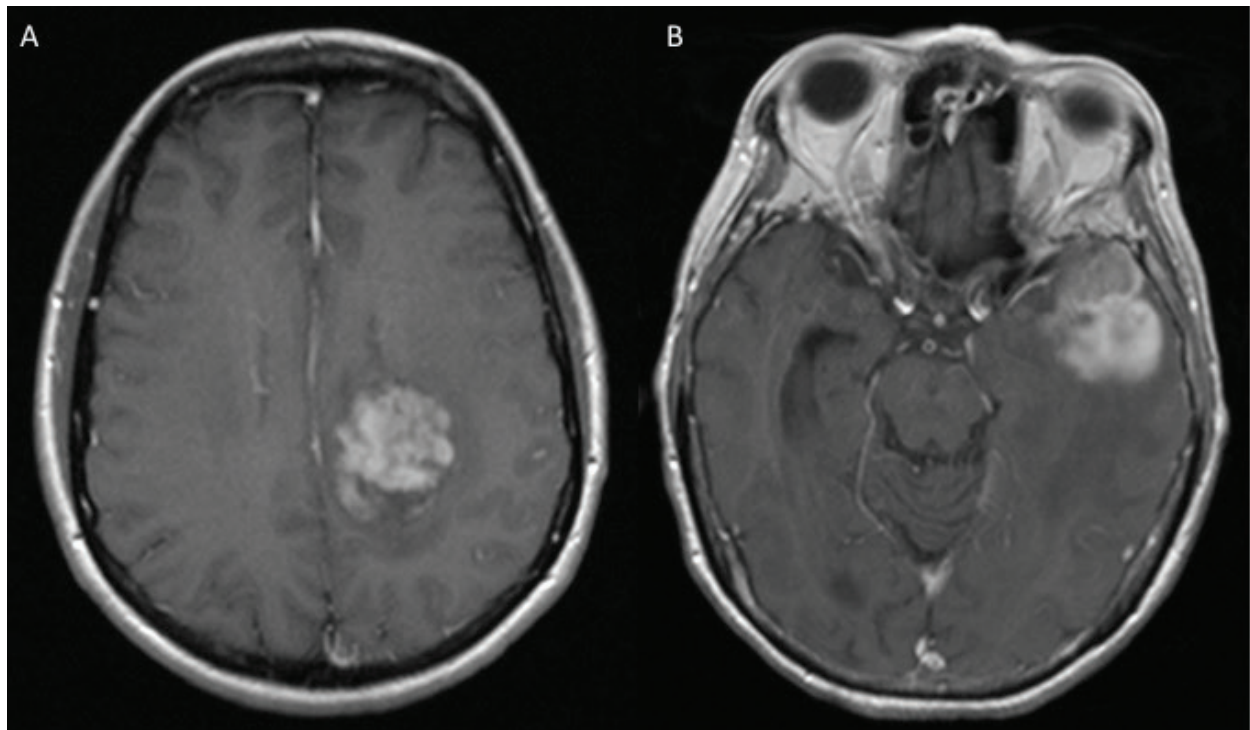

Figure 2. (A) and (B) Presenting T1 gadolinium contrast-enhanced MRI showing large left frontal and temporal lesions with oedema and mass effect.

for a large, symptomatic lesion among multiple, or for a lesion in a high-risk location for mass effect such as the cerebellum or temporal lobe.

Treatment decisions must consider the whole patient and consider the systemic context of their disease. At times, a decision is made on a case-by-case basis with discussion between the multidisciplinary management team and the patient. In this case, whole-brain radiation may be favoured, although surgical resection of the symptomatic lesion may be considered for rapid relief of mass effect.

Case 3: WBRT: alone, adjuvant or not at all

A 63-year-old woman presents to the emergency department with new-onset generalised seizure. She had a neck melanoma treated with local excision 2 years prior. Antiepileptic medication controls the seizures, and she has a normal neurologic exam. MRI of the brain demonstrates four enhancing cerebral lesions as well as two cerebellar lesions (Figure 3A and B). CT and PET scan of the body demonstrate no other lesions.

WBRT has traditionally been the mainstay of treatment for multiple cerebral metastases, as it provided a modest survival benefit to patients with a poor prognosis and few options [25]. However, improved treatment of primary and metastatic malignancy has altered the prognosis for many patients, and better strategies to control intracranial progression as well as reduce the neurotoxicity of WBRT have been sought. This is particularly true for metastatic melanoma, a disease with very poor prognosis that is also relatively radio-resistant. In patients with a limited number of brain metastases (≤4), randomised controlled trials
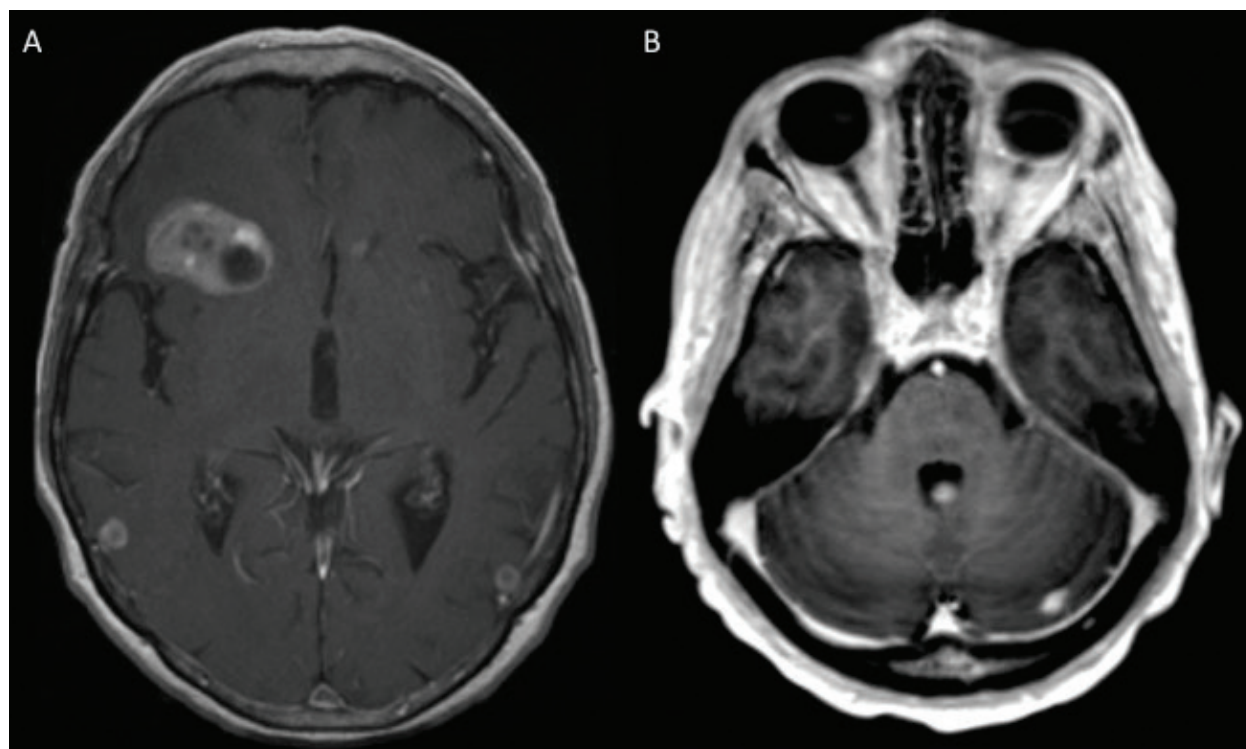

Figure 3. (A) and (B) Presenting T1 with gadolinium contrast MRI showing multiple enhancing cerebral lesions.

have demonstrated that addition of an SRS boost to WBRT improves local control compared to WBRT alone [51, 52]. More recently, a prospective series showed that multiple (2–10) tumours can be controlled with SRS alone, with no greater local or distant recurrence in patients with 5–10 lesions compared to 2–4 lesions [62]. Several randomised controlled trials have also shown that adjuvant WBRT following SRS compared to SRS alone decreases the rate of intracranial relapse at local and distant sites, although overall survival is not affected [90].

For some histologies, systemic treatment may be considered as an upfront treatment or as adjuvant to a local modality. In a phase II study, ipilimumab immunotherapy demonstrated effect against metastatic melanoma with intracranial involvement [87]. A retrospective study showed no difference in survival among patients with metastatic melanoma with or without intracranial involvement when treated with systemic ipilimumab [88]. Randomised controlled trial data are not yet available to directly compare the efficacy of WBRT with systemic therapies.

In this case, WBRT remains an acceptable treatment, although first-line SRS with close imaging follow-up may also be considered. Where available, immunotherapy may be offered.

Case 4: Radiation necrosis detection and management

A 56-year-old woman is referred for management of intracranial metastases identified on surveillance imaging (Figure 4A). She had HER2-positive breast cancer treated with mastectomy, and has been on trastuzumab therapy for 10 months with satisfactory control of primary disease and no evidence of systemic metastasis. MRI of the brain shows two small lesions, and she receives SRS (21 Gy to each of the two lesions in a single fraction) and a course of WBRT (20 Gy in 10 fractions). Follow-up imaging demonstrates that the lesions have decreased in size, and no new lesions have developed (Figure 4B). Ten months after treatment, the patient begins experiencing morning headaches. On MRI, the lesions have expanded in size with more avid enhancement and are associated with increased oedema (Figure 4C and D).

Radiographic progression of lesions treated with SRS may be evidence of tumour progression or of treatment effect (i.e. radiation necrosis). Imaging modalities used to distinguish between these entities include CT-PET, MR spectroscopy, MR diffusion, and MR perfusion. However, none of these techniques are yet definitive and clinical judgement and close imaging surveillance are indicated [91]. Radiation necrosis may occur in up to 50% of brain metastases treated with SRS [92–95], the risk increasing with larger target volume and fraction dose [92, 96]. Changes may become evident on imaging 3 months to 3 years following treatment, with a peak around 11 months. Pathological features include thrombosis and haemorrhage, fibrinous exudates and vascular fibrosis/hyalinization with luminal stenosis and occlusion. Congealed, fibrin-rich areas of gliosis contain dystrophic calcifications and macrophage infiltration. Excess extracellular proteolysis promotes cytokine activation and cytotoxic oedema, and other immune-mediated mechanisms may contribute to radiation-induced neurotoxicity [97].
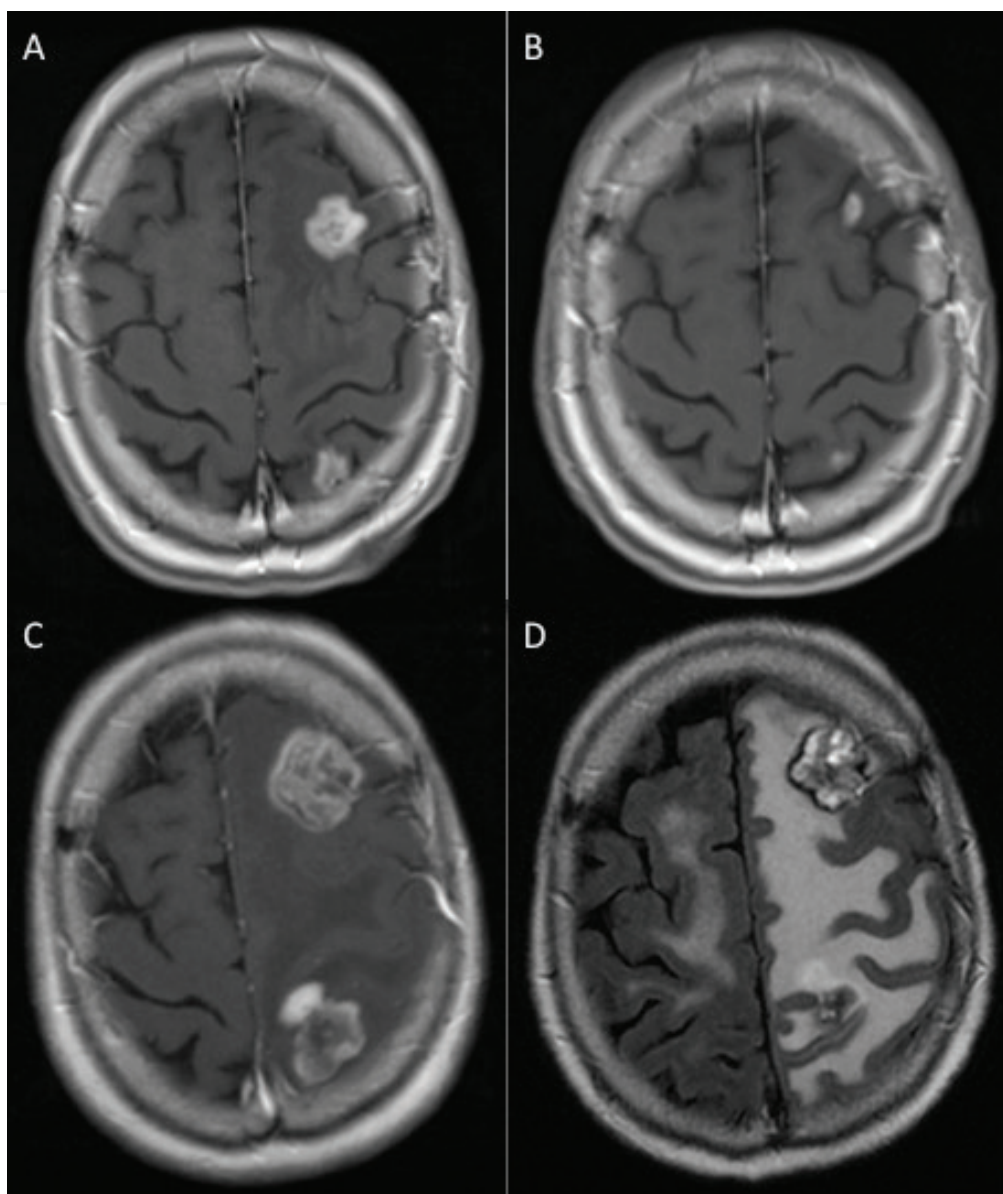
Figure 4. (A) Pre-treatment gadolinium contrast-enhanced T1 MRI showing two left-sided metastases. (B) Gadolinium contrast-enhanced T1 MRI showing decrease in lesion size after treatment. (C) T1 gadolinium contrast-enhanced and (D) T2 MRI 10 months after treatment, showing increase in enhancing lesion size and peri-lesional oedema.

The mainstay of treatment for symptomatic radiation necrosis is corticosteroids continued at the lowest effective dose until symptoms resolve [98]. In patients who develop adverse effects or are unable to tolerate corticosteroids, a small randomised placebo-controlled trial and some retrospective studies have shown that bevacizumab can be effective in reducing cerebral oedema and neurologic symptoms associated with radiation necrosis, as well as FLAIR and enhancement changes seen on MRI [99, 100]. While bevacizumab can markedly improve symptoms and imaging, adverse effects may include intracranial haemorrhage and wound healing complications should surgery become necessary, and careful patient selection is necessary [101]. In addition, several case reports and small series have suggested that

hyperbaric oxygen (HBO) can also have a role in treatment of intracerebral radiation necrosis, with improvement in neurologic symptoms, decreased steroid requirement and reduced lesion size on imaging [102, 103].

Surgical resection should be considered in patients refractory or intolerant to corticosteroids, if the radiation necrosis has significant mass effect, or if imaging is equivocal and tumour progression remains a concern. If a lesion is not safely accessible, a biopsy may be considered to rule out active disease.

In this case, oedema causing mass effect and headaches can be treated with corticosteroids. As the diagnosis is uncertain, repeat imaging and clinical follow-up should be carried out in a short interval.

Case 5: Molecular profiling and targeted therapy

A 63-year-old man presents to the emergency department for evaluation following a motor vehicle collision. A single 6-mm lesion is identified in the right posterior midbrain, which demonstrates ring-enhancement on MRI (Figure 5). The patient's past medical history is significant for melanoma treated with surgical excision 15 years prior.

In a patient who has undergone treatment for a cancer with a propensity for intracranial dissemination, a new brain lesion may be a metastatic deposit. However, in patients with a known primary malignancy, 11% may have a solitary brain lesion that is not metastatic [33]. Current imaging modalities have greatly improved the specificity of distinguishing brain metastases from primary tumours and other pathologies [104–106], but diagnostic certainty is essential to appropriate treatment planning and prognostication. In addition, some primary histologies include molecular subtypes that can benefit from targeted therapy, and patients who underwent diagnosis and treatment prior to the routine molecular profiling of such tumours may yet benefit from updated pathological analysis.

In melanoma containing the *BRAF* V600E mutation, the BRAF inhibitors dabrafenib [89] and vemurafenib [107] have demonstrated effect against brain metastases. The receptor tyrosine kinase inhibitors erlotinib and gefitinib show effect in NSCLC with an EGFR mutation [76], and crizotinib has shown some activity against NSCLC containing *ALK* rearrangement [79]. Furthermore, an alteration in oestrogen receptor (ER), progesterone receptor (PR) and HER2 expression between primary and metastatic deposits is observed in >10% of breast cancers, requiring an alteration in management [108]. In patients who have HER2-postive tumours, a phase II trial demonstrated a 66% rate of objective CNS response for the combination of lapatinib and capecitabine [86].

In this case, the long latency period since the patient's initial cancer presentation warrants histologic diagnosis of the cerebral lesion. In a deep location, needle biopsy would allow for safe extraction of diagnostic tissue.

Case 6: Prognostic considerations

A 78-year-old man who resides in a nursing home due to memory impairment undergoes evaluation for recurrent falls. MRI of the brain demonstrates atrophy and white matter
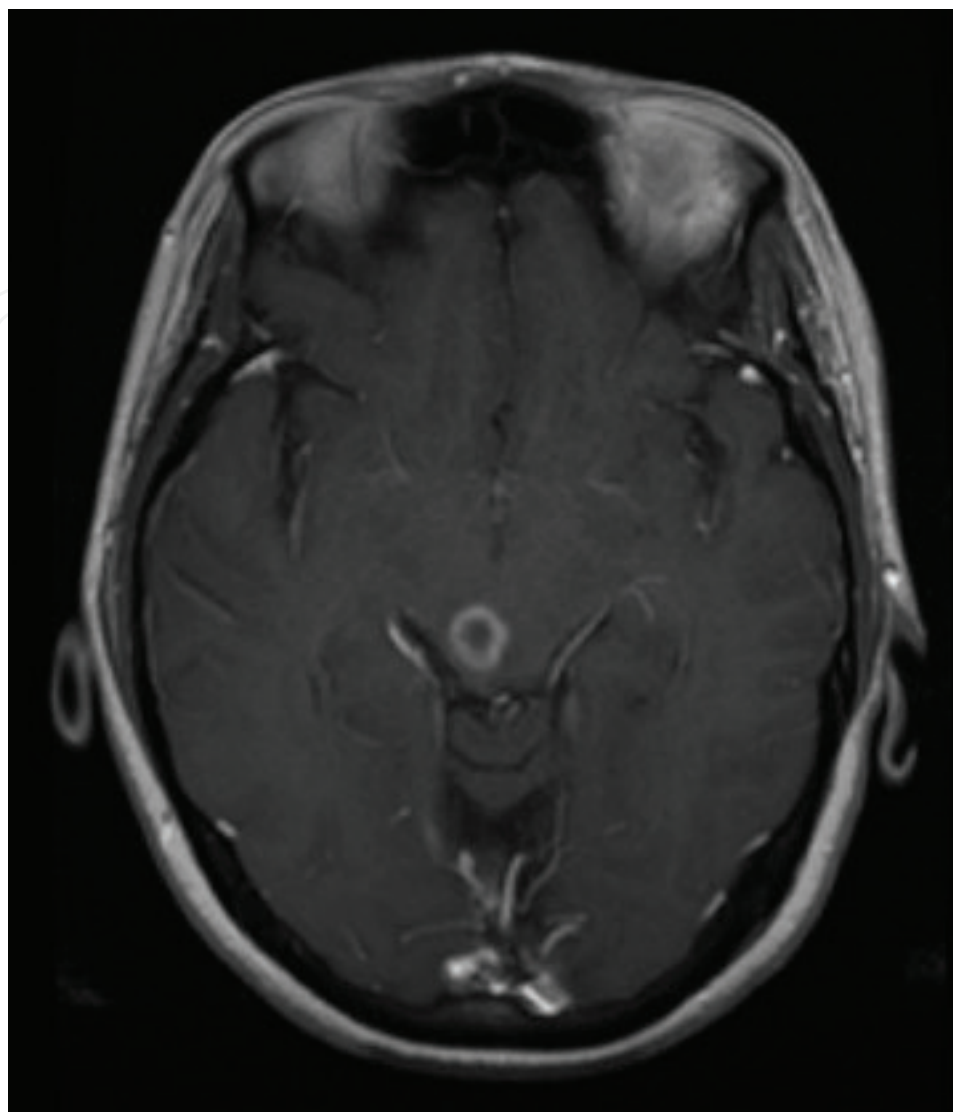
Figure 5. Gadolinium contrast-enhanced T1 MRI of incidentally found midbrain lesion.

changes as well as numerous enhancing lesions suggestive of metastatic deposits (Figure 6). Systemic work-up reveals a rectal mass, as well as extensive retroperitoneal lymphadenopathy and a hepatic lesion, consistent with metastatic colorectal carcinoma.

The RTOG recursive partitioning analysis (RPA) identified Karnofsky performance status (KPS) as a key prognostic factor in patients with brain metastases [18]. The diagnosis-specific graded prognostic assessment found that certain RPA factors were not significant for some primary histologies, but KPS retained significance in all diagnoses [109]. In a patient with poor functional status, aggressive treatment of brain metastases is not indicated due to a short expected survival. WBRT may be offered to palliate neurological symptoms caused by intracerebral lesions and associated oedema. A radiographic response is seen in 40–60% of patients, with neurologic improvement in 25–40% [25, 52]. Observational studies suggest
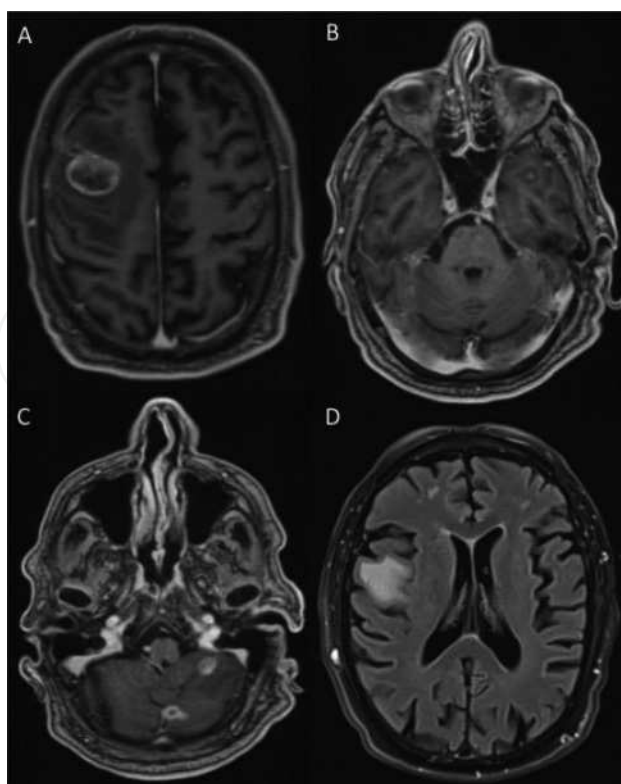
Figure 6. (A)–(C) T1 gadolinium contrast-enhanced MRI demonstrating cerebral atrophy and multiple metastases. (D) FLAIR sequence showing white-matter changes distinct from enhancing lesions.

an improvement in survival compared to corticosteroids/supportive therapy [110, 111]. However, radiotherapy requires daily treatment sessions for 10–15 days, and acute radiation toxicity may cause fatigue, nausea, vomiting, anorexia, alopecia, and radiation dermatitis [112]. Where numerous repeat treatments are not feasible, a single fraction of 6–8 Gy may be considered, accepting a lower rate of tumour control and possibly greater acute toxicity. Alternatively, in patients with poor medical and/or functional status, supportive care alone may be the most appropriate management.

In this case, without focal neurologic deficits, limited intervention with a focus on patient comfort is a reasonable approach.

5. Conclusion

The brain is a common site of progression for patients with cancer, and brain metastases are associated with significant morbidity and mortality. Many modalities of treatment are available aimed at controlling neurologic progression and overall survival, as well as palliating symptoms. A thoroughly multidisciplinary approach is therefore required for comprehensive and effective management of brain metastases.

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