

# Evolution of Multidisciplinary Brain Metastasis Management: Case Study and Literature Review

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Up to 40 percent of all cancer patients develop brain metastasis (BM†) during the course of their disease. Despite advances in diagnosis and therapy, prognosis in patients with BM remains poor for many patients, but for some, survival can be of the order of several years in duration. Difficulty in predicting long-term survivors has created controversy in contemporary management of BM. Minimizing medical and neurocognitive side effects (disease borne or iatrogenic) to enhance functional independence and improving overall quality of life in these individuals requires a coordinated approach of first-line and salvage surgical, chemotherapeutic (cytotoxic, targeted, or immune based), and radiation (whole brain radiotherapy or stereotactic radiosurgery) modalities. This goal needs to be balanced against the more traditional targets of management such as symptom relief, reducing tumor burden, and local tumor control, thereby increasing progression-free survival. This case study and literature review demonstrates the role of various treatment modalities in the management of BM.

## INTRODUCTION/CASE PRESENTATION

We present a 53-year-old female smoker initially diagnosed with non-small cell lung cancer (NSCLC) in October 2007. She presented with left flank pain; a computerized tomography (CT) scan of her abdomen revealed a 7 cm adrenal mass (Figure 1a), while a PET scan revealed a right sided intra-pulmonary lesion (Figure 1b). Following adrenalectomy, histopathology revealed an epidermal growth factor receptor (EGFR) negative adenocarcinoma of NSCLC origin. Other molecular markers such as K-ras, alk, and fibroblast growth factor receptor (FGFR) were not available at the time of diagnosis. Magnetic resonance imaging (MRI) screening was positive for three asymptomatic BrMets (Figure 2a-c), and she was treated with whole brain radiotherapy (WBRT) to 37.5 Gy in 2.5Gy fractions in November

2007. Using the Diagnostic Specific Graded Prognostic Assessment (DS-GPA), expected estimated survival would be 6.5 months (age 50-59, KPS 100, >3 brain metastases and extracranial metastasis present).

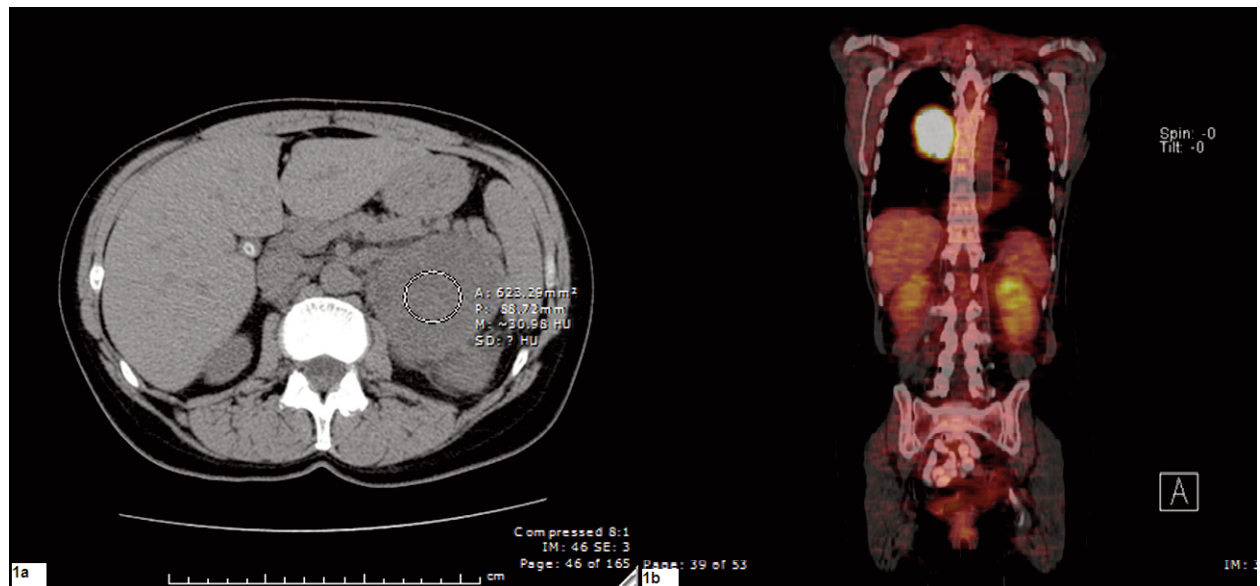
The patient subsequently received three different regimens of systemic chemotherapy including docetaxel, carboplatin with docetaxel and gemcitabine, as well as 50 Gy external beam radiation to the primary tumor in her right lung. In March 2008 (5 months after BM diagnosis), her follow-up imaging demonstrated good systemic clinical response (Figure 2d-f).

In November 2009 (25 months after initial BM diagnosis), the patient reported changes in her vision, and imaging revealed new brain metastases (BrMets). She was treated with stereotactic radiosurgery (SRS) and prescribed 20 Gy to the 50 percent isodose surface to all three lesions (Figure 3a-c).

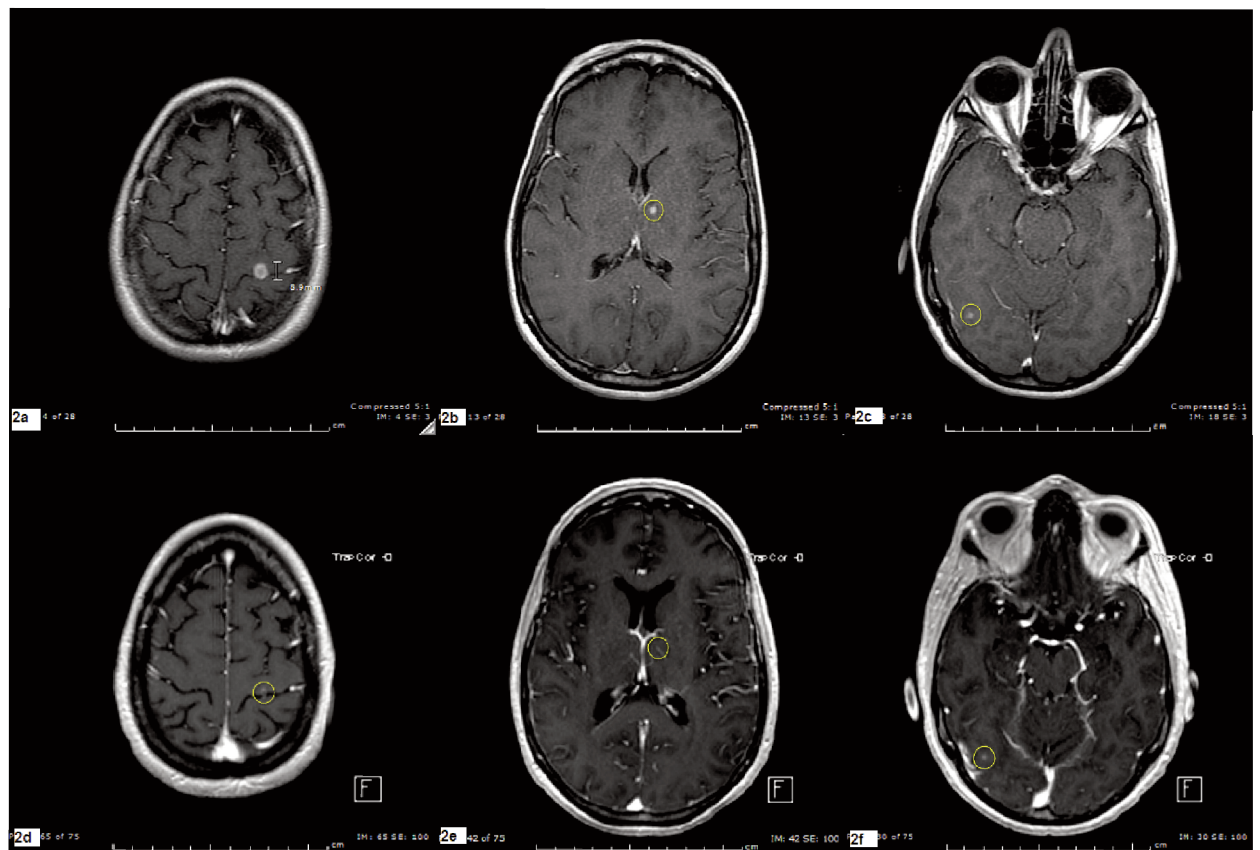
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†Abbreviations: BM, brain metastasis; BrMets, brain metastases; CT, computerized tomography; DS-GPA, Diagnostic Specific Graded Prognostic Assessment; GI, gastrointestinal; GKSRS, Gamma Knife Stereotactic Radiosurgery; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; RCC, renal cell carcinoma; SCLC, small cell lung cancer; RN, radiation necrosis; SR, surgical resection; WBRT, whole brain radiotherapy; BBB, blood-brain barrier; RPA, Recursive Partitioning Analysis; TMZ, temozolomide; TKIs, tyrosine kinase inhibitors; MRS, MR spectroscopy; DWI, diffusion weighted imaging; MRP, MR perfusion; EGFR, epidermal growth factor receptor; FDG-PET, fluoro-deoxyglucose positron emission technology; CNS, central nervous system; SPECT, single positron emission computer tomography.

Keywords: brain metastasis, chemotherapy, cytotoxic chemotherapy, immunotherapy, neurosurgery, stereotactic radiosurgery, whole brain radiotherapy



**Figure 1.** October 2007: a) Abdominal MRI demonstrating 7 cm adrenal mass. b) PET scan demonstrating right-sided intrapulmonary lesion.

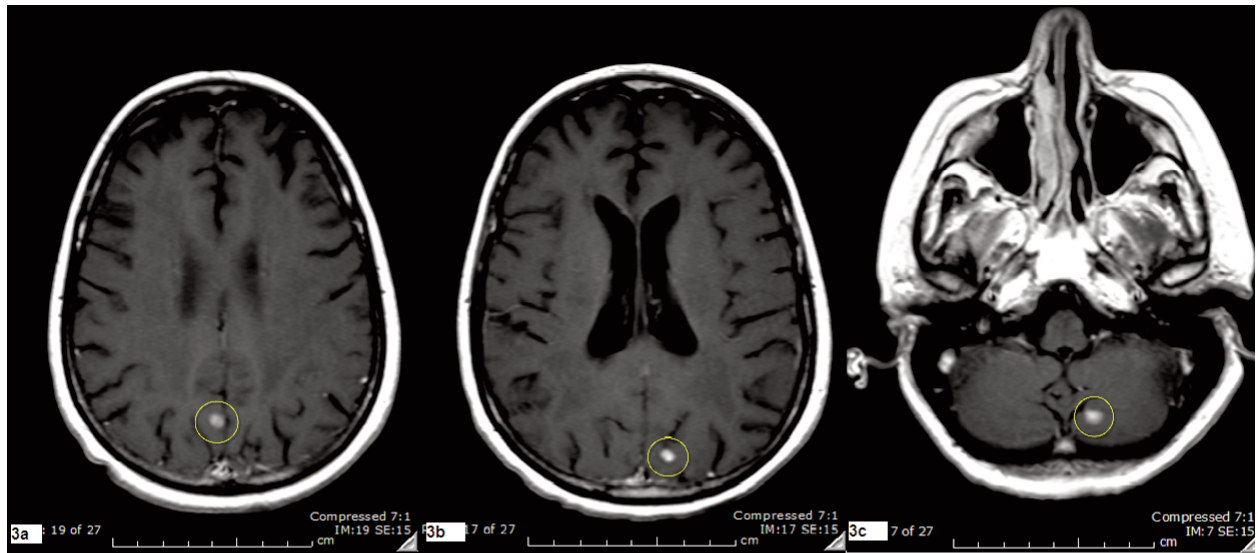


**Figure 2.** MRI of initial intracranial metastases. Images a, b, and c are from October 2007, pre-WBRT. Images d, e, and f are from March 2008, post-WBRT. Yellow circle denotes individual intracranial lesions. After WBRT, the lesions in d-f have decreased as compared to initial presentation, demonstrating good response.

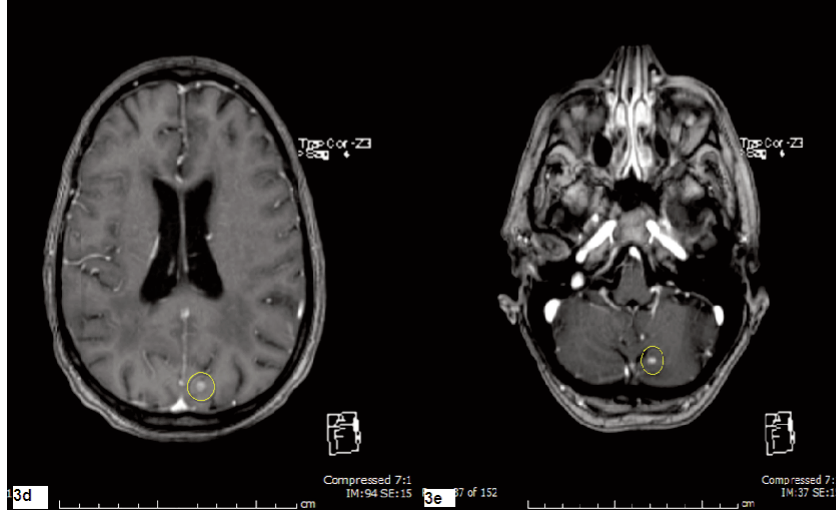
Systemic chemotherapy was discontinued in February 2010, and imaging in November 2010 showed stable systemic disease (Figure 3d,e).

In November 2011 (4 years after the original BrMets diagnosis and completion of WBRT and 2 years after radiosurgery), two new BrMets were seen on surveillance

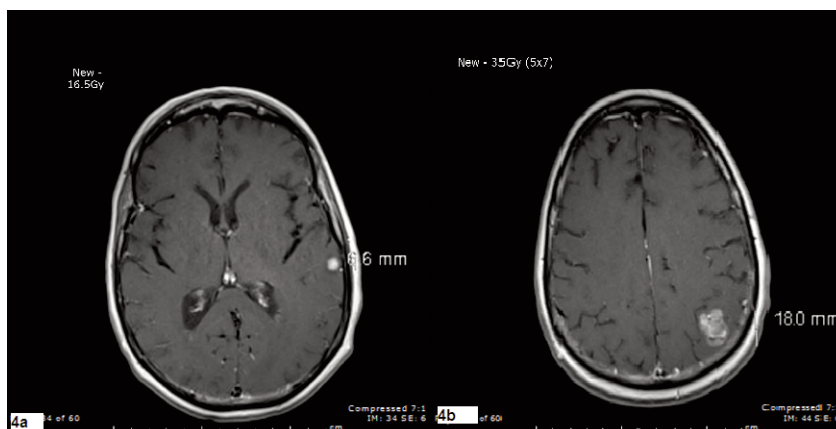
imaging (Figure 4). She received further SRS to two new lesions (35Gy to the 80 percent isodose line in five fractions to a left parietal lesion and 16.5Gy to the 80 percent isodose surface in a single fraction to a left temporal lesion). In addition, due to some concern for possible regrowth/persistence of tumor following prior SRS, two



**Figure 3.** MRI of new BrMets in bilateral occipital lobes and within the cerebellum. Images a, b, and c are from November 2009, pre-GKSRS. Images d and e are from November 2010, post-GKSRS. After GKSRS, the lesions in d and e decreased in size, demonstrating good response.



**Figure 4.** November 2011: MRI of 2 new intracranial lesions. a) left temporal lesions; and b) left parietal lesion. These new lesions later were treated with CyberKnife, and systemic therapy was reinitiated.

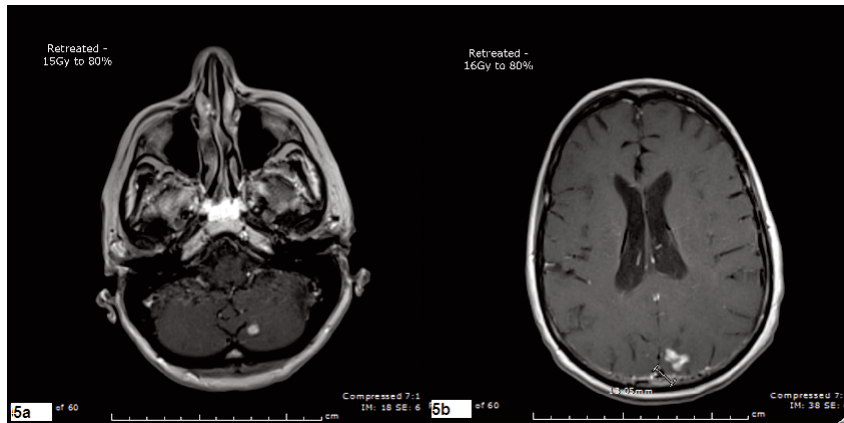


lesions were retreated (15Gy to the 80 percent isodose surface to the cerebellar lesion and 16Gy to the 80 percent isodose surface to the left occipital lesion [Figure 5]). Additionally, chemotherapy was restarted.

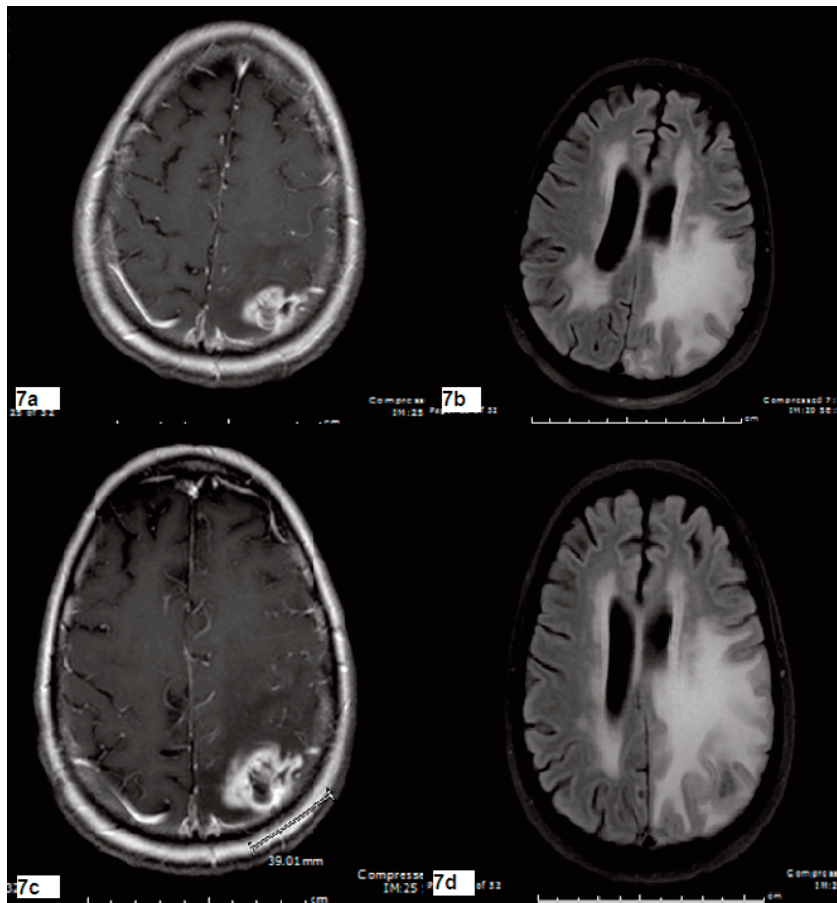
Follow-up MRI in June 2012 demonstrated regrowth in the size of the left cerebellar lesion that had been treated twice with SRS (Figure 6) and stability in the left temporal, parietal, and occipital lesions. Given the two previous SRS treatments, the growth in the cerebellar lesion was

most likely to be consistent with radiation necrosis, and it was observed with serial imaging.

In November 2012, she presented with right hemiparesis and hemisensory seizures. MRI revealed regrowth of the left parietal lesion (Figure 7a-d). FDG-PET scan of the brain was performed (Figure 8a) and showed a decreased uptake in the cerebellar lesion, confirming suspected radiation necrosis, but an increased uptake in the parietal lesion, which was concerning for tumor regrowth.



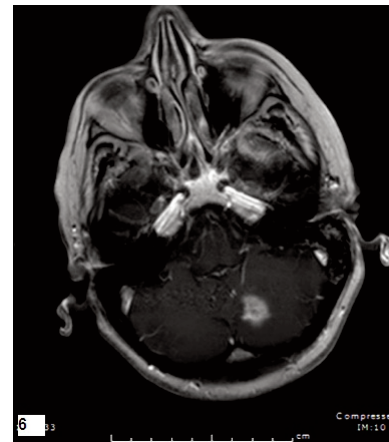
**Figure 5.** November 2011: MRI of 2 previous lesions. a) left cerebellar lesion and b) left occipital lesion. Both of these lesions were later retreated with CyberKnife, and systemic therapy was reinitiated.



**Figure 7.** a,c) T1 weighted MRI; b,d) corresponding FLAIR MRI. a,b) Images from November 2012 of symptomatic left parietal lesion; c,d) images from January 2013, which demonstrate that the left parietal lesion is not responding to steroids and conservative management.

Having failed conservative management, she was taken to the operating room, and the left parietal lesion was resected. Histopathology was consistent with re-growing tumor.

Brain MRI in May 2013 (6 months post-operative) demonstrated good resolution of the left parietal lesion (Figure 8b), but regrowth of the previously treated left temporal lesion (single treatment 16.5Gy) again resulted in seizures,



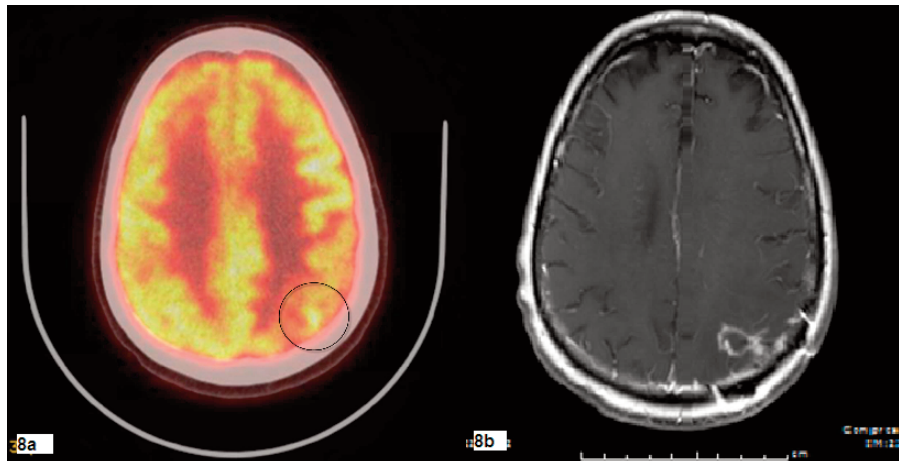
**Figure 6.** June 2012: Radiation changes noted in the left cerebellar lesion, which was treated twice with radiosurgery. Minimal changes noted in remaining three lesions.

dysphasia, and recurrent right hemiparesis (Figure 9a,b). The patient was taken back to the operating room for removal of the left temporal lesion, and again pathology was consistent with regrowing metastatic NSCLC. She was then started on bevacizumab and irinotecan. The patient's systemic chemotherapy was discontinued in February 2014 (6 months after re-initiation) due to side effects. Her last follow-up was in August 2014, 6.5 years after initial BrMets diagnosis (Figure 9c). All of her brain lesions remain stable at this time. She lives independently without focal neurological deficits, and her disease remains radiographically controlled. This educational case report describes the shift in management of brain metastases from traditional best supportive care to ongoing survivorship and the challenges posed as new treatments for managing brain metastases emerge.

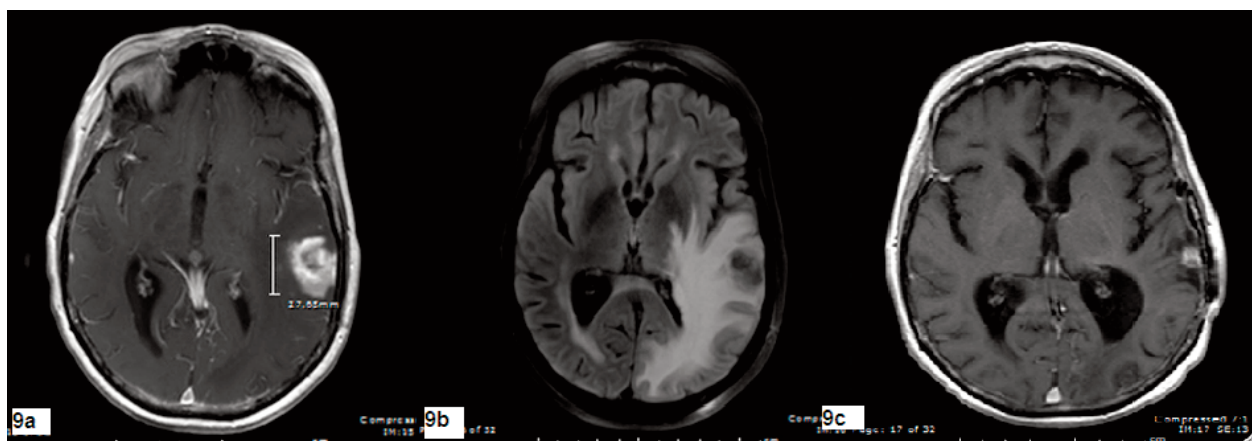
## TEACHING METHOD PRESENTATION

### Epidemiology

Up to 40 percent of cancer patients with metastases will develop BrMets [1], which translates to 200,000 new cases each year in the United States [2], 10 times more than primary brain tumors [3]. Factors contributing to increasing incidence of BrMets include improvement in both screening imaging modalities and systemic therapies for extracranial disease, resulting in longer survival in patients after initial diagnosis.



**Figure 8.** a) March 2013: PET scan of left parietal lesion consistent with regrowing tumor. Patient underwent SRS of the mass in June 2013. b) May 2013: T1 weighted MRI showing good resolution of left parietal lesion post SRS.



**Figure 9.** a,b) T1 weighted MRI with corresponding FLAIR from May 2013 demonstrating enlarging left temporal lesion; c) follow-up T1 weighted MRI from August 2014 after previous SRS for left temporal lesion and reinitiation of systemic therapy. Imaging revealed good resolution of left temporal lesion.

Nevertheless, the diagnosis of BrMets still portends a poor prognosis with life expectancy of untreated BrMets of 1 to 2 months, while median survival with aggressive treatment is still only 6 to 8 months [4].

Lung cancer is the most common presenting histology (30 to 60 percent of BrMets), while 40 percent of NSCLC patients will develop BrMets [5]. Other common primary histologies include breast carcinoma (15 to 25 percent) and malignant melanoma (5 to 20 percent) [6], while BrMets are uncommon with hepatocellular, ovarian, and prostate carcinomas [7].

While certain histologies such as RCC and GI may present as solitary BrMets [8], 80 percent of BrMets patients will have multifocal disease [9] similar to our patient. Eighty percent of BrMets are found in the cerebral hemispheres, 15 percent in the cerebellum, and 5 percent in the brainstem [10]. Of these, 10 to 15 percent will be in deep-seated regions of the CNS, ultimately precluding microsurgical access [11].

#### *Pathophysiology of Metastases*

Ongoing research has focused on the genetics and epigenetics of BrMets. Numerous hypotheses have been published to explain the mechanism of metastasis, in-

cluding the seed/soil, mechanical, epithelial-mesenchymal transition, and cancer stem cell hypotheses [12].

Despite the traditional understanding of local invasion progressing to metastasis, recent evidence demonstrates parallel progression of primary and metastatic disease, with circulating tumor cells detected in early stage patients [13]. In addition, the understanding of the interplay between metastatic cancer and the brain milieu is constantly evolving. Metastatic cells have to overcome the blood-brain barrier (BBB) and utilize the brain's nutrient resources and signaling pathways in order to survive and thrive. While much is not yet understood, evidence suggests that cytokines produced by cancer cells such as CXCL1, CCL12, COX-2, and HB-EGF are involved in BBB passage. Once across the BBB, metastatic cells can overexpress BRMETSP-2, which causes transition of neural stem cells into astrocytes and possible up-regulation of their tumor survival genes. These astrocytes then, through cytokine release, may protect the early survival of micrometastases [13,14,15].

#### *Symptomology*

The clinical presentations of BrMets can be either due to lesional growth causing raised intracranial pressure or

focal symptoms arising from compromised cerebral function due to hemorrhage, mass effect, or focal electrical disturbance. Presenting symptoms classically included headache (40 percent), motor weakness (25 percent), seizures (15 percent), and non-specific mental status changes (10 to 15 percent) [16]. More recently, however, due to an increasing use of screening and surveillance brain MRIs, the majority of patients now are more likely to be asymptomatic at presentation, as in our patient, or present with seizures rather than symptoms of mass effect.

### *Screening and Surveillance Imaging for BrMets in NSCLC*

Detection of BrMets before the development of symptoms by screening and surveillance imaging of the brain allows for prophylactic treatment. Earnest found occult brain metastases in 17 percent of patients initially thought to have localized NSCLC [17], and in a study of 177 patients with stage IIIA NSCLC, 34 percent had cancer recur in the brain as the first site of failure [18]. Despite the high probability of BrMets developing in patients with lung cancer, however, no standardized guidelines exist with regard to screening or surveillance imaging in this group of patients.

### *Prognosis*

Prior to the Patchell study in 1990 [19], it was believed that chemotherapy and surgery played almost no role in the treatment of BrMets, and therefore, whole brain radiation therapy (WBRT) became the cornerstone of treatment.

To aid in decision-making between aggressive versus palliative therapy, the Recursive Partitioning Analysis (RPA) was developed, grouping patients into one of three classes defined by age, KPS score, and control of extracranial disease [20]. Median overall survival after WBRT was estimated at 2.3 months for Class III patients, 4.2 months for Class II, and 7.1 months for Class I. RPA classification, however, is limited by the fact that 85 percent of patients fall into the Class II category. The newer Diagnosis-Specific Graded Prognostic Assessment Index (DS-GPA) better accounts for other prognostic factors, including primary tumor type and number of metastases [21]. The DS-GPA shows possible median survival for NSCLC patients ranging from 3 to 15 months, although our patient survived more than 6 years beyond her expected 6.5 month predicted survival. One limitation of the DS-GPA is that it does not account for the mutational status of some lung cancers. It is now known that NSCLC with EGFR or Alk mutations can expect increased response to treatment [22].

### *Use of Whole Brain Radiation Therapy*

WBRT emerged in the 1960s as a treatment for BrMets and by the 1970s was demonstrated to be effective in controlling intracranial progression, improving neurological function, and increasing overall survival [23,24].

WBRT has the advantage of being able to control visible tumor as well as decreasing distant intracranial recurrence by controlling possibly yet unseen micrometastases. The most widely used schedule for WBRT is 30Gy in 10x3Gy fractions, since studies have failed to show significant differences in treatment outcome based on changing dosage, fractionation, or timing [25]. With longer survival rates following WBRT, however, its neuro-cognitive side effects have become of increasing concern and are being addressed by ongoing trials such as RTOG 09-33 (a hippocampal sparing WBRT trial) and research into the concomitant administration of the agent memantine with WBRT [26,27].

### *Chemotherapy for BrMets*

Systemic chemotherapy remains a mainstay in cancer treatment, employed as either adjuvant or neoadjuvant therapy. There are three main categories of systemic chemotherapies: cytotoxic, targeted, and immune based.

Cytotoxic chemotherapy traditionally has not played a crucial role in BrMets, as it was believed to have limited bioavailability secondary to the highly selective BBB. Even in the presence of a theoretically disrupted BBB, drug accumulation in brain tumors can be limited [28]. Some drugs, including temozolomide (TMZ), etoposide, methotrexate, cisplatin, and irinotecan, have been shown to cross the BBB at an effective dose. Potentially synergistic effects, however, can exist between chemotherapy and radiotherapy, and understanding the appropriate timing of the delivery of each treatment option is important. Conflicting results have been reported using combination TMZ and WBRT [29,30,31,32], and, given its overall increased toxicity profile, TMZ is only used as possible salvage therapy today.

Targeted therapy involves the identification and subsequent dysregulation of crucial signaling pathways for tumor proliferation within cancer cells. The two main types of targeted chemotherapy include small molecule, less than 800 Dalton acting intracellularly, and monoclonal antibodies acting extracellularly, also known as immune-based therapy.

Ten to 25 percent of NSCLC patients have activating EGFR mutations. EGFR-specific tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib are small molecules that have been shown to have a 70 percent CNS response rate in chemotherapy-naïve Asian never smokers [33]. Moreover, 4 percent of NSCLC patients have ALK rearrangement, and crizotinib, as a selective inhibitor of the activated ALK pathway, also has been demonstrated to have an objective response [34].

The long-term of efficacy of targeted chemotherapies, however, is limited by the high rate of development of resistance, resulting in an expanding role for the newer immune based therapies [35]. Ipilimumab is a monoclonal antibody against CTLA-4, a molecule that down-regulates T cell activation. Used as first-line treatment in advanced melanoma, ipilimumab potentiates an antitumor immune

response [36], improving overall survival (OS) of some patients. Ipilimumab has been shown to have activity intracranially, and it is thought that this is likely to be due to the ability of T cells to pass through the BBB [37,38]. Ipilimumab showed promising results in a first-line NSCLC phase II study that combined carboplatin/paclitaxel chemotherapy [39], although the results have not been as robust as in melanoma, and its efficacy in BrMets remains unknown. Ongoing clinical trials are studying the efficacy of anti-PD1 agents such as pembrolizumab in the treatment of NSCLC and melanoma BrMets (NCT02085070) [40], as there is increasing interest in using these agents up front, ahead of radiation, particularly in patients with widespread, small volume BrMets and a potentially long term survival outcome, in whom early WBRT might result in debilitating long-term side effects.

#### *Choice of SRS versus WBRT as First-Line Treatment for Newly Diagnosed BrMets*

Not only are large metastases and certain histologies such as melanoma, sarcoma, and RCC more resistant to WBRT, but as discussed above, more recent literature has focused on the issue of long-term neurocognitive decline [41]. Our patient received standard WBRT, and all her lesions responded well to treatment. The lack of new metastases developing in the brain 2 years after WBRT might suggest that micrometastases were treated at the time of WBRT. While neurocognitive testing was never formally performed, our patient did not notice an impact of cognitive decline on her daily living from the WBRT. Insufficient data exists in the literature today to understand the full neurocognitive impact of WBRT on long-term cancer survivors and how it impacts decision-making regarding the timing of its use during the course of the disease.

Stereotactic radiosurgery (SRS) is the method by which highly conformal ionizing radiation can be administered to tumors with a steep dose fall off so that very little radiation is delivered to the surrounding brain. Indications for SRS historically mirrored those for surgical intervention until the past decade, when it was shown that it was safe to salvage patients failing WBRT with this technique [42-45]. RTOG-9508 demonstrated that the addition of SRS to WBRT resulted in improved survival in patients with single BrMets and resulted in better lesional control and neurological recovery in patients with one to four lesions [46]. Because of these studies, SRS was established as a safe treatment for brain metastases either with or after WBRT and traditionally has been reserved for patients with one to four BrMets.

Subsequent work by Aoyama et al. has shown equivalent local lesional control rates using SRS alone without WBRT compared with WBRT+SRS. Of note, while the rate of distant failure when using SRS alone was, as expected, significantly higher than after WBRT+SRS, a distant failure rate of 40 percent was still seen at 1 year [47].

The potential advantages of SRS (over WBRT) as first-line treatment, therefore, are that 1) treatment com-

pletion can occur in a shorter time period than WBRT and 2) it is associated with less acute and chronic toxicities due to avoidance of normal brain irradiation, thus enabling less delay in initiation or resumption of chemotherapy. Use of SRS alone, however, requires more frequent surveillance imaging of the brain with MRI given its higher rate of distant failure. Studies are needed to look at cost-benefit analysis for the two approaches, especially taking CNS disease control and neurocognitive outcome into account.

At time of distant failure, SRS as salvage therapy after WBRT is a viable option in patients with good performance status and controlled systemic disease. While an increased overall toxicity might be expected from repeat WBRT as a salvage option, no studies exist directly that compare the efficacy or toxicity of salvage SRS versus salvage repeat WBRT. Equally less well-studied is the dose of radiation that should be administered as first-line versus salvage radiosurgery that results in maximal efficacy with minimal toxicity.

#### *Adverse Radiation Effects: Radiation Necrosis*

Adverse radiation effects are typically divided into acute, subacute, and late groups. With increased survivorship, the long-term complication of SRS treatment known as radiation necrosis (RN) is now being increasingly reported. First described in 1930, RN most commonly occurs after multiple courses of radiotherapy associated with increasing total dose, increasing treatment volume, and increasing dose per fraction. RN manifests within the first 3 to 12 months after high-dose brain irradiation in 80 percent of cases and estimates for the incidence of RN range from 4.9 percent to 13.3 percent [10,48-51]. More recently, the influence of systemic therapy has been brought into question. A recent retrospective study of SRS-treated BrMets at our institution demonstrated that patients receiving immunotherapy were at an increased risk of developing RN [52].

Distinguishing tumor recurrence from RN is extremely difficult. On MRI, both diagnoses are characterized as enhancing on T1 with gadolinium and associated with peri-lesional T2 FLAIR changes [53]. Other imaging techniques that have been reported to assist in differentiating tumor recurrence from RN include MR spectroscopy (MRS), diffusion weighted imaging (DWI), MR perfusion (MRP), SPECT, and PET scans, although results have been highly variable [51], and therefore biopsy is often still required to make the diagnosis.

Management of RN depends on symptomatology. If the patient remains asymptomatic, then serial imaging eventually may show spontaneous resolution. If symptomatic, first-line treatment involves corticosteroids to manage cerebral edema. Other proposed interventions have included the use of antiplatelet agents, vitamin E, anticoagulants, and hyperbaric oxygen. More recently, bevacizumab (a VEGF inhibitor) has been shown in some patients to result in clinical and radiological improvement, although it also carries its own toxicity profile [54]. Finally, surgical management, including craniotomy for re-

section or laser thermocoagulation, can be very effective for patients with single symptomatic RN lesions [55].

## DISCUSSION

This case study and literature review highlights the changing roles of the various treatment modalities involved in the management of BrMets as well as the limitations of the literature in guiding decision-making for individual patients.

Our patient was diagnosed with synchronous presentation of her primary and metastatic NSCLC. She received WBRT to treat both macrometastases and subclinical brain disease followed by chemotherapy for extracranial control. In many centers nationally, this sequence of treatment remains the standard of care. If our patient would have had limited survival, it is likely that WBRT alone would have been sufficient for BrMets control. At distant failure, our patient only had two new lesions, and SRS was possible. Technically, however, if >10 lesions were seen at time of failure, then SRS treatment would have been significantly more complex. It may therefore be worth considering using SRS for oligometastatic first-line treatment, saving WBRT for salvage.

At her second distant failure, treatment options became even more complex due to the difficulty of differentiating radiation necrosis from tumor regrowth. Because of the perceived need to treat possibly regrowing lesions, a complex radiation plan had to be created for a total of four lesions (two new and two previously treated), possibly resulting in the under-dosing of the two new lesions. Our patient, therefore, concurrently developed radiation necrosis and tumor regrowth, further complicating diagnosis and management. Fortunately, she was amenable to multiple surgical salvage procedures followed by initiation of CNS-penetrating systemic agents that allowed her to gain CNS control.

Our patient was EGFR negative, while other newer molecular markers such as K-ras and alk were not, to our knowledge, specifically tested in her case either at time of diagnosis or subsequently during her treatment course. She, therefore, did not receive the possible benefit of targeted systemic therapies or immune therapies that now play an increasing role in decision-making related to the management of BrMets. Research will be needed to understand the interaction of WBRT and/or SRS in patients undergoing treatment with these newer systemic agents, and a multidisciplinary team approach must be taken to ensure best management for cases such as our patient.

## CONCLUSIONS

Survival in cancer patients is dependent on multiple factors both intrinsic to the patient and their cancer as well as to the treatment biases of their physicians. As shown above, while there is much data to assist in determining the best management for each individual patient, there are

still many unanswered questions in the management of BrMets. Of principal importance is the need for ongoing multi-disciplinary discussion of the role of screening and surveillance imaging, the use of standard and well as newer options for initial and salvage treatment in terms of CNS disease control and functional outcome, and a better understanding of post-treatment imaging changes.

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