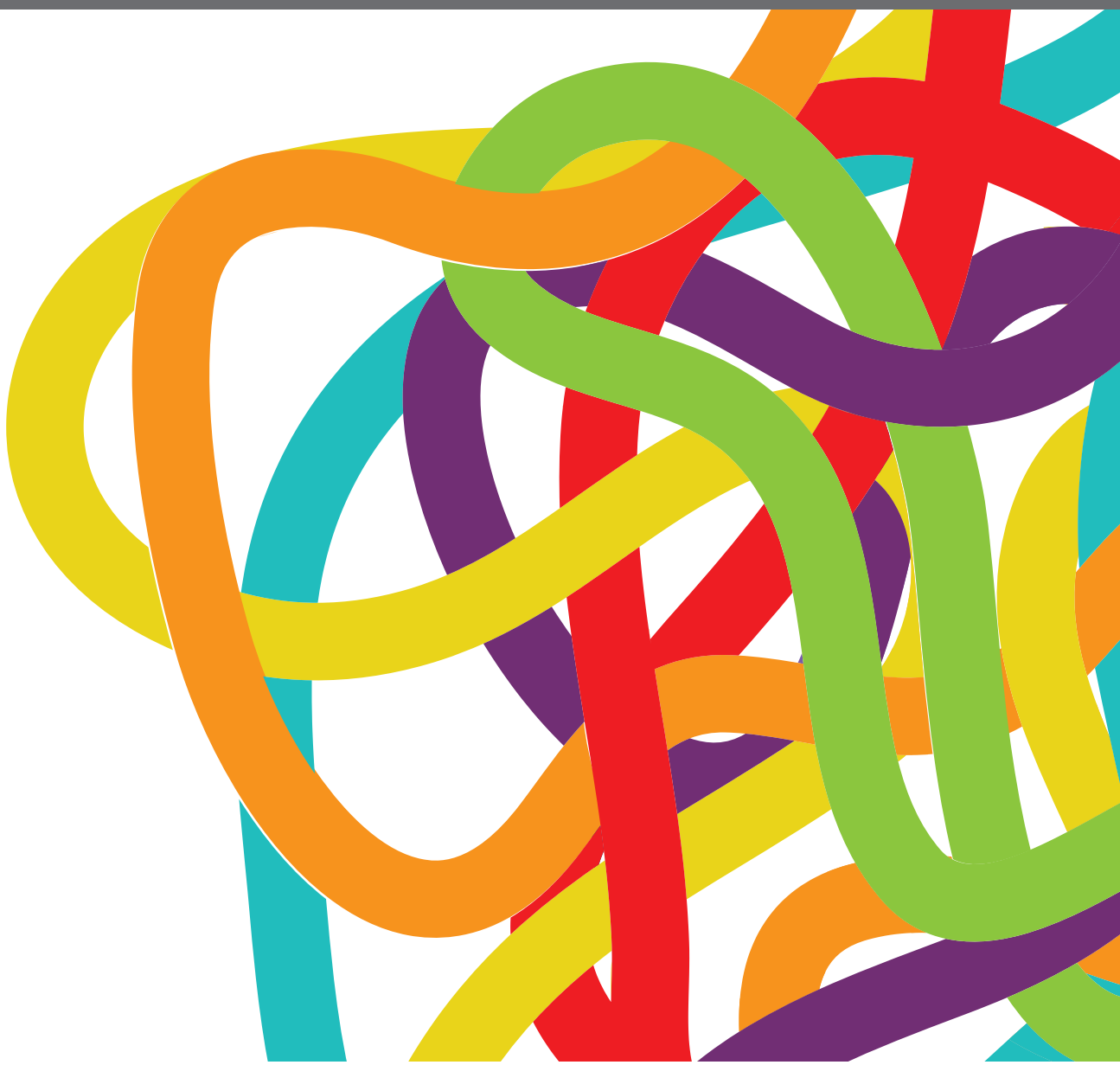
CONTEMPORARY MANAGEMENT OF INTRACRANIAL METASTATIC DISEASE

EDITED BY: Sunit Das and Arjun Sahgal
PUBLISHED IN: Frontiers in Oncology and Frontiers in Neurology



frontiers Research Topics

Frontiers Copyright Statement

© Copyright 2007-2019 Frontiers Media SA. All rights reserved.

All content included on this site, such as text, graphics, logos, button icons, images, video/audio clips, downloads, data compilations and software, is the property of or is licensed to Frontiers Media SA ("Frontiers") or its licensees and/or subcontractors. The copyright in the text of individual articles is the property of their respective authors, subject to a license granted to Frontiers.

The compilation of articles constituting this e-book, wherever published, as well as the compilation of all other content on this site, is the exclusive property of Frontiers. For the conditions for downloading and copying of e-books from Frontiers' website, please see the Terms for Website Use. If purchasing Frontiers e-books from other websites or sources, the conditions of the website concerned apply.

Images and graphics not forming part of user-contributed materials may not be downloaded or copied without permission.

Individual articles may be downloaded and reproduced in accordance with the principles of the CC-BY licence subject to any copyright or other notices. They may not be re-sold as an e-book.

As author or other contributor you grant a CC-BY licence to others to reproduce your articles, including any graphics and third-party materials supplied by you, in accordance with the Conditions for Website Use and subject to any copyright notices which you include in connection with your articles and materials.

All copyright, and all rights therein, are protected by national and international copyright laws.

The above represents a summary only. For the full conditions see the Conditions for Authors and the Conditions for Website Use.

ISSN 1664-8714
ISBN 978-2-88963-129-2
DOI 10.3389/978-2-88963-129-2

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

CONTEMPORARY MANAGEMENT OF INTRACRANIAL METASTATIC DISEASE

Topic Editors:
Sunit Das, St. Michael's Hospital, University of Toronto, Canada
Arjun Sahgal, Sunnybrook Hospital, University of Toronto, Canada

The development of intracranial metastatic disease (IMD) complicates the course of 20% of patients with cancer. Despite improvements in patient survival with more aggressive treatment options as compared to the prior standard of palliative whole brain radiation, outcomes for patients who develop IMD remain dispiriting. There is need to celebrate our advances; but a major collaborative multidisciplinary effort is needed to push the field to achieve more meaningful survival benefits for our patients with IMD.

In this Research Topic collection, we have assembled work detailing the latest innovations in brain metastases imaging and management, spanning from minimally invasive surgery to immunotherapy. We hope that you find it a valuable resource.

Citation: Das, S., Sahgal, A., eds. (2019). Contemporary Management of Intracranial Metastatic Disease. Lausanne: Frontiers Media. doi: 10.3389/978-2-88963-129-2

Table of Contents

frontiers in Oncology

EDITORIAL
published: 28 August 2019
doi: 10.3389/fonc.2019.00818

Editorial: Contemporary Management of Intracranial Metastatic Disease

Sunit Das[1,2]* *and Arjun Sahgal*[3]

[1] *Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada,* [2] *Division of Neurosurgery, University of Toronto, Toronto, ON, Canada,* [3] *Department of Radiation Oncology, Sunnybrook Hospital, Toronto, ON, Canada*

Keywords: brain metastases (BM), surgery, immunotherapy, focused ultrasound, chemotherapy, targeted therapy, radiotherapy, SRS

Editorial on the Research Topic

Contemporary Management of Intracranial Metastatic Disease

On behalf of my radiation oncology partner, Dr. Arjun Sahgal, I am pleased to offer to the readers of *Frontiers in Oncology* our Research Topic entitled, "Contemporary management of intracranial metastatic disease." The development of intracranial metastatic disease (IMD) complicates the course of ∼20% of patients with cancer, with the highest frequency of brain metastases arising in patients with melanoma, breast cancer, and lung cancer (1, 2). Modern therapeutic options available for treatment of IMD include surgical resection, stereotactic radiosurgery (SRS) and to an expanding degree, targeted, and immuno-therapies (3). Despite improvements in patient survival with more aggressive treatment options as compared to the prior standard of palliative whole brain radiation, outcomes for patients who develop IMD remain dispiriting. There is need to celebrate our advances; but a major collaborative multidisciplinary effort is needed to push the field to achieve more meaningful survival benefits for our patients with IMD.

In this Research Topic, we have assembled work detailing the latest innovations in brain metastases imaging and management. Mehrabian et al. have reviewed work in the MR imaging field to identify advanced biomarkers that characterize the cellular, biophysical, micro-structural, and metabolic features of tumors to improve the management of brain metastases from early detection and diagnosis, to evaluating treatment response. Venur et al. review the contribution of genomic analysis of brain metastases to our understanding of variations in the driver mutations compared to the primary malignancy, and provide an in-depth review of the completed and ongoing clinical trials of drugs targeting the molecular pathways enriched in brain metastases. Kamath and Kumthekar review the biological rationale for systemic immunotherapy to treat CNS metastatic disease, and summarize existing clinical data on immune checkpoint inhibitors in this setting and ongoing clinical trials designed to study immune checkpoint inhibitor therapy in patients with IMD. Meng et al. review the prospect of focused ultrasound-mediated blood-brain barrier disruption to improve local drug delivery for patients with IMD. Minimally invasive surgical strategies using tubular retractors or laser interstitial thermal therapy (LITT) have been presented by Marenco-Hillembrand et al. and Salehi et al., respectively. Routman et al. review data to support the use of SRS as a neoadjuvant therapy to improve treatment contouring and diminish the risk of tumor cell dissemination during surgical resection and associated leptomeningeal spread. Masucci and Routman et al. detail the role of hyprofractionated SRS and post-operative SRS, respectively, for patients with IMD. Robin and Rusthoven and Schwendner et al. have reviewed efforts to minimize disease- and treatment-related cognitive and motor decline in patients with IMD. Vellayappan et al. explore the pathophysiology of radiation necrosis, risk factors for its development, and the strategies for its evaluation and management.

OPEN ACCESS

Edited and reviewed by:
Erik P. Sulman,
New York University, United States

***Correspondence:**
Sunit Das
sunit.das@utoronto.ca

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *18 June 2019*
Accepted: *09 August 2019*
Published: *28 August 2019*

Citation:
Das S and Sahgal A (2019) Editorial: Contemporary Management of Intracranial Metastatic Disease. Front. Oncol. 9:818. doi: 10.3389/fonc.2019.00818

Finally, Samuel Chao and colleagues define a treatment algorithm to guide treatment of patients with a limited number of brain metastases, while Roberge et al. describe plans for a prospective randomized control trial to define the role of SRS in patients with more severe burden of IMD.

In all of this, we owe thanks to our many colleagues who contributed to this Research Topic and offered us their time, intellect and energy. Many thanks as well to Jakob Mainusch and the editorial team at *Frontiers*. We thank Frontiers for appreciating the importance of this topic and for supporting the collection. We hope that you find it a valuable resource.

AUTHOR CONTRIBUTIONS

SD wrote and edited the manuscript. AS edited the manuscript and provided guidance on its writing.

REFERENCES

1. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, et al. Brain metastases. *Nat Rev Dis Primers.* (2019) 5:5. doi: 10.1038/s41572-018-0055-y
2. Cagney DN, Martin AM, Catalano PJ, Redig AJ, Lin NU, Lee EQ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol.* (2017) 19:1511–21. doi: 10.1093/neuonc/nox077
3. Kotecha R, Gondi V, Ahluwalia MS, Brastianos PK, Mehta MP. Recent advances in managing brain metastasis [version 1; peer review: 2 approved]. *F1000Res.* (2018) 7:1772. doi: 10.12688/f1000research.15903.1

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Das and Sahgal. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 04 June 2019
doi: 10.3389/fonc.2019.00440

Advanced Magnetic Resonance Imaging Techniques in Management of Brain Metastases

Hatef Mehrabian[1,2*], *Jay Detsky*[3,4], *Hany Soliman*[3,4], *Arjun Sahgal*[1,3,4] *and Greg J. Stanisz*[1,5]

[1] *Physical Sciences, Sunnybrook Research Institute, Toronto, ON, Canada,* [2] *Radiology and Biomedical Imaging, University of California, San Francisco (UCSF), San Francisco, CA, United States,* [3] *Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada,* [4] *Radiation Oncology, University of Toronto, Toronto, ON, Canada,* [5] *Department of Neurosurgery and Pediatric Neurosurgery, Medical University, Lublin, Poland*

Brain metastases are the most common intracranial tumors and occur in 20–40% of all cancer patients. Lung cancer, breast cancer, and melanoma are the most frequent primary cancers to develop brain metastases. Treatment options include surgical resection, whole brain radiotherapy, stereotactic radiosurgery, and systemic treatment such as targeted or immune therapy. Anatomical magnetic resonance imaging (MRI) of the tumor (in particular post-Gadolinium T_1-weighted and T_2-weighted FLAIR) provide information about lesion morphology and structure, and are routinely used in clinical practice for both detection and treatment response evaluation for brain metastases. Advanced MRI biomarkers that characterize the cellular, biophysical, micro-structural and metabolic features of tumors have the potential to improve the management of brain metastases from early detection and diagnosis, to evaluating treatment response. Magnetic resonance spectroscopy (MRS), chemical exchange saturation transfer (CEST), quantitative magnetization transfer (qMT), diffusion-based tissue microstructure imaging, trans-membrane water exchange mapping, and magnetic susceptibility weighted imaging (SWI) are advanced MRI techniques that will be reviewed in this article as they pertain to brain metastases.

Keywords: brain metastases, quantitative MRI, magnetic resonance spectroscopy (MRS), chemical exchange saturation transfer (CEST), diffusion tensor imaging (DTI), magnetization transfer (MT), susceptibility weighted imaging (SWI), relaxometry

OPEN ACCESS

Edited by:
Antonio Di Ieva,
Macquarie University, Australia

Reviewed by:
Edjah K. Nduom,
National Institutes of Health (NIH), United States
Christine Marosi,
Medical University of Vienna, Austria

***Correspondence:**
Hatef Mehrabian
hatef.mehrabian@sunnybrook.ca

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *31 July 2018*
Accepted: *08 May 2019*
Published: *04 June 2019*

Citation:
Mehrabian H, Detsky J, Soliman H, Sahgal A and Stanisz GJ (2019) Advanced Magnetic Resonance Imaging Techniques in Management of Brain Metastases. Front. Oncol. 9:440. doi: 10.3389/fonc.2019.00440

INTRODUCTION

Brain metastases originate from a large number of primary cancers in the body with breast cancer, lung cancer and melanoma being the most likely to metastasize to the brain (1). Up to 40% of all cancers metastasize to the brain with significant impact on patients' quality of life and survival (2). Surgery is reserved for selected patients with tumors amenable to surgical resection, usually for patients presenting with a solitary, large, symptomatic brain metastasis or when pathological diagnosis is needed. Radiotherapy options include stereotactic radiosurgery (SRS) which precisely delivers high doses of radiation to the tumor—in a single or a few fractions—with the intent of tumor ablation (2, 3); whole brain radiotherapy (WBRT) typically given at doses of 3–4 Gy per fraction over 5–10 treatments sessions; and a combination of SRS and WBRT. Systemic treatment is also being increasingly used to treat brain metastases, especially with new targeted agents and immunotherapy drugs (4–7).

Magnetic resonance imaging (MRI) is widely used in diagnosing brain metastases and differentiating them from other intracranial tumors. MRI is also used in assessing tumor response to treatment, although typically through monitoring changes in the tumor volume alone (8). In clinical practice, two main MRI sequences are routinely acquired: T_1-weighted acquisition after intravenous injection of gadolinium-based contrast agents (post-Gd T_{1w}) which highlights the regions of blood brain barrier disruption and delineates the tumor with relatively high accuracy; and T_2-weighted fluid-attenuated inversion recovery (T_{2w}-FLAIR) acquisition which elucidates areas of vasogenic edema around the tumor. In some clinical protocols, diffusion weighted MRI—usually with three diffusion b-values of 0, 500, and 1,000 [s/mm^2]—is also acquired in order to provide information about tumor cellularity through measurement of the apparent diffusion coefficient (ADC) (9, 10).

The Response Assessment in Neuro-Oncology—Brain Metastases (RANO-BM) criteria (11) is commonly used in clinical practice and relies on changes in tumor size—which may take weeks or months to occur—to determine response to treatment. Early changes in tumor size do not always correlate with later outcomes (11), which necessitates following patients serially before response can be evaluated reliably. In cases where assessment of local response is uncertain, histopathological evaluation of the tumor via biopsy may be informative; however, it is typically not performed due to associated risks. Also, a needle biopsy often may not be definitive due to sampling error, as a biopsy cannot adequately capture the heterogeneity of the tumor and its response to radiation (12). Typically, serial structural MRI is performed and clinical judgement is exercised to determine the most likely response category: stable disease, progressive disease, or radiation necrosis.

There is an urgent need for advanced imaging biomarkers that provide information about structural, functional, and metabolic changes in the tumor to determine and predict response to treatment sooner and more robust. Such biomarkers should not only characterize tumor morphology and cellularity, but also tumor metabolism, as well as biophysical and microstructural changes (such as apoptosis or cell membrane disintegration) that the cells undergo due to the treatment. These metabolic and microstructural changes generally occur at a much earlier time point than morphological manifestations. For instance, apoptosis begins as early as 4 h post-radiation (13) while volumetric changes may not stabilize until weeks or months post-treatment (8). Such biomarkers have the potential to allow for altering treatment strategies while still within an effective therapeutic time-window.

In addition to diagnosis and treatment response evaluation, MRI is used in monitoring brain metastases after treatment to detect and manage treatment-induced side-effects, as well as detecting tumor recurrence or the development of new metastases. Clinically, the same imaging sequences (post-Gd T_{1w} and T_{2w} FLAIR) are used in follow-up scans which suffer from lack of sensitivity to the underlying metabolic, biophysical and microstructural changes. Therefore, advanced quantitative MRI might enable the much-needed personalization of therapeutic decision making for patients who have undergone treatment for brain metastases.

The current article reviews the advanced quantitative MRI (qMRI) biomarkers that have been applied to brain metastases. Quantitative Imaging section introduces the qMRI techniques that are reviewed in this article and provides background information for understanding the underlying physiological or metabolic processes that each technique probes. In section qMRI in Brain Metastases the applications of each technique in detection and diagnosis of brain metastases, evaluating therapeutic response of the tumor, managing treatment-induced late-effects (e.g., radiation necrosis), and assessing the effects of the treatment on normal brain tissues are discussed. In section Clinical Translation and Limitations clinical translation of these technique and their associated issues as well as their current technical limitations are briefly presented.

QUANTITATIVE IMAGING

There exist a large number of quantitative imaging techniques that have been extensively applied to brain metastases. Non-MRI metabolic imaging methods such as fluorodeoxyglucose (FDG) and non-FDG based positron emission tomography (PET) (14), and single-photon emission computed tomography (SPECT) (15), have shown great promise in management of brain metastases. They are however expensive, represent additional imaging (increasing cost and time), and are not in routine clinical use partly due to limited availability.

There is a long history of functional and microstructural MRI-based techniques developed and applied to brain metastases. Dynamic contrast enhanced (DCE)-MRI can be analyzed with a two-compartment Tofts-Key model to provide quantitative evaluation of vascular permeability and blood flow (16, 17); dynamic susceptibility contrast (DSC)-MRI characterizes tumor perfusion, relative cerebral blood flow (rCBF) and relative cerebral blood volume (rCBV) (18); while ADC measurements calculated from diffusion-weighted MRI reflect tissue cellularity. These functional and microstructural MRI contrasts have also shown promising results in response monitoring and managing treatment side-effects for brain metastases; however, they usually lack the specificity and sensitivity to guide clinical decision-making on their own (19). As MRI has advanced, so has the ability to image with novel qMRI sequences which—if translated to routine clinical practice—have the potential to render biomarkers with the sensitivity and specificity to be clinically useful and will be the focus of the current article.

Trans-membrane Water Exchange

Each MRI voxel is comprised of cells, microvessels, and extracelluar matrix, etc. Standard MRI measures the "average" signal of water in these tissue compartments, while quantitative MRI tries to disentangle different contributions to the MRI signal. The water molecules constantly move between tissue compartments having different physio-chemical properties in each compartment. The exchange rate of water molecules between intracellular and extracellular compartments, k_{IE}, depends on the permeability of the cell membrane as well as

the size and shape of the cell (20, 21). This exchange rate is inversely related to the time, τ, that the water molecules spend on average in each compartment (22). This cellular characteristic (k_{IE}) changes with treatment; in particular as a result of apoptosis induced by radiotherapy. Apoptosis leads to increased membrane permeability, decreased cell size, and increased irregularity of its shape (21), all of which results in an increase in k_{IE}.

The water exchange rate increases in apoptotic cells due to the increased surface-to-volume ratio of the cell either by transformation of the cell into a more irregular shape or decreased overall cell diameter (21, 23), and to a lesser extent due to increased cellular membrane permeability caused by loss of cell membrane integrity (21). In biological tissues, the MR properties (longitudinal, T_1 and transverse, T_2 relaxation times) of the intracellular and extracellular compartments cannot be distinguished. However, Gd-based MRI contrast agents do not cross the cell membrane and are purely extracellular. Gd alters both T_1 and T_2 of the extracellular compartment in which it is located and also affects the relaxation times of the adjacent compartments indirectly through the exchange of water molecules between compartments (24, 25).

Gd administration disrupts the relaxation equilibrium and makes measuring these relaxation times as well as the trans-membrane water exchange rate constant possible. Trans-membrane water exchange rate, k_{IE}, is very sensitive to treatment-induced changes such as apoptosis. In small-scale clinical and pre-clinical studies, k_{IE} has been shown to increase significantly within days after inducing apoptosis (24, 25).

Susceptibility Weighted Imaging (SWI)

Susceptibility weighted imaging (SWI) exploits the differences in the effective magnetic field in the tissues caused by diamagnetic or paramagnetic substances such as deoxyhemoglobin, iron and calcification (26). SWI signal depends on the deoxy/oxyhemoglobin content in the vasculature which changes due to radiotherapy-induced alterations in tissue microvasculature, specifically caused by the formation of micro-bleeds in the brain (27). Both SWI and the apparent transverse relaxation rate imaging (R_2^*) have high sensitivity to hemorrhage and are capable of detecting radiation necrosis. In a pilot study, lower R_2^* was measured (particularly in the tumor rim) in pseudo-progression compared to progression in patients with GBM (28).

Magnetic Resonance Spectroscopy (MRS)

Proton magnetic resonance spectroscopy (^{1}H-MRS) is sensitive to concentration of tissue metabolites that play crucial role in cancer (29). ^{1}H-MRS exploits the fact that in different molecules, there are slight difference in resonance frequency of protons, due to the local magnetic field generated by the local electron cloud surrounding them, a phenomenon called "chemical shift" (30). Molecules detectable with MRS have relatively low molecular weight; are generally able to move between different tissue compartments; and are present in relatively large quantities (>few mM). Some of these metabolites are involved in metabolic pathways of tumors such as involvement of N-acetylaspartate (NAA) in lipogenesis pathways (31); the role of choline (Cho) in the Kennedy pathway [i.e., involvement in genesis of cell membrane phospholipids (32)]; and role of creatine (Cr) in energy metabolism (33), making MRS sensitive to tumor environment (34).

^{1}H-MRS data is acquired using either single voxel MRS (SV-MRS) which generates signal from brain sub-regions of approximately a few cubic centimeters; or magnetic resonance spectroscopic imaging (MRSI) which provides higher spatial resolution compared to SV-MRS (35). Neither technique provides sufficient spatial resolution and brain coverage in clinically feasible scan durations, making MRS a region-based acquisition and analysis technique.

Figure 1 shows the MRS spectrum of a 2 cm^3 region of the brain encompassing the tumor in a representative brain cancer patient. The most commonly quantified metabolites with MRS that have been shown—in several small-scale patient studies—to change in tumors and due to treatment are creatine, choline, and NAA (36–42). MRS allows for correlating the concentrations of these sub-cellular molecules with changes in tumor and normal tissue due to treatment (43). However, due to the large voxel sizes MRS is prone to partial volume artifact and its quantitative accuracy is undermined by high tumor heterogeneity within the imaged voxel.

Micro-Structural MRI

Tissue microstructure and its treatment-induced changes can be probed with diffusion MRI. In addition to the widely-used ADC that is sensitive to cellular density, two more advanced diffusion-based techniques have been used to evaluate intracranial brain tumors: intra-voxel incoherent motion (IVIM) (44–46), and diffusion tensor imaging (DTI) (47).

IVIM measures pseudo-diffusion in tissue caused by slow flow of blood through the disoriented capillaries. IVIM model assumes the diffusion MRI signal decay of each voxel is bi-exponential. The fast decaying component represents the motion of the blood in capillaries and the amplitude of this fast decaying component is proportional to microvascular fraction of the voxel. The slow decaying component on the other hand represents the diffusion properties of the tissue (48). The microvascular fraction can also be measured with a simplified IVIM model that focuses on large diffusion b-values (49), and has been used in several pilot studies investigating human brain metastases (45, 46). **Figure 2** shows perfusion and ADC maps of microvascular fraction quantification with IVIM for two patients with brain metastases, one having radiation necrosis, and the other with tumor recurrence (46).

DTI on the other hand characterizes the tissue microstructure and water diffusion directionality by performing diffusion sensitization in multiple orientations (50). DTI is sensitive to changes in fiber orientations and also to destruction of white matter tracts caused by radiation or chemotherapy and has been used in several pilot studies to characterize radiation-induced damage to normal brain structures and subsequent cognitive dysfunction (47, 51).

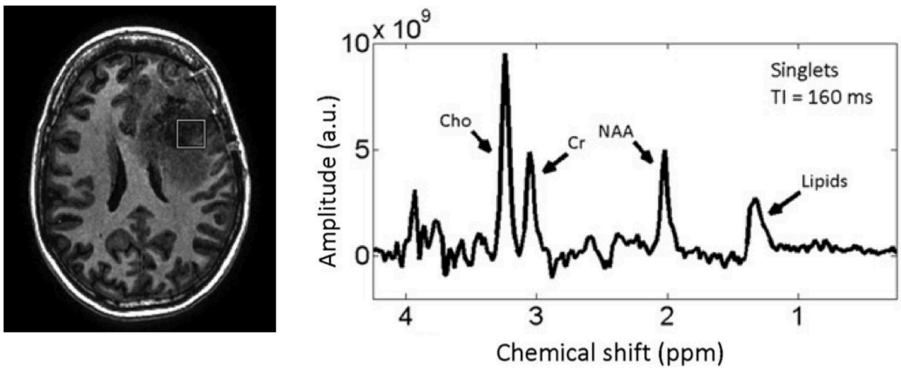


FIGURE 1 | T_{1W} MRI of a patient with a high-grade glioma **(left)** with MRS spectrum **(right)** corresponding to the voxel (white Square) inside the tumor. Reproduced, with permission from Landheer et al. (36).

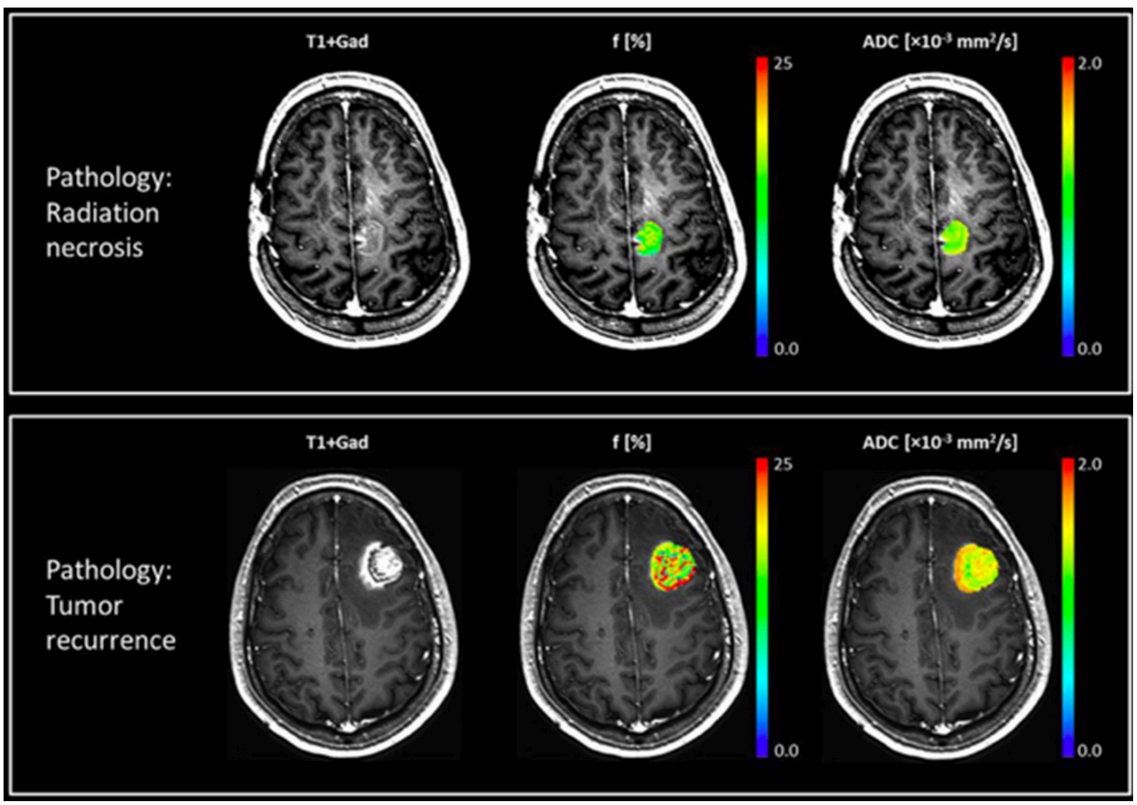


FIGURE 2 | Two patients with brain metastases presenting with enlarging enhancing mass after treatment with SRS. Top row shows a case of radiation necrosis, and bottom row shows a case of recurrent tumor. Post-Gd T_{1W}-MRI (left), perfusion fraction *f*-map (middle), and ADC map (right) are shown for both cases, where the patient with radiation necrosis exhibits a uniformly low perfusion fraction while the patient with recurrent tumor has more heterogeneous maps with a higher perfusion fraction. In these two case the ADC values were similar but slightly higher for radiation necrosis. Reproduced, with permission from Detsky et al. (46).

Quantitative Magnetization Transfer (qMT)

Magnetization transfer (MT)-MRI is sensitive to protons associated with large immobile macromolecules that are exchanging with free water protons. Such macromolecules include lipids associated with myelin and cell membranes. Quantitative MT (qMT) data acquisition requires imaging a large range of offset frequencies relative to free water resonance frequency, and a relatively high radiofrequency (RF) power for its magnetization preparation pulse (typically 3–6 μT) (52). This technique characterizes the concentration of the macromolecular protons (i.e., bound proton fraction), the exchange rate between these protons and free water protons, as

well as the relaxation rates of the bound and free water pools. All of these characteristics are altered in tumors and also due the the treatment. **Figure 3** shows the MT spectrum of a representative patient for tumor and its contra-lateral normal appearing white matter (cNAWM), showing the significant differences between these two tissue types.

qMT mostly represents myelin integrity and to a lesser extent cell membrane integrity (54). qMT has been shown in multiple sclerosis (55, 56) to be sensitive to demyelination resulting from damage to neurons. Smaller MT effect has also been reported in glioblastoma (GBM) tumors and edema as compared to white matter (57). In a pilot study of 20 patients, changes in MT properties of the tumor were found to be more sensitive to treatment-induced changes [such as apoptosis (58)] and reflected these changes much earlier—as early as 2 week into standard chemo-radiation in patients with GBM (53)—than clinically used metrics that rely on morphological changes in the tumor.

Chemical Exchange Saturation Transfer (CEST)

Chemical exchange saturation transfer (CEST)-MRI is sensitive to concentration and exchange of labile protons including amide (-NH) protons on the backbone of proteins and peptides, amine ($-NH_2$) protons on amino acid side-chains, fast exchanging hydroxyl (-OH) protons, as well as intramolecular transfer of magnetization from aliphatic (-CH) protons to labile protons termed as relayed nuclear Overhauser effect (rNOE) (59). These protons can be found in metabolites such as glutamate, lactate, myo-inositol and glucose that play crucial role in brain tumors and their response to therapy (60–62).

CEST relies on the chemical shift between exchanging protons of the metabolites due to their local electron cloud. The dependence of CEST on the exchange as well as the concentration of the proton groups allows for amplification of the CEST effect (using proper imaging and preparation techniques) with several orders of magnitude, making it more sensitive (compared to MRS) to metabolites with very low tissue concentration (62, 63). However, CEST lacks specificity to individual metabolites as it detects chemical groups (e.g., amides, amines, etc.) that are associated with various proteins (64). Certain CEST techniques have recently been developed that are sensitive to chemical groups with a specific range of exchange rates which improve specificity of the measurements (65). The chemical exchange rate in CEST experiments depends on various micro-environmental factors, making CEST a suitable technique for non-invasive measurement of pH (66, 67), which also plays an important role in tumor response to therapy.

Figure 3C shows the CEST spectrum of a brain tumor and its contralateral normal appearing white matter (cNAWM) for a representative patient. The differences in these CEST spectrums arise from the fact that both concentrations and exchange rates of several metabolites—detectable with CEST—change in tumors compared to normal tissue.

Due to relatively high sensitivity to changes in molecular interactions and metabolite concentrations, several pilot studies have shown the potential of CEST in detecting treatment-induced metabolic changes such as radiotherapy induced apoptosis (68, 69). The most commonly used CEST metrics in cancer are amide proton transfer (APT) (70), and magnetization transfer ratio for amide and rNOE (71). These metrics reflect a combination of the CEST effect alongside magnetization transfer and direct water saturation (72). More advanced CEST analysis techniques that better isolate the CEST effect from confounding factors such as Lorentzian decomposition of the spectrum (69), and apparent exchange-dependent relaxation (AREX) (73, 74) have also been developed and applied to cancer.

qMRI IN BRAIN METASTASES

Advanced qMRI techniques have been used in five major aspects of managing patients with brain metastases (all of these investigations were performed on a small number of patients and no large-scale randomized trials have been conducted). Most studies have focused on differentiating brain metastases from other brain tumors such as high and low-grade gliomas (38, 53, 71, 74–81). Assessing tumor response to therapy and attempting to perform such evaluation early after the treatment has been less explored; however, this topic has been gaining significant attention recently (21, 25, 45, 58, 68, 69, 82). Management of treatment-induced late-effects, specifically differentiating radiation necrosis from tumor progression or recurrence, has also been attempted with qMRI techniques. The applications of qMRI that have received little attention are assessing the effects of the tumor and also the treatment on normal brain tissues and their subsequent impact on patients' quality of life (43, 51, 83).

Detection and Diagnosis of Brain Metastases

Intracranial tumors such as brain metastases, gliomas, and meningiomas may often be differentiated morphologically by their pattern of enhancement on post-Gd scans; however, they sometimes appear similar on anatomical scans, rendering differentiation difficult (84, 85). Although the gold standard for diagnosis is still biopsy, non-invasive methods could be valuable in clinical settings, particularly if a biopsy is not possible.

Significant metabolic, structural, and biophysical differences exist between different brain tumor types that can be exploited by advanced qMRI techniques. N-acetylaspartate (NAA), a major brain neuro-transmitter, is abundant in neurons and its levels correspond to the degree of neuronal destruction (42); High levels of choline (Cho) are associated with increased cell membrane turnover; and increased creatine (Cr) concentration is reported in areas of high energy metabolism (86–88). Increased metabolism and cellularity has been correlated with increased concentration of amide protons and consequently CEST effect (89–91), while a decreased MT effect has been reported in tumors compared to normal brain tissue (53, 57, 77), which could be used in differentiating tumor types.

MRS

Brain metastases, similar to GBM, express elevated lipid signal which has been used to differentiate these two tumor types

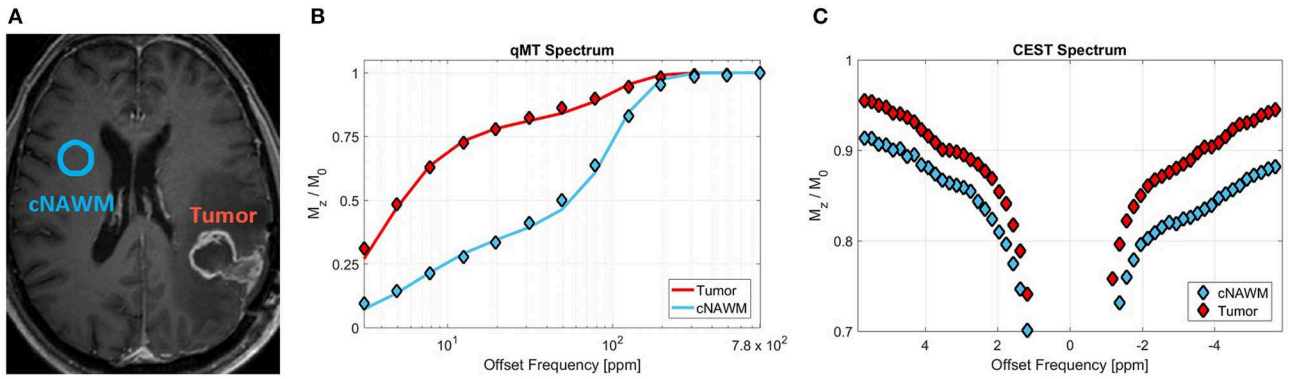


FIGURE 3 | (A) Post-Gd T_{1w} MRI of a representative primary brain tumor patient (glioblastoma), showing the tumor and contralateral normal appearing white matter (cNAWM) ROIs. **(B)** The MT spectrums averaged over Tumor and cNAWM, showing the acquired data points as well as the two-pool MT model fit to the data. **(C)** The CEST spectrum averaged over the tumor and cNAWM ROIs. Reproduced, with permission from Mehrabian et al. (53) (License: https://creativecommons.org/licenses/by/4.0/).

from other brain neoplasms (38). On the other hand, GBM almost always extends beyond the tumor margins as seen on conventional morphological contrast-enhanced MRI (38, 53, 71, 75, 76), while brain metastases are predominantly encapsulated within the enhancing tumor rim (38, 69, 76).

Ishimaru et al. (38), studied 31 patients with high grade glioma and 25 patients brain metastases (primary cancer: 18 lung, 2 breast, 3 colon, 1 ovarian, and 1 malignant fibrous histiocytoma) using single-voxel MRS. They demonstrated lipid signal elevation around 1.3 ppm in majority of patients with GBM and brain metastases. They also showed lipid peak is better detectable in MRS with short echo time, TE (TE = 30 ms) compared to long TE (TE = 136 ms). Caivano et al. (39) has investigated a large cohort of patients involving 32 patients with high-grade glioma, 14 patients with low-grade glioma, and 14 patient with brain metastases (primary cancer: 4 lung, 7 breast, 2 gastric, and 1 melanoma) using multi-voxel 2D MRSI with long TE (TE = 288 ms) to diagnose tumor type. This study concluded that in tumor core the ratios of NAA to creatine (NAA/Cr) and choline to creatine (Cho/Cr) have larger values in brain metastases compared to high and low-grade gliomas (NAA/Cr = 4.43 ± 4.5, 1.68 ± 0.9, 1.04 ± 0.6, and Cho/Cr = 4.88 ± 7.0, 2.7 ± 2.1, 3.4 ± 1.7, for brain metastases, low-grade glioma, and high-grade glioma, respectively). Moreover, in the peri-tumoural edema NAA/Cr and Cho/Cr in brain metastases have larger values compared to high-grade gliomas and smaller values compared to low-grade gliomas (NAA/Cr = 2.53 ± 1.13, 3.73 ± 2.61, 1.49 ± 0.83, and Cho/Cr = 2.72 ± 2.55, 4.62 ± 6.95, 2.49 ± 2.02 for brain metastases, low-grade glioma, and high-grade glioma, respectively), indicating that MRS has the potential to differentiate these three tumor types.

Ishimaru et al. (38) also observed similar trends for NAA/Cr using single-voxel MRS (voxel size ~1.5 cm^3) with long TE (TE = 136 ms) in 4 brain metastases, 6 patients with low-grade glioma, and 9 patients with high-grade glioma. This study reported statistically significantly higher NAA/Cr ratio for brain metastases compared to gliomas (NAA/Cr = 1.58 ± 0.56, 0.70 ± 0.23, 0.76 ± 0.40 for brain metastases, low-grade glioma, and high-grade glioma, respectively) suggesting its ability to differentiate brain metastases from different types of glioma.

Tissue Microstructure

Salice et al. (92) has used a combination of several qMRI techniques including diffusion tensor imaging (DTI), MRS, ADC, and cerebral blood volume (CBV) evaluation, to differentiate benign and malignant brain lesions in 14 patients with similar lesion appearances on anatomical MRI (ring enhancement on post-Gd T_{1w} and surrounding edema on T_{2w} FLAIR). When considering a single parameter, malignant lesions (compared to benign lesions) show lower ADC relative to cNAWM (rADC = ADC/ADC_{cNAWM}) on perilesional edema (rADC = 1.4 ± 0.3 vs. 2.1 ± 0.5), and lower fractional anisotropy (FA) of the internal cavity (FA = 0.15 ± 0.09 vs. 0.3 ± 0.02). Malignant lesions also show higher rADC in internal cavity (rADC = 1.8 ± 0.7 vs. 0.6 ± 0.3), and higher FA in perilesional edema (FA = 0.20 ± 0.07 vs. 0.14 ± 0.02) compared to benign lesions. Several combinations of qMRI parameters provided an excellent (>0.9) area under the curve (AUC) of receiver operating characteristic (ROC) curves, with the combination of rADC on the internal cavity, and NAA on the perilesional edema or FA from DTI measurements providing the very high AUC of 0.97, demonstrating their potential in differentiating benign and malignant brain tumors.

Magnetization Transfer (MT)

Ainsworth et al. (93) measured magnetization transfer ratio (MTR) and ADC in a mouse model of brain metastases twice a week for 31 days after intracardiac injection of brain-homing breast cancer cell line MDA-MB231-BR. The tumors showed significantly lower MTR and ADC values compared to contralateral normal appearing brain tissue. More importantly, in 24% of cases, they observed significant reduction in both MTR and ADC long before the lesions were detectable on T_{2w} MRI (texture analysis of MTR maps showed 77% sensitivity 2–4 days

and 46% sensitivity 5–8 days before lesions were detectable on T_{2w} MRI).

Garcia et al. (77) investigated performance of magnetization transfer ratio (MTR) and qMT parameters in differentiation of brain metastases from other brain tumors in a cohort of 26 patients. They report statistically significantly different MTR and qMT properties (on both the tumor rim and core) for patients with GBM, meningiomas and brain metastases. MTR on the non-contrast-enhancing (CE) region of tumor could only separate brain metastases from meningiomas (MTR [%] = 35.1 ± 0.5, 28.9 ± 1.6, 33.8 ± 1.2 for brain metastases, meningiomas, and GBM, respectively), and MTR on CE region could only separate GBM from meningiomas (MTR [%] = 27.4 ± 1.0, 30.5 ± 1.2, 25.2 ± 0.6 for brain metastases, meningiomas, and GBM, respectively), showing the limited potential of a simple MTR measurement. When considering parameters derived from qMT analysis, macromolecular fraction on the non-CE region of the tumor (M_{0b} [%] = 7.2 ± 0.7, 5.6 ± 0.2, 3.6± 0.7 for brain metastases, meningiomas, and GBM, respectively) and the MT exchange rate on CE region of the tumor (k_f [s^{-1}] = 0.8 ± 0.1, 1.1 ± 0.1, 0.6 ± 0.0 for brain metastases, meningiomass, and GBM, respectively) could separate all three tumor types.

Furthermore, MT maps show changes in the brain regions that appear unaffected on standard MRI—MT properties are decreased on the ipsilateral and contralateral NAWM of patients compared to healthy controls but are higher than tumor and vasogenic edema—suggesting these advanced techniques provide additional information that could be helpful in the management of these patients (53, 75, 77).

CEST

Several studies have used CEST in differentiating brain tumors and also grading them (74, 78–81). However, all of these CEST studies have focused on gliomas or meningiomas, and none included brain metastases. The value of CEST in differentiating brain metastases from other brain tumors remains unexplored.

Early Treatment Response Evaluation

Determining tumor response to therapy early after the treatment, allows for adjusting strategies for non-responders, while for responders reassures patients and their treating physicians about the treatment effectiveness. Treatment response in clinical practice is currently determined by assessing changes in tumor size on anatomical MRI (11). The earliest clinical time-point for response evaluation in brain metastases is between 4 and 6 weeks after the end of the treatment (11). Radiation-induced effects can mimic tumor growth and may confound response assessment, necessitating longer (3–6 month) follow-up.

Early response evaluation using qMRI can be of great utility, particularly due to its high sensitivity to underlying metabolic, biophysical, and microstructural changes that the treatment induces but are typically too subtle for routine clinically used approaches to detect. Clinically, early identification of non-responders may significantly improve outcomes by allowing for early use of salvage treatments such as surgery or additional radiation.

Radiation-induced changes in cells, such as apoptosis, begin within hours after treatment and preclinical studies have shown the potential of qMRI in detecting radiotherapy-induced changes that are secondary to apoptosis as early as 48 h after treatment (21, 58, 68). Such changes include detection of decreased metabolism through measuring concentration and exchange of amide protons using CEST (68), micro-structural changes in cell membrane integrity through measuring the increased water exchange rate constant between intracellular and extracellular spaces using relaxometry (21), and decreased macromolecular content measured using qMT and increased MTR (mainly due to change in free ware relaxation properties) (58).

Perfusion Imaging

Conventional radiotherapy results in an initial increase in perfusion (94, 95); in contrast, stereotactic radiosurgery (SRS) induces a significant reduction in perfusion within a few hours after treatment due to damage to the vascular endothelium (96). These changes can be quantified with perfusion measurement techniques such as IVIM and DCE-MRI (45, 48, 97). Kapadia et al. (45) measured an increase in perfusion index (measured with IVIM) four weeks after treatment (f = 0.08 ± 0.02, 0.10 ± 0.03 at baseline and 4 weeks post-SRS, respectively). The study included brain metastases from primary lung (n = 8), breast (n = 5) and colorectal (n = 2) cancers. However, neither perfusion index, which is proportional to tumor blood volume, nor the vascular fraction measured from DCE-MRI were able to differentiate responders from non-responders (45).

MRS

Predicting which patients are likely to demonstrate favorable response to radiotherapy (through assessment of tumor aggressiveness), or early prediction of response within a few days after treatment could have a significant clinical impact. Sjobakk et al. (40) measured single voxel proton MRS data (voxel size between 1.0 and 1.5 cm^3) from 21 patients with brain metastases before treatment (primary cancer: 8 lung, 8 breast, 2 colon, and 3 malignant melanoma). By applying a clustering technique to the MRS spectra between lipids and total choline (between 0.7 and 3.45 ppm), they observed that pre-treatment MRS spectra correlated with 5-month survival of these patients, where patients with higher lipid signal at baseline survived longer. Also, of the four patients that had repeat MRS after treatment, lipid signal decreased after treatment, and among the two patients whose repeat MRS spectrum is shown in the article the patient with larger drop in lipid signal survived longer (16 months vs. 3 months). These results demonstrate the potential of MRS in determining response early after the treatment.

CEST

Positive response to treatment is often characterized by decreased tumor metabolism. Metabolism can be probed through characterizing glucose metabolism pathway with FGD-PET. FDG is a widely-used tracer for PET that is preferentially taken up by cancer cells. Using a mouse model, Rivlin et al. (82) showed a similar preferential uptake for 2-Deoxy-D-glucose (2DG). The hydroxyl (-OH) group on 2DG has a

strong CEST effect making 2DG-CEST a potential candidate to replace PET without the need for radio-isotopes (82). It could potentially be used in detection and also response monitoring of patients with brain metastases through measuring changes in tumor metabolism.

Desmond et al. (69) applied endogenous CEST-MRI (i.e., without administering a CEST agent) to determine response of patients with brain metastases to single-fraction SRS within 1 week after the treatment (with majority of metastases from primary cancers in lung and breast, and instances of rectum and melanoma). They observe reduced CEST signals after SRS in responders and increased CEST in non-responders (an example for Amide CEST signal is shown in **Figure 4**). Changes in CEST signals 1-week post treatment (compared to baseline) correlated with the change in tumor volume measured 1 month post-treatment (compared to baseline) with width of NOE peak in the tumor (correlation coefficient, $r = -0.55$, $p = 0.028$) and amplitude of NOE peak on the NAWM ($r = 0.69$, $p = 0.002$) providing the highest correlations (69). Furthermore, the CEST signal amplitude of the NOE peak on cNAWM at baseline scan (before even receiving the treatment) may predict the degree of tumor volume change 1 month post-treatment

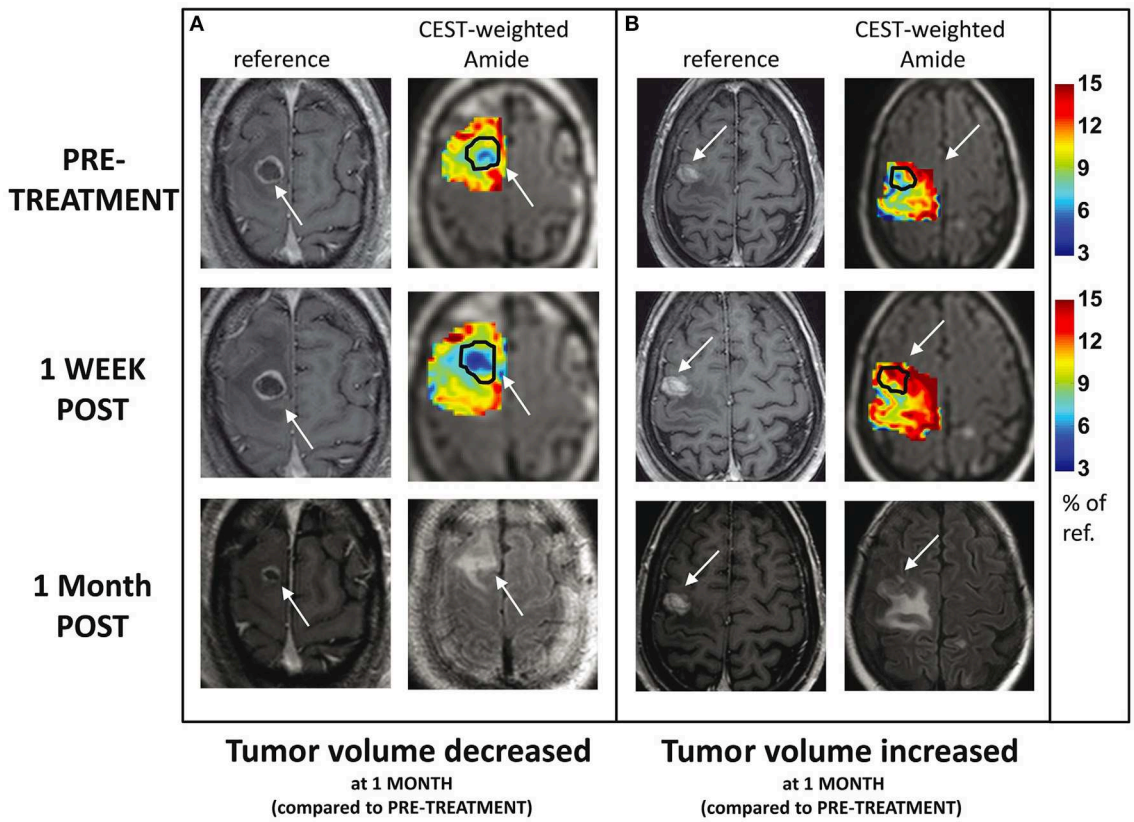


FIGURE 4 | CEST amide MTR maps (tumor and surrounding tissue) for two patients with brain metastases treated with single-dose SRS, at baseline and 1 week after treatment: **(A)** the tumor volume decreased 1 month post-SRS and **(B)** tumor volume increased 1 month post-SRS. The maps are overlaid on T2w FLAIR images. The enhancing tumor region is indicated with arrows and outlined on CEST maps. For comparison, the corresponding slice from the post-Gd T1w MRI is also shown at all three scan time-points. Reproduced, with permission, from Desmond et al. (69).

TABLE 1 | Performance of qMRI techniques in determining response to therapy.

Biomarker (imaging technique)	Response evaluation time	Performance
Perfusion index (IVIM)	4–6 weeks post-treatment	Unable to identify non-responders
Vascular fraction (DCE-MRI)	4–6 weeks post-treatment	Unable to identify non-responders
Spectrum between lipids and choline (MRS)	Baseline	Correlated with 5-month survival
NOE peak width (CEST) NOE peak amplitude (CEST)	1 week post-treatment	Correlated with tumor volume change at 4 weeks
NOE peak amplitude (CEST)	Baseline	Correlated with tumor volume change at 4 weeks
Trans-membrane water exchange (relaxometry)	1 week post-treatment	Correlated with tumor volume change at 4 weeks

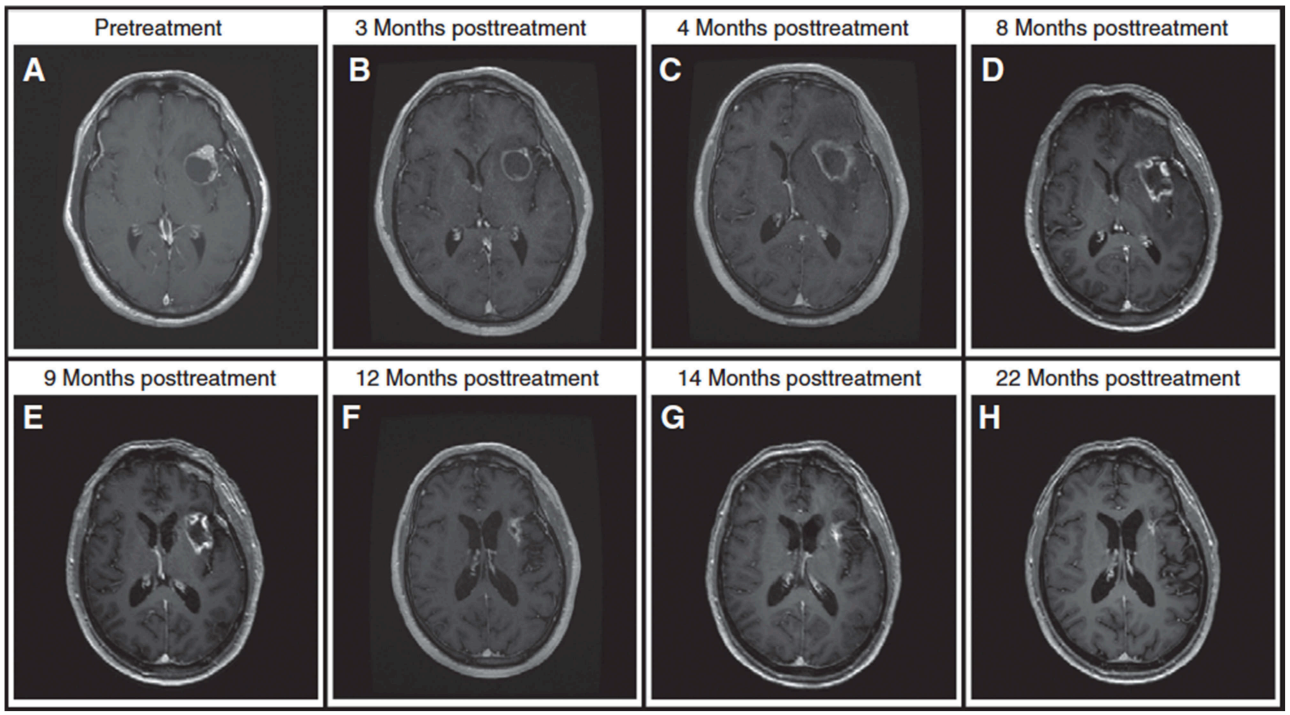


FIGURE 5 | A patient with brain metastasis treated with SRS and presenting with an enlarging enhancing mass after treatment. **(A)** Pre-treatment. **(B)** An enlarging, enhancing mass at the 3-month follow up scan, **(C)** lesion is larger at 4-month follow up. Standard MRI at 3-month and 4-month follow up scans is unable to determine if the lesion is tumor progression or radiation necrosis (lesion is near the language center prohibiting its complete resection). **(D)** A trial of steroids leads to a slight reduction in the enhancing mass but a significant decrease in the surrounding FLAIR at 8-month follow up. **(E)** Continuing steroids leads to further reduction in enhancing lesion at 9-month follow up. **(F–H)** Follow-up MRIs at 12 to 22 months post-treatment scans demonstrate significant decrease in tumor size, rendering a diagnosis of radiation necrosis (the diagnosis is also confirmed with DWI and T_{2w} FLAIR). In two occasions during the period of uncertainly, the patient was admitted to hospital with neurological symptoms. For this patient, it took longer than 9 months to render a diagnosis, demonstrating the challenges faced in clinic in differentiating radiation necrosis from tumor progression. Reproduced, with permission from Mehrabian et al. (72).

(compared to baseline) with high negative correlation ($r = -0.69$, $p = 0.002$), indicating its potential in characterizing tumor aggressiveness (69).

Relaxometry

Radiotherapy induces microstructural and biophysical changes in the tumor cells undergoing apoptosis which result in increased cell membrane permeability and increased irregularity and shrinkage of the cells (21). The changes in cell membrane integrity as a result of radiotherapy can be probed with the quantification of trans-membrane water exchange rate constant (21). A study of 19 patients with brain metastases treated with SRS (primary cancer: 9 lung, 6 breast, 1 lung and breast, 1 thyroid, 1 endometrium, and 1 rectal), measured a significant increase in trans-membrane water exchange rate constant (due to significant apoptosis) within 1 week after treatment in responders [determined according to RANO-BM criteria (11)], while small changes were measured in non-responders (25).

These studies (25, 69) demonstrate the potential of qMRI in detecting and quantifying radiation-induced metabolic and micro-structural changes in the tumor cells—that precede morphological changes—within days after treatment while adjustment to therapy is still an option. **Table 1** summarizes the performance of each technique in evaluating treatment and also their time to detectable response, reported in the studies that were reviews in this section.

Treatment-Induced Late-Effects

Radiotherapy may cause damage in the form of radiation necrosis that may appear several months or even years after the treatment. The likelihood of radiation necrosis increases with radiation dose. Thus, patients treated with high-dose SRS have higher likelihoods of developing radiation necrosis [reported in up to 22% of patients (3, 98)] which can be difficult to manage. It is often impossible to differentiate these radiation-induced changes from tumor progression using standard clinical approaches (98–101); both conditions present with an enlarging enhancing mass in post-Gd T_{1w} MRI and vasogenic edema in T_{2w} FLAIR (3). **Figure 5** shows a case where 9 months of follow up imaging was required to determine whether the observed anatomical change represented tumor recurrence or radiation necrosis.

Pathological studies have shown that in most cases there is a mixture of necrosis and residual or recurrent tumor (102) making the diagnosis challenging. **Figure 6** shows a case of post-SRS tumor recurrence alongside small areas of radiation necrosis (46).

Differentiating between primarily tumor recurrence vs. primarily radiation necrosis is necessary to guide management. Tumor progression is managed with surgery or further radiotherapy while radiation necrosis is managed with observation, steroid therapy, or vascular endothelial growth factor inhibitors such as bevacizumab (8, 103, 104). In the current clinical setting with ineffective means of differentiating tumor progression from radiation necrosis, clinicians have to use their clinical judgment (which may or may not be ultimately correct) or resort to invasive sampling via a biopsy. This leads to significant delays in the appropriate care management [which is palliative in many cases (105)] and can have negative effects on patient's quality of life and survival.

It is hypothesized that radiation necrosis results from radiation damage to the normal white matter, the microvasculature, or a combination of both (106–109). Pre-clinical and clinical studies have shown promising results in differentiating radiation necrosis from tumor progression through characterization of lesion metabolism using CEST and MRS, and probing damage to its macromolecular content using magnetization transfer (MT) (70, 72).

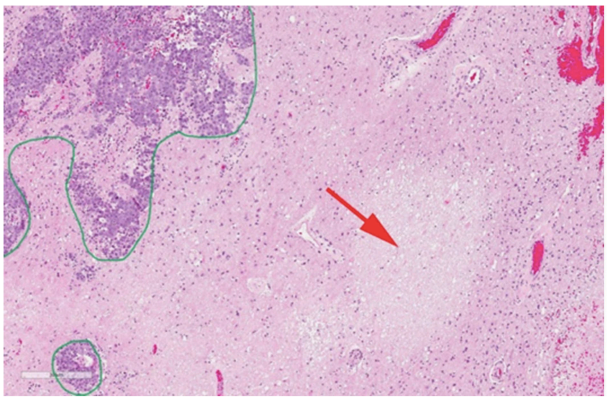


FIGURE 6 | Histopathology of a resected brain metastasis that was previously treated with SRS. The green outline demonstrates residual viable tumor cells while the red arrow shows a region of radiation necrosis. Reproduced, with permission from Detsky et al. (46).

MRS

MRS, which evaluates tissue metabolism, has been used extensively in differentiating radiation necrosis from tumor progression in brain metastases. Weybright et al. (37) performed MRS in 29 patients with suspicious lesions after radiotherapy and measured significantly higher ratios of Cho/Cr and Cho/NAA in tumor compared to radiation necrosis. Similar results have been obtained in other studies with Schlemmer et al. (41) reporting that MRS was capable of correct classification of 82% of the lesions in 56 patients with brain tumors (6 metastases, 2 meningiomas, 6 astrocytoma grade I, 6 grade II, 29 grade III, and 9 grade IV) who presented with suspicious lesions and/or clinical symptoms after SRS. Chuang et al. (88) performed a meta-analysis of 13 studies and concluded that in the total of 397 examined lesions, Cho/NAA and Cho/Cr ratios were elevated in tumors (although there was large overlap between values for radiation necrosis and tumor progression reported among different studies). However, in case of the patient shown in **Figure 5** (and several other cases), MRS was unsuccessful to render diagnosis (MRS at 4 months post-therapy scan incorrectly suggested the lesion in **Figure 5** was tumor progression). These studies show the promise and also some of the limitations of MRS in differentiating radiation necrosis from tumor progression.

CEST

Recently several studies have used CEST (in animal models and patients) in differentiating radiation necrosis from tumor progression (70, 72). CEST data was acquired in a study of 16 patients with brain metastases (primary cancer: 6 breast, 2 lung, 3 renal cell carcinoma, 1 melanoma, and 2 non-small cell lung cancer, NSCLC) where 9 patients were later diagnosed—based on clinical guidelines—with radiation necrosis and 7 with tumor progression. Higher CEST signals corresponding to Amide protons (MTR_{Amide} [%] = 8.2 ± 1.0, 12.0 ± 1.9, in radiation necrosis and tumor progression, respectively), and nuclear Overhauser effect (NOE) (MTR_{NOE} [%] = 8.9 ± 0.9, 12.6 ± 1.6, in radiation necrosis and tumor progression, respectively) were measured in progressive tumors compared to radiation necrosis. These CEST metrics differentiated the two lesion types with high accuracy ($p < 0.0001$ for both MTR_{NOE} and MTR_{Amide} (72) in this small-scale clinical study, demonstrating their potential in patient management.

SWI

Changes to the micro-vasculature has been studied with susceptibility weighted imaging (SWI) and transverse relaxation rate, R_2^*, mapping. Although these techniques have not been examined in patients with brain metastases, Belliveau et al. (28) used SWI and R_2^* mapping in nine patients with GBM suspected of having progressive disease ($n = 5$) or pseudo-progression ($n = 4$). They measured higher R_2^* on both contrast enhancing (CE) and non-CE regions of the lesions in tumor progression compared to pseudo-progression (R_2^* was approximately 60% higher in the CE regions and approximately 14% higher in the non-CE region of the progression cases) (28).

Moreover, in an animal model of radiation necrosis, R_2^* increased (compared to controls) after radiation in hippocampus—supporting the neuro-inflammatory response to radiotherapy (110)—up to 10 weeks before other radiological signs were detectable (111), demonstrating its high sensitivity to radiation-induced changes in the brain and its promise in differentiating radiation necrosis from tumor progression.

Tumor Effects on Normal Brain Tissue

qMRI techniques are sensitive to damage to the normal brain structures, in particular neuronal damage. Several studies have observed that even the presence of an intracranial tumor (without any treatment) may lead to alteration or damage to remote brain structures and tissues that appear normal on anatomical imaging. Boorstein et al. (112) studied 15 patients with brain

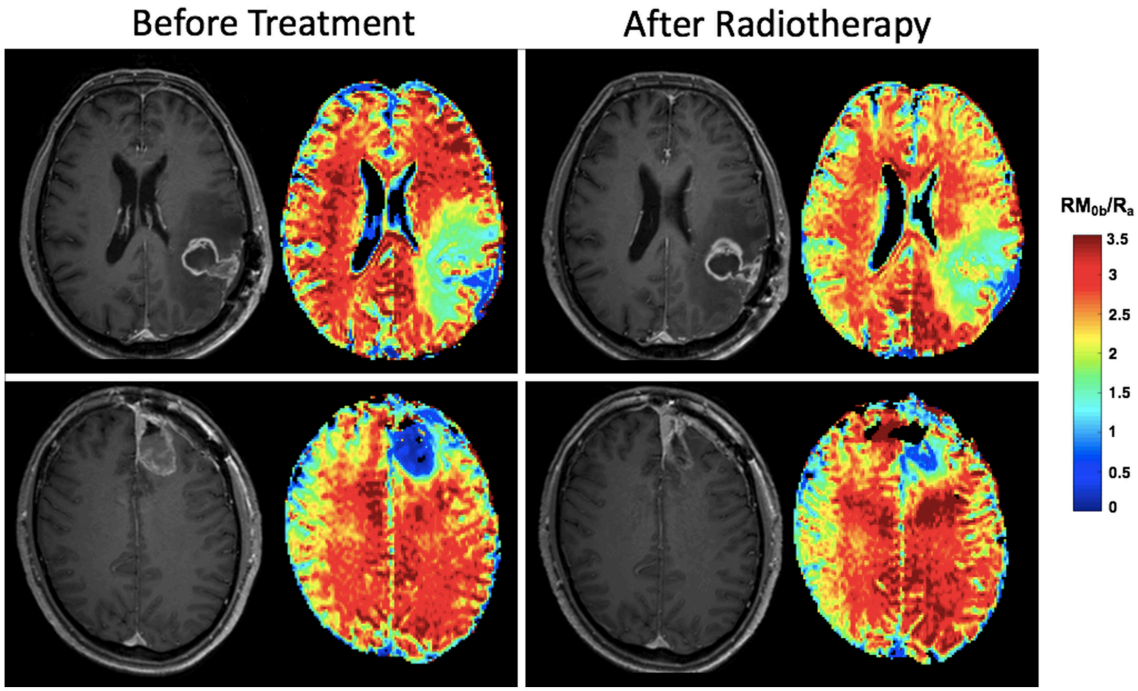


FIGURE 7 | Effects of radiotherapy plus Temozolomide on normal tissue of two patients with GBM. Both patients received IMRT at a dose of 2Gy/day. After the first 10 fractions, the white matter on the contralateral side of the brain on post-Gd T_{1w}-MRI appears normal before and after treatment for both patients. The parametric maps show the amount of magnetization transfer (MT), RM_{0b}/R_a which quantifies white matter integrity. The patient in the top row experiences significant decrease in amount of MT showing significant white matter damage, while for the patient in the bottom row, the amount of MT has not changed showing the patient's resistance to radiation.

metastases (with non-CNS primary neoplasms) before treatment, to assess the effects of the tumor on the normal appearing brain structures (exclusion criteria was previous cranial radiotherapy or systemic chemotherapy). This study reported no change in the MTR on the cNAWM of the patients; however, they measured significantly lower MTR on the ipsilateral NAWM (outside areas of edema), which may be caused by the destruction of myelin or increased intracellular fluid. Another potential cause of these changes is early formation of new micro-metastases not visible on anatomical MRI.

Similarly, damage to normal brain structures (prior to any treatment) has been reported in other intracranial tumors such as GBM, likely due to their widely invasive and infiltrative nature (75, 113). Such tumor-related normal appearing tissue changes have been detected with DTI (increased fractional anisotropy, FA due to destruction of neurons in cNAWM) (113), qMT (increased direct effect of the free water pool, $1/(R_aT_{2a})$ calculated from qMT measurements in cNAWM) (75), and CEST (altered metabolism measured with decrease in Amide and Amine CEST signals in cNAWM) (75). The results of these pilot studies highlight the potential sensitivity of qMRI to tumor-related changes in brain tissues that appear normal on clinical MRI scans.

Treatment Effects on Normal Brain Tissue

In addition to the effects of the tumor on distant brain tissues, the treatment (radiotherapy and chemotherapy) also significantly impacts the normal (or normal appearing) brain structures. Whole brain radiotherapy (WBRT) plays an important role in the management of patients with multiple brain metastases and can reduce the rate of distant brain failure (114, 115). However, it comes at a cost of decreased cognitive function due to damage to the normal brain structures and results in a detriment to the patients' quality of life, particularly those with extended survival (51, 106). Considering the palliative nature of the treatment for brain metastases, sparing normal brain function and avoiding impairment to patients' quality of life is of utmost importance in their management.

Once the tumor is treated with radiation, a decrease in qMT parameters (such as amount of magnetization transfer, RM_{0b}/R_a) is observed even after a few radiotherapy sessions due to disruption of the white matter integrity. Unpublished data in **Figure 7** shows effects of 10 treatment session with 2Gy/day on two patients with GBM, showing the different response of the normal brain tissue of the patients to radiotherapy plus chemotherapy where one patient experiences significant change in qMT parameter and the other patient experiencing no change.

Pospisil et al. (43) investigated 18 patients with brain metastases (primary cancer: 1 lung, 5 breast, 5 renal cell carcinoma, 3 NSCLC, 2 gastrointestinal, 1 gynecological, and 1 other cancer type) undergoing WBRT with MRS (before and 4 months after WBRT). This study reported significant

decrease in hippocampus NAA after treatment (a marker of neuronal loss), which was accompanied by a decrease in the patients' quality of life. The loss of hippocampal NAA has also been correlated with cognitive decline after WBRT (83).

DTI has also been used in assessing radiotherapy effects on normal brain microstructure. Chapman et al. (51) acquired DTI data before radiotherapy, during radiotherapy (3 weeks and 6 weeks after start of radiotherapy), and after radiotherapy (10, 30, and 78 weeks after start of radiotherapy) in 10 brain cancer patients and performed neurocognitive functional tests as well as measuring quality of life metrics. They reported decreased longitudinal diffusivity (significant at 6-week scan compared to pre-treatment) and increased perpendicular diffusivity (significant at 10-week scan compared to pre-treatment)—both indicators of neuronal integrity destruction. They also observed positive correlation in percent change (compared to pre-treatment) of longitudinal diffusivity at 6-week scan, with its change at 30-week scan (correlation coefficient, $r = 0.70$, $p < 0.05$) indicating early changes in this parameter may be able to predict its later changes.

Chapman et al. (51) also reported dose dependence of the DTI changes; particularly for perpendicular diffusivity which at 3-week scan correlated with radiation dose ($r = 0.49$, $p < 0.05$). In addition, they reported linear correlation between longitudinal diffusivity post-radiotherapy (30-week scan), and verbal recall scores of the patients ($r = 0.73$, $p < 0.02$); and observed that longitudinal diffusivity during radiotherapy (3-week and 6-week scans) could predicts post-radiotherapy verbal recall scores ($p < 0.05$) (51). These studies, although performed in small number of patients, demonstrate the potential of qMRI techniques in characterizing treatment-induced changes in normal appearing brain structures, which may be useful in patient management.

CLINICAL TRANSLATION AND LIMITATIONS

Brain metastases originate from multitude of primary cancers with breast cancer, lung cancer, and melanoma being the most frequent cancers to metastasize to the brain. Brain metastases carry several characteristics of the primary tumor, for instance microvasculature of the brain metastases is different from that of the normal brain and mimics the microvasculature of the original tumor (i.e., lack of neuro-vascular unit components that leads to uniformly increased vasogenic edema) (116). The similarities between brain metastases and their primary tumors necessitates investigating the qMRI markers for each primary site, since what is true for metastasis from one tumor might not necessarily be true for metastasis from another primary site. This issue was not considered in any of the studies that were reviewed here. These studies were all pilot studies and were evaluating the potential of new MRI techniques in management of brain metastases, with the goal of developing new biomarkers. Thus, they enrolled as many patients as possible with metastases from different primary sites. Clinical studies with focus on metastases from one primary site are needed to determine if the primary site has an impact on the performance of these biomarkers.

qMRI techniques have the potential to assist physicians in managing patients with brain metastases. However, the evaluation of these techniques has been limited to small, single-center studies due to limited availability of the imaging sequences, as well as lack of expertise and standardization for widespread clinical use. All the studies that were reviewed here were conduct on a small number of patients, many of them at one institution and were conducted by research teams that either developed the technique or are experts in applying them. Large multi-center clinical trials are needed to fully assess the potential of these biomarkers and their clinical utility. Standardization of the techniques and development of analysis tools that could be used by users in a clinical setting is crucial for their clinical translation.

Incorporation of advanced qMRI techniques in clinical practice results in longer MRI scans (usually 60–90 min). Given the general health state of brain metastasis patients, they may not be able to easily tolerate the requirement for staying still in the MRI scanner for long scans. In the authors experience around 60-min scans were well-tolerated by the patients, however, attrition rate of 20–30% was reported in patients that attended the first scan but did not complete the study (71). Optimization of the scan protocols and establishing the benefit of the added MRI sequences to the patient care might increase patient participation rate. Finally, many of these techniques such as CEST, qMT, and MRS require very long scan times and provide reduced brain coverage, limiting their value in clinical decision making. Technological developments are needed to accelerate these techniques to allow for better coverage without losing specificity and sensitivity. Many of these technical issues have not been studied for the introduced qMRI techniques and need to be investigated and addressed before any clinical translation.

AUTHOR CONTRIBUTIONS

HM performed the literature review and prepared the manuscript. JD, HS, AS, and GJS contributed equally to the preparation of the manuscript.

FUNDING

This study was funded by the Canadian Institute of Health Research (CIHR TJT156252), Terry Fox Research Institute (TFRI 1083), and the Canadian Cancer Society Research Institute (CCSRI 705083).

REFERENCES

1. Stelzer KJ. Epidemiology and prognosis of brain metastases. *Surg. Neurol. Int.* (2013) 4:S192–202. doi: 10.4103/2152-7806.111296

2. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised

trial. *Lancet.* (2004) 363:1665–72. doi: 10.1016/S0140-6736(04)16250-8
3. Hoefnagels FW, Lagerwaard FJ, Sanchez E, Haasbeek CJ, Knol DL, Slotman BJ, et al. Radiological progression of cerebral metastases after radiosurgery: assessment of perfusion MRI for differentiating between necrosis and recurrence. *J. Neurol.* (2009) 256:878–87. doi: 10.1007/s00415-009-5034-5
4. Caponnetto S, Draghi A, Borch TH, Nuti M, Cortesi E, Svane IM, et al. Cancer immunotherapy in patients with brain metastases. *Cancer Immunol Immunother.* (2018) 67:703–11. doi: 10.1007/s00262-018-2146-8
5. Di Lorenzo R, Ahluwalia MS. Targeted therapy of brain metastases: latest evidence and clinical implications. *Ther Adv Med Oncol.* (2017) 9:781–96. doi: 10.1177/1758834017736252
6. Agarwala SS, Kirkwood JM, Gore M, Dreno B, Thatcher N, Czarnetski B, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol.* (2004) 22:2101–7. doi: 10.1200/JCO.2004.11.044
7. Cohen JV, Kluger HM. Systemic immunotherapy for the treatment of brain metastases. *Front Oncol.* (2016) 6:49. doi: 10.3389/fonc.2016.00049
8. Sharpton SR, Oermann EK, Moore DT, Schreiber E, Hoffman R, Morris DE, et al. The volumetric response of brain metastases after stereotactic radiosurgery and its post-treatment implications. *Neurosurgery.* (2014) 74:9–15. doi: 10.1227/NEU.0000000000000190
9. Geijer B, Holtås S. Diffusion-weighted imaging of brain metastases: their potential to be misinterpreted as focal ischaemic lesions. *Neuroradiology.* (2002) 44:568–73. doi: 10.1007/s00234-002-0792-0
10. Duygulu G, Ovali GY, Calli C, Kitis O, Yunten N, Akalin T, et al. Intracerebral metastasis showing restricted diffusion: correlation with histopathologic findings. *Eur J Radiol.* (2010) 74:117–20. doi: 10.1016/j.ejrad.2009.03.004
11. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol.* (2015) 16:e270–8. doi: 10.1016/S1470-2045(15)70057-4
12. Hall WA. The safety and efficacy of stereotactic biopsy for intracranial lesions. *Cancer.* (1998) 82:1749–55. doi: 10.1002/(SICI)1097-0142(19980501)82:9<1756::AID-CNCR23>3.0.CO;2-2
13. Crowther A, Ocasio J, Fang F, Meidinger J, Wu J, Deal AM, et al. Radiation sensitivity in a preclinical mouse model of medulloblastoma relies on the function of the intrinsic apoptotic pathway. *Cancer Res.* (2016) 76:3211–23. doi: 10.1158/0008-5472.CAN-15-0025
14. Kim YH, Oh SW, Lim YJ, Park CK, Lee SH, Kang KW,et al. Differentiating radiation necrosis from tumor recurrence in high-grade gliomas: assessing the efficacy of 18F-FDG PET, 11C- methionine PET and perfusion MRI. *Clin. Neurol. Neurosurg.* (2010) 112:758–65. doi: 10.1016/j.clineuro.2010.06.005
15. Togawa T, Yui N, Kinoshita F, Yanagisawa M, Namba H. [A study on thallium-201 SPECT in brain metastases of lung cancer: with special reference to tumor size and tumor to normal brain thallium uptake ratio]. *Kaku Igaku.* (1995) 32:217–25.
16. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced T1-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging.* (1999) 10:223–32.
17. Sourbron SP, Buckley DL. Tracer kinetic modelling in MRI: estimating perfusion and capillary permeability. *Phys Med Biol.* (2012) 57:R1–33. doi: 10.1088/0031-9155/57/2/R1
18. Sugahara T, Korogi Y, Tomiguchi S, Shigematsu Y, Ikushima I, Kira T, et al. Posttherapeutic intraaxial brain tumor: the value of perfusion-sensitive contrast-enhanced MR imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue. *Am. J. Neuroradiol.* (2000) 21:901–9.
19. Hein PA, Eskey CJ, Dunn JF, Hug EB. Diffusion-weighted imaging in the follow-up of treated high-grade gliomas: tumor recurrence versus radiation injury. *Am J Neuroradiol.* (2004) 25:201–9.
20. Stanisz GJ, Li JG, Wright GA, Henkelman RM. Water dynamics in human blood via combined measurements of T2 relaxation and diffusion in the presence of Gadolinium. *Magn Reson Med.* (1998) 39:223–33. doi: 10.1002/mrm.1910390209
21. Bailey C, Giles A, Czarnota GJ, Stanisz GJ. Detection of apoptotic cell death *in vitro* in the presence of Gd-DTPA-BMA. *Magn Reson Med.* (2009) 62:46–55. doi: 10.1002/mrm.21972
22. Springer CS. Using1H2O MR to measure and map sodium pump activity *in vivo*. *J Magn Reson.* (2018) 291:110–26. doi: 10.1016/j.jmr.2018.02.018
23. Darzynkiewicz Z, Juan G, Li X, Gorczyca W, Murakami T, Traganos F. Cytometry in cell necrobiology: analysis of apoptosis and accidental cell death (necrosis). *Cytometry.* (1997) 27:1–20.
24. Bailey C, Moosvi F, Stanisz GJ. Mapping water exchange rates in rat tumor xenografts using the late-stage uptake following bolus injections of contrast agent. *Magn Reson Med.* (2014) 71:1874–87. doi: 10.1002/mrm.24847
25. Mehrabian H, Desmond LK, Chavez S, Bailey C, Sahgal A, Czarnota JG, et al. Water exchange rate constant as a biomarker of treatment efficacy in patients with brain metastases undergoing stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* (2017) 98:47–55. doi: 10.1016/j.ijrobp.2017.01.016
26. Chiang F, Tedesqui G, Mauricio Varon D, Wanderley E, Mamata H, Castillo M. Imaging spectrum of brain microhemorrhages on SWI. *Neurographics.* (2016) 6:174–86. doi: 10.3174/ng.3160157
27. Varon D, Simons M, Chiang F, Tedesqui G, Pacheco G, Martinez P, et al. Brain radiation-related black dots on susceptibility-weighted imaging. *Neuroradiol J.* (2014) 27:445–51. doi: 10.15274/NRJ-2014-10071
28. Belliveau JG, Bauman GS, Macdonald D, Macdonald M, Klassen LM, Menon RS. Apparent transverse relaxation (R2*) on MRI as a method to differentiate treatment effect (pseudoprogression) versus progressive disease in chemoradiation for malignant glioma. *J Med Imaging Radiat Oncol.* (2018) 62:224–31. doi: 10.1111/1754-9485.12694
29. Toft PB, Leth H, Lou HC, Pryds O, Henriksen O. Metabolite concentrations in the developing brain estimated with proton MR spectroscopy. *J Magn Reson Imaging.* (2018) 4:674–80. doi: 10.1002/jmri.1880040510
30. Proctor WG, Yu FC. The dependence of a nuclear magnetic resonance frequency upon chemical compound. *Phys Rev.* (1950) 77:717. doi: 10.1103/PhysRev.77.717
31. Burri R, Steffen C, Herschkowitz N. N-acetyl-L-aspartate is a major source of acetyl groups for lipid synthesis during rat brain development. *Dev. Neurosci.* (1991) 13:403–11. doi: 10.1159/000112191
32. Wehrl HF, Schwab J, Hasenbach K, Reischl G, Tabatabai G, Quintanilla-Martinez L, et al. Multimodal elucidation of choline metabolism in a murine glioma model using magnetic resonance spectroscopy and 11C-choline positron emission tomography. *Cancer Res.* (2013) 73:1470–80. doi: 10.1158/0008-5472.CAN-12-2532
33. Li Y, Park I, Nelson SJ. Imaging tumor metabolism using *in vivo* magnetic resonance spectroscopy. *Cancer J.* (2015) 21:123–8. doi: 10.1097/PPO.0000000000000097
34. Mori N, Wildes F, Takagi T, Glunde K, Bhujwalla ZM. The tumor microenvironment modulates choline and lipid metabolism. *Front Oncol.* (2016) 6:262. doi: 10.3389/fonc.2016.00262
35. Ricci PE, Pitt A, Keller PJ, Coons SW, Heiserman JE. Effect of voxel position on single-voxel MR spectroscopy findings. *Am J Neuroradiol.* (2000) 21:367–74.
36. Landheer K, Sahgal A, Myrehaug S, Chen AP, Cunningham CH, Graham SJ. A rapid inversion technique for the measurement of longitudinal relaxation times of brain metabolites: application to lactate in high-grade gliomas at 3 T. *NMR Biomed.* (2016) 29:1381–90. doi: 10.1002/nbm.3580
37. Weybright P, Sundgren PC, Maly P, Hassan DG, Nan B, Rohrer S, et al. Differentiation between brain tumor recurrence and radiation injury using MR spectroscopy. *Am J Roentgenol.* (2005) 185:1471–6. doi: 10.2214/AJR.04.0933
38. Ishimaru H, Morikawa M, Iwanaga S, Kaminogo M, Ochi M, Hayashi K. Differentiation between high-grade glioma and metastatic brain tumor using single-voxel proton MR spectroscopy. *Eur Radiol.* (2001) 11:1784–91. doi: 10.1007/s003300000814
39. Caivano R, Lotumolo A, Rabasco P, Zandolino A, D'Antuono F, Villonio A, et al. 3 Tesla magnetic resonance spectroscopy: cerebral gliomas vs. metastatic brain tumors. Our experience and review of the literature. *Int J Neurosci.* (2013) 123:537–43. doi: 10.3109/00207454.2013.774395
40. Sjøbakk TE, Johansen R, Bathen TF, Sonnewald U, Kvistad KA, Lundgren S, et al. Metabolic profiling of human brain metastases

using *in vivo* proton MR spectroscopy at 3T. *BMC Cancer.* (2007) 7:141. doi: 10.1186/1471-2407-7-141
41. Schlemmer HP, Bachert P, Herfarth KK, Zuna I, Debus J, van Kaick G. Proton MR spectroscopic evaluation of suspicious brain lesions after stereotactic radiotherapy. *Am J Neuroradiol.* (2001) 22:1316–24.
42. Magalhaes A, Godfrey W, Shen Y, Hu J, Smith W. Proton magnetic resonance spectroscopy of brain tumors correlated with pathology. *Acad Radiol.* (2005) 12:51–7. doi: 10.1016/j.acra.2004.10.057
43. Pospisil P, Kazda T, Hynkova L, Bulik M, Dobiaskova M, Burkon P, et al. Post-WBRT cognitive impairment and hippocampal neuronal depletion measured by *in vivo* metabolic MR spectroscopy: results of prospective investigational study. *Radiother Oncol.* (2017) 122:373–9. doi: 10.1016/j.radonc.2016.12.013
44. Kim DY, Kim HS, Goh MJ, Choi CG, Kim SJ. Utility of intravoxel incoherent motion MR imaging for distinguishing recurrent metastatic tumor from treatment effect following gamma knife radiosurgery: initial experience. *Am J Neuroradiol.* (2014) 35:2082–90. doi: 10.3174/ajnr.A3995
45. Kapadia A, Mehrabian H, Conklin J, Symons SPSP, Maralani PJ, Stanisz GJGJ, et al. Temporal evolution of perfusion parameters in brain metastases treated with stereotactic radiosurgery: comparison of intravoxel incoherent motion and dynamic contrast enhanced MRI. *J Neurooncol.* (2017) 135:119–27. doi: 10.1007/s11060-017-2556-z
46. Detsky JS, Keith J, Conklin J, Symons S, Myrehaug S, Sahgal A, et al. Differentiating radiation necrosis from tumor progression in brain metastases treated with stereotactic radiotherapy: utility of intravoxel incoherent motion perfusion MRI and correlation with histopathology. *J Neurooncol.* (2017) 134:433–41. doi: 10.1007/s11060-017-2545-2
47. Connor M, Karunamuni R, McDonald C, White N, Pettersson N, Moiseenko V, et al. Dose-dependent white matter damage after brain radiotherapy. *Radiother Oncol.* (2016) 121:209–16. doi: 10.1016/j.radonc.2016.10.003
48. Le Bihan D, Breton E, Lallemand D, Aubin M-L, Vignaud J, Laval-Jeantet M. separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology.* (1988) 168:497–505.
49. Conklin J, Heyn C, Roux M, Cerny M, Wintermark M, Federau C. A simplified model for intravoxel incoherent motion perfusion imaging of the brain. *Am J Neuroradiol.* (2016) 37:2251–7. doi: 10.3174/ajnr.A4929
50. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics.* (2007) 4:316–29. doi: 10.1016/j.nurt.2007.05.011
51. Chapman CH, Nagesh V, Sundgren PC, Buchtel H, Chenevert TL, Junck L, et al. Diffusion tensor imaging of normal-appearing white matter as biomarker for radiation-induced late delayed cognitive decline. *Int J Radiat Oncol Biol Phys.* (2012) 82:2033–40. doi: 10.1016/j.ijrobp.2011.01.068
52. Henkelman RM, Huang X, Xiang QS, Stanisz GJ, Swanson SD, Bronskill MJ. Quantitative interpretation of magnetization transfer. *Magn Reson Med.* (1993) 29:759–66.
53. Mehrabian H, Myrehaug S, Soliman H, Sahgal A, Stanisz GJGJ. Quantitative magnetization transfer in monitoring glioblastoma (GBM) response to therapy. *Sci Rep.* (2018) 8:2475. doi: 10.1038/s41598-018-20624-6
54. Newbould RD, Nicholas R, Thomas CL, Quest R, Lee JS, Honeyfield L, et al. Age independently affects myelin integrity as detected by magnetization transfer magnetic resonance imaging in multiple sclerosis. *Neuroimage Clin.* (2014) 4:641–8. doi: 10.1016/j.nicl.2014.02.004
55. Levesque IR, Giacomini PS, Narayanan S, Ribeiro LT, Sled JG, Arnold DL, et al. Quantitative magnetization transfer and myelin water imaging of the evolution of acute multiple sclerosis lesions. *Magn. Reson. Med.* (2010) 63:633–640. doi: 10.1002/mrm.22244
56. Horsfield MA. Magnetization transfer imaging in multiple sclerosis. *J Neuroimaging.* (2005) 15:58S−67S. doi: 10.1177/1051228405282242
57. Tozer DJ, Rees JH, Benton CE, Waldman AD, Jäger HR, Tofts PS. Quantitative magnetisation transfer imaging in glioma: preliminary results. *NMR Biomed.* (2011) 24:492–8. doi: 10.1002/nbm.1614
58. Bailey C, Desmond KL, Czarnota GJ, Stanisz GJ. Quantitative magnetization transfer studies of apoptotic cell death. *Magn. Reson. Med.* (2011) 66:264–9. doi: 10.1002/mrm.22820
59. Van Zijl PCM, Yadav NN. Chemical exchange saturation transfer (CEST): what is in a name and what isn't? *Magn Reson Med.* (2011) 65:927–48. doi: 10.1002/mrm.22761
60. DeBrosse C, Nanga RPR, Bagga P, Nath K, Haris M, Marincola F, et al. Lactate chemical exchange saturation transfer (LATEST) imaging *in vivo* a biomarker for LDH activity. *Sci Rep.* (2016) 6:1–10. doi: 10.1038/srep19517
61. Wang J, Weygand J, Hwang K-P, Mohamed ASR, Ding Y, Fuller CD, et al. Magnetic resonance imaging of glucose uptake and metabolism in patients with head and neck cancer. *Sci Rep.* (2016) 6:30618. doi: 10.1038/srep30618
62. van Zijl PCM, Lam WW, Xu J, Knutsson L, Stanisz GJ. Magnetization transfer contrast and chemical exchange saturation transfer MRI. Features and analysis of the field-dependent saturation spectrum. *Neuroimage.* (2018) 168:222–41. doi: 10.1016/j.neuroimage.2017.04.045
63. Zhou J, Wilson DA, Sun PZ, Klaus JA, Van Zijl PCM. Quantitative description of proton exchange processes between water and endogenous and exogenous agents for WEX, CEST, and APT experiments. *Magn Reson Med.* (2004) 51:945–52. doi: 10.1002/mrm.20048
64. Zhang XY, Wang F, Xu J, Gochberg DF, Gore JC, Zu Z. Increased CEST specificity for amide and fast-exchanging amine protons using exchange-dependent relaxation rate. *NMR Biomed.* (2018) 31:1–13. doi: 10.1002/nbm.3863
65. Zu Z, Louie EA, Lin EC, Jiang X, Does MD, Gore JC, et al. Chemical exchange rotation transfer imaging of intermediate-exchanging amines at 2 ppm. *NMR Biomed.* (2017) 30:1–12. doi: 10.1002/nbm.3756
66. Sun PZ, Sorensen AG. Imaging pH using the chemical exchange saturation transfer (CEST) MRI: correction of concomitant RF irradiation effects to quantify CEST MRI for chemical exchange rate and pH. *Magn Reson Med.* (2008) 60:390–7. doi: 10.1002/mrm.21653
67. Zhou J, Payen J-F, Wilson DA, Traystman RJ, Van Zijl PCM. Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. *Nat Med.* (2003) 9:1085–90. doi: 10.1038/nm907
68. Desmond KL, Moosvi F, Stanisz GJ. Mapping of amide, amine, and aliphatic peaks in the CEST spectra of murine xenografts at 7 T. *Magn Reson Med.* (2014) 71:1841–53. doi: 10.1002/mrm.24822
69. Desmond KL, Mehrabian H, Chavez S, Sahgal A, Soliman H, Rola R, et al. Chemical exchange saturation transfer for Predicting response to stereotactic radiosurgery in human brain metastasis. *Magn Reson Med.* (2017) 78:1110–20. doi: 10.1002/mrm.26470
70. Zhou J, Tryggestad E, Wen Z, Lal B, Zhou T, Grossman R, et al. Differentiation between glioma and radiation necrosis using molecular magnetic resonance imaging of endogenous proteins and peptides. *Nat Med.* (2011) 17:130–4. doi: 10.1038/nm.2268
71. Mehrabian H, Myrehaug S, Soliman H, Sahgal A, Stanisz GJ. Evaluation of glioblastoma response to therapy with chemical exchange saturation transfer. *Int J Radiat Oncol Biol Phys.* (2018) 101:713–23. doi: 10.1016/j.ijrobp.2018.03.057
72. Mehrabian H, Desmond KL, Soliman H, Sahgal A, Stanisz GJ. Differentiation between radiation necrosis and tumor progression using chemical exchange saturation transfer. *Clin Cancer Res.* (2017) 23:3667–75. doi: 10.1158/1078-0432.CCR-16-2265
73. Xu J, Zaiss M, Zu Z, Li H, Xie J, Gochberg DF, et al. On the origins of chemical exchange saturation transfer (CEST) contrast in tumors at 9.4T. *NMR Biomed.* (2014) 27:406–16. doi: 10.1002/nbm.3075
74. Zaiss M, Windschuh J, Paech D, Meissner JE, Burth S, Schmitt B, et al. Relaxation-compensated CEST-MRI of the human brain at 7T: unbiased insight into NOE and amide signal changes in human glioblastoma. *Neuroimage.* (2015) 112:180–8. doi: 10.1016/j.neuroimage.2015.02.040
75. Mehrabian H, Lam WW, Myrehaug S, Sahgal A, Stanisz GJ. Glioblastoma (GBM) effects on quantitative MRI of contralateral normal appearing white matter. *J Neurooncol.* (2018) 139:97–106. doi: 10.1007/s11060-018-2846-0
76. Chiang IC, Kuo Y-T, Lu C-Y, Yeung K-W, Lin W-C, Sheu F-O, et al. Distinction between high-grade gliomas and solitary metastases using peritumoral 3-T magnetic resonance spectroscopy, diffusion, and perfusion imagings. *Neuroradiology.* (2004) 46:619–27. doi: 10.1007/s00234-004-1246-7
77. Garcia M, Gloor M, Bieri O, Radue EW, Lieb JM, Cordier D, et al. Imaging of primary brain tumors and metastases with fast quantitative 3-dimensional magnetization transfer. *J Neuroimaging.* (2015) 25:1007–14. doi: 10.1111/jon.12222

78. Paech D, Windschuh J, Oberhollenzer J, Dreher C, Sahm F, Meissner JE, et al. Assessing the predictability of IDH mutation and MGMT methylation status in glioma patients using relaxation-compensated multipool CEST MRI at 7.0 T. *Neuro Oncol.* (2018) 20:1661–71. doi: 10.1093/neuonc/noy073
79. Jones CK, Schlosser MJ, van Zijl PCM, Pomper MG, Golay X, Zhou J. Amide proton transfer imaging of human brain tumors at 3T. *Magn Reson Med.* (2006) 56:585–92. doi: 10.1002/mrm.20989
80. Zhao X, Wen Z, Zhang G, Huang F, Lu S, Wang X, Hu S, et al. Three-dimensional turbo-spin-echo amide proton transfer MR imaging at 3-Tesla and its application to high-grade human brain tumors. *Mol Imaging Biol.* (2013) 15:114–22. doi: 10.1007/s11307-012-0563-1
81. Jing Y, Chen S, King AD, Zhou S, Bhatia KS, Zhang Q, et al. Amide proton transfer-weighted imaging of the head and neck at 3 T: a feasibility study on healthy human subjects and patients with head and neck cancer. *NMR Biomed.* (2014) 27:1239–47. doi: 10.1002/nbm.3184
82. Rivlin M, Horev J, Tsarfaty I, Navon G. Molecular imaging of tumors and metastases using chemical exchange saturation transfer (CEST) MRI. *Sci Rep.* (2013) 3:3045. doi: 10.1038/srep03045
83. Pospisil P, Kazda T, Bulik M, Dobiaskova M, Burkon P, Hynkova L, et al. Hippocampal proton MR spectroscopy as a novel approach in the assessment of radiation injury and the correlation to neurocognitive function impairment: initial experiences. *Radiat Oncol.* (2015) 10:211. doi: 10.1186/s13014-015-0518-1
84. Cha S, Lupo JM, Chen M-H, Lamborn KR, McDermott MW, Berger MS, et al. Differentiation of glioblastoma multiforme and single brain metastasis by peak height and percentage of signal intensity recovery derived from dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *Am J Neuroradiol.* (2007) 28:1078–84. doi: 10.3174/ajnr.a0484
85. Patel M, Nguyen HS, Doan N, Gelsomino M, Shabani S, Mueller W. Glioblastoma mimicking meningioma: report of 2 cases. *World Neurosurg.* (2016) 95:624.e9–13. doi: 10.1016/j.wneu.2016.08.048
86. Matsusue E, Fink JR, Rockhill JK, Ogawa T, Maravilla KR. Distinction between glioma progression and post-radiation change by combined physiologic MR imaging. *Neuroradiology.* (2010) 52:297–306. doi: 10.1007/s00234-009-0613-9
87. Huang J, Wang A-M, Shetty A, Maitz AH, Yan D, Doyle D, et al. Differentiation between intra-axial metastatic tumor progression and radiation injury following fractionated radiation therapy or stereotactic radiosurgery using MR spectroscopy, perfusion MR imaging or volume progression modeling. *Magn Reson Imaging.* (2011) 29:993–1001. doi: 10.1016/j.mri.2011.04.004
88. Chuang MT, Liu YS, Tsai YS, Chen YC, Wang CK. Differentiating radiation-induced necrosis from recurrent brain tumor using MR perfusion and spectroscopy: a meta-analysis. *PLoS ONE.* (2016) 11:1–13. doi: 10.1371/journal.pone.0141438
89. Zhou J, Lal B, Wilson DA, Laterra J, Van Zijl PCM. Amide proton transfer (APT) contrast for imaging of brain tumors. *Magn Reson Med.* (2003) 50:1120–6. doi: 10.1002/mrm.10651
90. Jia G, Abaza R, Williams JD, Zynger DL, Zhou J, Shah ZK, et al. Amide proton transfer MR imaging of prostate cancer: a preliminary study. *J Magn Reson Imaging.* (2011) 33:647–54. doi: 10.1002/jmri.22480
91. Paech D, Burth S, Windschuh J, Meissner J-E, Zaiss M, Eidel O, et al. Nuclear overhauser enhancement imaging of glioblastoma at 7 Tesla: region specific correlation with apparent diffusion coefficient and histology. *PLoS ONE.* (2015) 10:1–16. doi: 10.1371/journal.pone.0121220
92. Salice S, Esposito R, Ciavardelli D, Delli Pizzi S, di Bastiano R, Tartaro A. Combined 3 Tesla MRI biomarkers improve the differentiation between benign vs malignant single ring enhancing brain masses. *PLoS ONE.* (2016) 11:e0159047. doi: 10.1371/journal.pone.0159047
93. Ainsworth NL, McLean MA, McIntyre DJO, Honess DJ, Brown AM, Harden SV, et al. Quantitative and textural analysis of magnetization transfer and diffusion images in the early detection of brain metastases. *Magn Reson Med.* (2017) 77:1987–95. doi: 10.1002/mrm.26257
94. Mantyla MJ, Toivanen JT, Pitkanen MA, Rekonen AH. Radiation-induced changes in regional blood flow in human tumors. *Int J Radiat Oncol Biol Phys.* (1982) 8:1711–7.
95. Pirhonen JP, Grenman SA, Bredbacka AB, Bahado-Singh RO, Salmi TA. Effects of external radiotherapy on uterine blood flow in patients with advanced cervical carcinoma assessed by color Doppler ultrasonography. *Cancer.* (1995) 76:67–71.
96. Kocher M, Treuer H, Voges J, Hoevels M, Sturm V, Muller RP. Computer simulation of cytotoxic and vascular effects of radiosurgery in solid and necrotic brain metastases. *Radiother Oncol.* (2000) 54:149–56. doi: 10.1016/s0167-8140(99)00168-1
97. Hatzoglou V, Tisnado J, Mehta A, Peck KK, Daras M, Omuro AM, et al. Dynamic contrast-enhanced MRI perfusion for differentiating between melanoma and lung cancer brain metastases. *Cancer Med.* (2017) 6:761–7. doi: 10.1002/cam4.1046
98. Ross DA, Sandler HM, Balter JM, Hayman JA, Archer PG, Auer DL. Imaging changes after stereotactic radiosurgery of primary and secondary malignant brain tumors. *J Neurooncol.* (2002) 56:175–81. doi: 10.1023/A:1014571900854
99. Huber PE, Hawighorst H, Fuss M, Van Kaick G, Wannenmacher MF, Debus J. Transient enlargement of contrast uptake on MRI after linear accelerator (linac) stereotactic radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* (2001) 49:1339–49. doi: 10.1016/s0360-3016(00)01511-x
100. Peterson AM, Meltzer CC, Evanson EJ, Flickinger JC, Kondziolka D. MR imaging response of brain metastases after gamma knife stereotactic radiosurgery. *Radiology.* (1999) 211:807–14.
101. Varlotto JM, Flickinger JC, Niranjan A, Bhatnagar A, Kondziolka D, Lunsford LD. The impact of whole-brain radiation therapy on the long-term control and morbidity of patients surviving more than one year after gamma knife radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* (2005) 62:1125–32. doi: 10.1016/j.ijrobp.2004.12.092
102. Alomari A, Rauch PJ, Orsaria M, Minja FJ, Chiang VL, Vortmeyer AO. Radiologic and histologic consequences of radiosurgery for brain tumors. *J Neurooncol.* (2014) 117:33–42. doi: 10.1007/s11060-014-1359-8
103. Kim WH, Kim DG, Han JH, Paek SH, Chung H-T, Park C-K, et al. Early significant tumor volume reduction after radiosurgery in brain metastases from renal cell carcinoma results in long-term survival. *Int J Radiat Oncol Biol Phys.* (2012) 82:1749–55. doi: 10.1016/j.ijrobp.2011.03.044
104. Patel U, Patel A, Cobb C, Benkers T, Vermeulen S. The management of brain necrosis as a result of SRS treatment for intra-cranial tumors. *Transl Cancer Res.* (2014) 3:373–82. doi: 10.3978/j.issn.2218-676X.2014.07.05
105. Klos KJ, O'Neill BP. Brain metastases. *Neurologist.* (2004) 10:31–46. doi: 10.1097/01.nrl.0000106922.83090.71
106. Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. *Nat Rev Neurol.* (2016) 13:52–64. doi: 10.1038/nrneurol.2016.185
107. Marsa GW, Goffinet DR, Rubinstein LJ, Bagshaw MA. Megavoltage irradiation in the treatment of gliomas of the brain and spinal cord. *Cancer.* (1975) 36:1681–9. doi: 10.1002/1097-0142(197511)36:5<1681::AID-CNCR2820360523>3.0.CO;2-Z
108. Constine LS, Konski A, Ekholm S, McDonald S, Rubin P. Adverse effects of brain irradiation correlated with MR and CT imaging. *Int J Radiat Oncol Biol Phys.* (1988) 15:319–30. doi: 10.1134/S1062359011100141
109. Remler MP, Marcussen WH, Tiller-Borsich J. The late effects of radiation on the blood brain barrier. *Int J Radiat Oncol Biol Phys.* (1986) 12:1965–9. doi: 10.1016/0360-3016(86)90133-1
110. Jenrow KA, Brown SL, Lapanowski K, Naei H, Kolozsvary A, Kim JH. Selective inhibition of microglia-mediated neuroinflammation mitigates radiation-induced cognitive impairment. *Radiat Res.* (2013) 179:549–56. doi: 10.1667/RR3026.1
111. Belliveau J-G, Jensen MD, Stewart JMP, Solovey I, Klassen LM, Bauman GS, et al. Prediction of radiation necrosis in a rodent model using magnetic resonance imaging apparent transverse relaxation (R_2^*). *Phys Med Biol.* (2018) 63:34. doi: 10.1088/1361-6560/aaa034
112. Boorstein JM, Wong KT, Grossman RI, Bolinger L, McGowan JC. Metastatic lesions of the brain: imaging with magnetization transfer. *Radiology.* (1994) 191:799–803. doi: 10.1148/radiology.191.3.8184068

113. Horvath A, Perlaki G, Toth A, Orsi G, Nagy S, Doczi T, et al. Increased diffusion in the normal appearing white matter of brain tumor patients: is this just tumor infiltration? *J Neurooncol.* (2016) 127:83–90. doi: 10.1007/s11060-015-2011-y
114. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys.* (2015) 91:710–7. doi: 10.1016/j.ijrobp.2014.10.024
115. Ayala-Peacock DN, Peiffer AM, Lucas JT, Isom S, Kuremsky JG, Urbanic JJ, et al. A nomogram for predicting distant brain failure in patients treated with gamma knife stereotactic radiosurgery without whole brain radiotherapy. *Neuro Oncol.* (2014) 16:1283–8. doi: 10.1093/neuonc/nou018
116. Barajas RF Jr., Cha S, Barajas RF Jr., Cha S. Metastasis in adult brain tumors. *Neuroimaging Clin N Am.* (2016) 26:601–20. doi: 10.1016/j.nic.2016.06.008

Conflict of Interest Statement: AS declares past educational seminars with Elekta AB, Accuray Inc., and Varian medical systems; research grant with Elekta AB; and travel accommodations/expenses by Elekta and Varian. AS also belongs to the Elekta MR Linac Research Consortium.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Mehrabian, Detsky, Soliman, Sahgal and Stanisz. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 04 March 2019
doi: 10.3389/fonc.2019.00099

Targeting Molecular Pathways in Intracranial Metastatic Disease

*Vyshak Alva Venur, Justine V. Cohen and Priscilla K. Brastianos**

Divisions of Neuro-Oncology and Hematology/Oncology, Departments of Neurology and Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

The discovery and clinical application of agents targeting pivotal molecular pathways in malignancies such as lung, breast, renal cell carcinoma, and melanoma have led to impressive improvements in clinical outcomes. Mutations in epidermal growth factor receptor (*EGFR*), and rearrangements of anaplastic lymphoma kinase (*ALK*) are targetable in lung cancer, while *BRAF* mutations have been successfully targeted in metastatic melanoma. Targeting estrogen receptors, cyclin dependent kinases, and *HER2* (Human Epidermal Receptor) have resulted in improvement in survival in breast cancer. Major strides have been made in the management of metastatic renal cell carcinoma by targeting the vascular endothelial growth factor (VEGF) pathway. However, intracranial metastases remain a major hurdle in the setting of targeted therapies. Traditional treatment options for brain metastases include surgery, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). Surgery is effective in symptomatic patients with dominant lesions or solitary intracranial metastases, however, recovery time can be prolonged, often requiring an interruption in systemic treatment. WBRT and SRS provide symptomatic relief and local control but data on improving overall survival is limited. Most targeted therapies which provide extracranial control have limited penetration through the blood brain barrier. Given the limited therapeutic options and increasing prevalence of brain metastases, finding new strategies for the management of intracranial metastatic disease is critical. Genomic analysis of brain metastases has led to a better understanding of variations in the driver mutations compared to the primary malignancy. Furthermore, newer generations of targeted agents have shown promising intracranial activity. In this review, we will discuss the major molecular alterations in brain metastases from melanoma, lung, breast, and renal cell carcinoma. We will provide an in-depth review of the completed and ongoing clinical trials of drugs targeting the molecular pathways enriched in brain metastases.

Keywords: brain metastases (BM), targeted therapy, breast cancer, lung cancer, melanoma

OPEN ACCESS

Edited by:
Arjun Sahgal,
University of Toronto, Canada

Reviewed by:
Riccardo Soffietti,
University of Turin, Italy
Alfredo Conti,
Università degli Studi di Messina, Italy
Parneet K. Cheema,
William Osler Health System, Canada

****Correspondence:***
Priscilla K. Brastianos
pbrastianos@mgh.harvard.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *04 November 2018*
Accepted: *04 February 2019*
Published: *04 March 2019*

Citation:
Venur VA, Cohen JV and Brastianos PK (2019) Targeting Molecular Pathways in Intracranial Metastatic Disease. Front. Oncol. 9:99. doi: 10.3389/fonc.2019.00099

INTRODUCTION

Brain metastases, a common manifestation of advanced solid malignancies, are associated with significant morbidity and mortality. The incidence of brain metastases varies with primary tumor type, and the overall estimate of the incidence is unclear. Lung cancer is the most common cause of brain metastases; small cell lung cancer contributes to up to 50% of brain metastases from lung cancer (1). Breast cancer is the second most common cause of brain metastases; about half of

all brain metastases in breast cancer patients occur in *HER2* (human epidermal growth factor-2) overexpressing breast cancer, followed by triple negative breast cancer, and hormone receptor positive breast cancer (2). The highest frequency of brain metastases is seen in patients with metastatic melanoma. Approximately 50% of metastatic melanoma patients are diagnosed with brain metastases, while an additional 40% are noted to have brain metastases at autopsy (3).

Due to a paucity of reliable animal models with brain metastases, our understanding of the underlying mechanisms of brain metastases is limited. Metastasis is a complex multistep process that includes cell proliferation, invasion of basement membrane, intravasation into blood circulation, survival in blood stream, organ tropism, extravasation, and colonization into specific organs (4). At each step the cell interacts with its surroundings and is under constant survival pressure. A critical component in this process is the epithelial to mesenchymal transformation (EMT) (5). Similarly, when the metastatic cell exits the blood stream and enters the destination organ it again changes from mesenchymal to epithelial phenotype (MET). Multiple genetic and epigenetic factors play a role in EMT and MET, SMAD and non-SMAD signaling, MAP kinase pathway including BRAF alterations, and PI3K/AKT pathway (6–11).

BLOOD BRAIN BARRIER

The presence of the blood brain barrier (BBB) makes brain metastases unique compared to other sites of metastases. The BBB serves a protective role by restricting the movement of cellular components and solutes between systemic circulation and brain. It is comprised of endothelial cells with tight junctions on the systemic circulation side, and pericytes, astrocyte endfoot, and nerve endings on the neuronal side (12). Several efflux transporters of the ATP-binding cassette (ABC) gene family, such as the P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), are upregulated in the endothelial cells of the BBB. These transporters, in addition to being drug specific transporters, play a crucial role in the elimination of toxins and drugs from the CNS (13). While the endothelial barrier restricts the movement of cells across the BBB, it may paradoxically enable the transmigration of malignant cells during the process of diapedesis. The exact mechanism of BBB penetration is unknown however there is data to suggest extravasation of malignant cells which proliferate intravascularly, damage the vessels, and disrupt the BBB, thereby leading to metastases formation. Once the metastatic cells are intracranial, the protective BBB limits the immune surveillance and penetrance of systemic therapies (12). Data from Osswald et al. shows brain metastases can be effectively targeted by certain drugs that are designed to cross the BBB, specifically, small molecular inhibitors (14). Similarly, the blood-tumor barrier (BTB) significantly impacts the efficacy of therapeutic agents in brain metastases. This was clearly described by Lockman et al. (15) with an analysis of the variable permeability of brain metastases from breast cancer human and murine models, impeding the delivery of therapeutic drugs into metastases. Additionally, MRI contrast enhancement to electron-dense tracers demonstrates increased BTB permeability in some brain metastases (16, 17). Since measurements of drug levels in active brain metastases are difficult to obtain, data on the exact mechanism of the BTB is limited. Published results emphasize the need for molecularly targeted therapies with a higher potential for penetration of the BTB in order to reach therapeutic levels within tumors (18).

GENOMICS OF BRAIN METASTASES

The advent of more efficient next-generation sequencing techniques have enhanced our understanding of genomic alterations in brain metastases. Whole exome analysis of brain metastases and matched primary tumor from 86 patients showed genomic heterogeneity and branched evolution (19). These results indicate that although metastatic sites share common genes with primary tumors, they develop unique genetic alterations, providing survival advantage in the brain (19). This study also revealed increased frequency of *PI3K/Akt, mTOR, CDK* alterations in brain metastases. Another relevant study analyzed 16 melanoma brain metastases and matched extracranial sites, with hotspot mutations, mRNA expression patterns, protein expression and activation, and copy number variations (20). The *PI3K/Akt* pathway was enriched in the brain metastases. Overall similarity was noted in most other driver mutations. A multicenter next generation sequencing and gene expression study of ∼17,000 unmatched primary tumors from non-small cell lung cancer (NSCLC), breast cancer and melanoma demonstrated higher TOP2A expression in brain metastases (21). There was also increased expression of proteins critical in DNA synthesis and repair. This research provides important genetic information for future drug development in the treatment of brain metastases.

ALK FUSIONS AND OTHER GENE FUSIONS

Anaplastic lymphoma kinase (*ALK*) fusions were first noted in a subset of anaplastic large cell lymphoma (22) with translocations involving *ALK* on chromosome 2p and molecular partners such as *NPM-ALK*, *TPM3-ALK*, and *TFG-ALK* (23). *ALK* fusions occur in ∼3% of non-small cell lung cancer (NSCLC). The identification of inversions of echinoderm microtubule-associated protein-like 4 (*EML4*) with *ALK* in Japanese women with lung cancer led to the development of drugs targeting *EML4-ALK* fusions (24). This aberrant fusion leads to activation of ALK kinase and downstream signaling pathways including the RAS–mitogen-activated protein kinase (MAPK), JAK-STAT and, phosphoinositide 3-kinase (PI3K) –AKT. One study estimates the incidence of brain metastases in ALK-fusion harboring NSCLC (ALK-NSCLC) to be >45% in 3 years (25). Several tyrosine kinase inhibitors (TKI) are developed for the management of ALK-NSCLC. Crizotinib, the first FDA approved TKI for ALK-NSCLC, has limited CNS penetration with a CSF serum ratio of <0.1 to 0.26% (26, 27). The phase 3 clinical trial of crizotinib in ALK-NSCLC included 79 patients with previously

treated and stable brain metastases, with 39 randomized to receive crizotinib while 40 received chemotherapy (28). The intracranial disease control rate at 12 weeks was 85% in patients treated with crizotinib compared to 45% in those treated with chemotherapy ($p < 0.001$) (29). A retrospective analysis of two randomized clinical trials of crizotinib in treatment naïve ALK-NSCLC showed that 20% of the patients who had extracranial disease progression, developed new brain metastases (30). In summary, although crizotinib provides better intracranial disease control, it has poor CNS penetration and 1 in 5 patients treated with crizotinib develop brain metastases.

The next generation of ALK inhibitors, including ceritinib and alectinib, have improved intracranial activity. The ASCEND-1, a phase 1 trial of ceritinib, included 124 patients with stable brain metastases (31). Data for measurable intracranial lesions was available for 14 patients, 10 of whom had prior exposure to an ALK inhibitor. Intracranial responses were reported in 7 patients and 3 had stable disease. In a phase 2 trial of ceritinib, 100 of 140 total patients had brain metastases, however, only 20 had measurable target lesions. The intracranial response rate was 45%, demonstrating good CNS activity (32).

Alectinib is another ALK inhibitor that has been studied in patients with brain metastases. A phase 3 Japanese study compared alectinib to crizotinib in ALK-NSCLC (J-ALEX study). In the analysis of 207 patients, 43 had brain metastases at enrollment. The 1-year cumulative incidence rates for intracranial progression was lower in alectinib group at 5.9% compared to 16.8% in the crizotinib group (33). Similar results were reported in the international phase 3 trial comparing alectinib to crizotinib (ALEX) in newly diagnosed metastatic ALK-NSCLC where 18 of the 152 patients (12%) in the alectinib group and 68 of the 151 patients (45%) had CNS progression at 18 months (34). All patients in the study had MRI brain at enrollment. The time to CNS progression was longer in patients' treatment with alectinib compared to crizotinib, additionally, 12-month cumulative incidence of brain metastases was 41.4% in the crizotinib group compared to 9.4% in the alectinib group. Data from two phase 2 studies of alectinib were pooled to evaluate the intracranial efficacy and included 136 patients with brain metastases from ALK-NSCLC who had progressed on crizotinib (35). The CNS disease response rate was 64%. In conclusion, alectinib has better CNS activity compared to crizotinib.

There is early clinical data to support intracranial activity with a new ALK inhibitor, brigatinib. Up to 70% of patients with crizotinib resistant ALK-NSCLC in the early phase clinical trials of brigatinib had brain metastases (36). In total, 59 patients had measurable brain metastases, and 31 (53%) of them had intracranial responses to brigatinib. Another exploratory analysis of two phase 2 clinical trials confirmed the intracranial activity of brigatinib (37). Phase 3 clinical trial with brigatinib are showing promising results (38).

ROS1 fusions are reported in 2% of advanced NSCLC (39). Approximately 20% of these patients have brain metastases at diagnosis (40). Crizotinib also has activity against ROS1 fusion, however, as mentioned earlier, it has limited intracranial penetration (41). Lorlatinib is a TKI with activity in ROS1 fusion NSCLC, and preliminary results from an ongoing phase 2 study indicate intracranial responses in 3 of 12 patients with brain metastases (42).

The TRK family of tyrosine kinases, TRKA, TRKB, and TRKC are encoded by *NTK* genes (43). NTK gene fusions lead to activation of the TRK receptors, which increase cell proliferation and survival by PI3K and Ras/MAPK/ERK pathways. Entrectinib is a TKI with activity against *ALK*, *ROS1*, and *NTRK* gene fusions. In a phase 1–2 clinical trial of entrectinib, 5 of the 8 patients with primary or metastatic disease to the brain demonstrated intracranial responses (44). Larotrectinib is another *NTK* fusion inhibitor in clinical development. Although this drug showed limited CNS penetration in preclinical studies, one patient with NSCLC in the phase I study had 18% reduction in the size of brain metastases (45).

LOXO-292 selectively targets RET and early studies show activity against activating *RET* fusions/mutations. Drilon et al. recently presented data from a phase I study of patients with *RET* fusion± malignancies including NSCLC, papillary thyroid cancer, and medullary thyroid cancer (42, 46). The NSCLC cohort included 3 patients with brain metastases with a significant reduction in the tumor burden suggesting activity in the brain. BLU-667 is another highly selective RET inhibitor which shows promise in patients with brain metastases (47).

BRAF MUTATION

V-raf murine sarcoma viral oncogenes homolog B1 (BRAF) is a potent activator of the mitogen-activated protein kinase (MAPK) signaling pathway. The RAS/BRAF/MAPK/ERK pathway, critical for cell survival and proliferation, is altered in ∼30% of all malignancies (48). The *BRAF* gene mutation has been identified in melanoma, lung, colon, and thyroid cancers (49). In melanoma, $BRAF^{V600E}$ mutation accounts for 90% of all *BRAF* mutations, while $BRAF^{V600K/R/D}$ are less common (50).

Up to 50% of all advanced melanoma patients harbor *BRAF* mutations, making it a good target for BRAF inhibitors. Conservative estimates suggest that about 20% of *BRAF* mutant metastatic melanoma patients develop brain metastases (51).

Early studies with BRAF inhibitors show intracranial activity. An intracranial response rate of 16% was noted with single agent vemurafenib in unresectable brain metastases from metastatic melanoma (52). A phase I study of dabrafenib demonstrated intracranial responses in 9 of 10 melanoma patients (53) whereas a larger multicenter phase 2 study with single agent dabrafenib enrolled 172 patients with $BRAF^{V600E/K}$ mutant melanoma with brain metastases (54). *BRAF* mutated patients had improved intracranial responses, with 40% (29 of 74) of treatment naïve and 30% (20 of 65) of previously treated brain metastases patients responding to single agent dabrafenib.

The combination of BRAF inhibitor and MEK inhibitor was found to be superior with less adverse effects in the treatment of advanced melanoma (55, 56). The combination of dabrafenib and trametinib was evaluated in BRAF mutated metastatic melanoma patients with brain metastases in the COMBI-MB trial (57). Patients were enrolled into four cohorts. Cohort A included patients with $BRAF^{V600E}$ mutation who had good

performance status, no symptoms from brain metastases and had not received intracranial therapy. $BRAF^{V600E}$ patients who had good performance status, asymptomatic brain metastases with progression of intracranial metastases after initial local therapy were enrolled to cohort B. Cohort C had asymptomatic patients with a good performance status but had $BRAF^{V600D/K/R}$ mutation. Finally, cohort D had patients with symptomatic brain metastases, from metastatic melanoma with $BRAF^{V600E/D/K/R}$ mutation. The response rates in cohorts A through D were 58% (44 of 76 patients), 56% (9 of 16 patients), 44% (7 of 16 patients), and 59% (10 of 17 patients), respectively. These encouraging responses across all the cohorts make the combination of BRAF + MEK inhibitors a reasonable strategy in the management of patients with BRAF mutated metastatic melanoma with brain metastases. Studies with new BRAF and MEK inhibitor combinations will also provide more data (58, 59). BRAF directed therapy, dabrafenib plus trametinib is now approved for treatmentlung cancer patients where BRAF mutations are noted in about 2–4% of patients (60), however, their utility in lung cancer with brain metastases is yet to be evaluated.

CDK PATHWAY ALTERATIONS

Cell cyclin dependent kinases (CDK4/6) play a role in transitioning cells from G1 to S phase of cell division. The phosphorylation of tumor suppressor proteins like retinoblastoma protein is a key function of CDK4/6 which leads to cell division and proliferation (61). *CDKN2A* alterations are common in hormone receptor positive breast cancer patients. Palbociclib, abemaciclib, and ribociclib are the three CDK inhibitors that are approved for management of hormone receptor positive advanced breast cancer. Whole exome analysis of matched brain metastases patients and primary tumors showed increased frequency of alterations which might sensitize brain metastases to CDK inhibitors (19). Currently, clinical trials with CDK inhibitors in patients with brain metastases are enrolling patients, including a phase 2 study of palbociclib in recurrent brain metastases (NCT 02896335).

EGFR MUTATION

Epidermal Growth Factor Receptor (EGFR) is a transmembrane protein of the Human Epidermal Receptor (HER) family. The HER family encompasses 4 different receptors namely: EGFR/erbB1/HER1, erbB2/HER2, erbB3/HER3, and erbB4/HER4 receptors. All these receptors have tyrosine kinase roles that activate signal transduction inducing cell proliferation. *EGFR* overexpression or mutations are common in NSCLC, head and neck cancer, and colon cancer.

EGFR targeted therapies have been successful in the treatment of advanced lung cancer. Gefitinib and erlotinib are the two first-generation EGFR-TKIs that have improved progression-free survival (PFS) in advanced EGFR-NSCLC patients (62, 63). In the pivotal studies leading to their FDA-approval, patients with brain metastases were excluded. Both gefitinib and erlotinib have CSF concentrations higher than inhibitory concentration *in vitro*, despite being substrates for efflux pumps (64, 65). More recently, studies have evaluated the efficacy of gefitinib and erlotinib in EGFR-NSCLC patients with brain metastases (66–68). For example, Wu et al. enrolled 48 NSCLC patients with intracranial progressive disease after initial platinum-based chemotherapy to receive erlotinib (67). Although patients were not enriched for *EGFR*, the intracranial PFS and overall survival (OS) was 10.1 and 18.9 months, respectively. With an aim of obtaining higher intracranial concentration for erlotinib, investigators tried higher pulse doses which show promising results (69–71). The combination of erlotinib and radiation therapy was evaluated in two studies (66, 68). In a phase 2 study, 40 patients with brain metastases from NSCLC were treated with erlotinib and WBRT (68). There was no increase in toxicity, and an impressive response rate of 60% was noted. The median OS was 11.8 months, and the median survival was 19.1 months in *EGFR* mutated patients. A larger phase 3 attempted to evaluate the efficacy of radiation therapy and erlotinib in NSCLC patients with 1–3 brain metastases. The study design included three groups: WBRT plus stereotactic radiosurgery (SRS), WBRT plus SRS plus temozolomide, and WBRT plus SRS plus erlotinib. The study did not meet accrual and was not enriched for EGFR mutant patients, and it did not show significant differences in OS. Significant toxicity was noted with the combination of WBRT plus erlotinib, with ∼50% of the patients experiencing serious adverse effects, including myocardial ischemia and hemorrhagic stroke. Gefitnib is another first generation TKI has modest intracranial activity (72, 73). The intracranial activity of afatinib was reported in a case series of 100 patients with brain metastases where afatinib in a compassionate use program, however, the median time to intracranial progression was 3.9 months. Osimertinib is an EGFR inhibitor with activity against T790M, a mutation that confers resistance to first and second generation EGFR tyrosine kinase inhibitors. Pooled analysis from two phase 2 studies of 50 patients with measurable brain metastases showed intracranial response rates of 54%; 75% of patients at 9 months had an ongoing response (74). Most ongoing clinical trials with osimertinib have now allowed enrollment of patients with stable asymptomatic brain metastases. In the recently reported phase III clinical trial of upfront osimertinib, median intracranial PFS at 6 months was 87% in the osimertinib group compared to 71% in the standard EGFR-TKI group (75). This progression free survival benefit was sustained at 18 months. The CNS progression was lower in the osimertinib compared to standard EGFR-TKI (6 vs. 15%) (76). Osimertinib has activity in leptomeningeal disease as well (77). At the initial efficacy assessment of a phase 1 clinical trial of osimertinib in EGFR mutant NSCLC with leptomeningeal disease, 33% (7 of 21) of patients were responding to treatment (77).

HER2 ALTERATIONS

HER2 receptor, a transmembrane EGFR receptor, with no known ligands for the HER2 receptor, is activated by

homodimerization and heterodimerization (78). When activated, HER2 receptors lead to tumor growth, proliferation, and more invasiveness. The Ras/MAP kinase and PIK3/mTOR are the common downstream signaling pathways activated by HER2 overexpression and mutation. HER2 overexpression is primarily identified in 20% of breast cancer (79) but can be present in 30% of upper gastrointestinal malignancies like esophageal adenocarcinoma and gastro-esophageal junction carcinoma (80). HER2 overexpression generally indicates aggressive behavior (79). Several different strategies have been adopted to improve outcomes in these patients including monoclonal antibodies like trastuzumab, and pertuzumab, TKIs such as lapatinib, neratinib, tesevatinib, and the antibody drug conjugate trastuzumab-emtansine (T-DM1).

Trastuzumab was the first monoclonal antibody that showed improvement in OS in the metastatic, adjuvant, and neo-adjuvant setting (81, 82). However, a number of trastuzumab treated patients had intracranial disease recurrence. This is likely partly due to the inherent biology of HER2 overexpressing breast cancer, and partly because trastuzumab has poor penetration across the BBB (83, 84). The plasma-to-CSF concentration of trastuzumab has been evaluated in patients with brain metastases by using immunoenzymatic tests (85). Notably, intracranial trastuzumab levels can change dramatically with radiation therapy; prior to radiation therapy the CSF to plasma levels of trastuzumab were reported to be low (1:420), with an increase (1:79) after radiotherapy. Other studies with radio-labeled-trastuzumab have corroborated this finding (86, 87). Although some retrospective studies have shown improvement in OS patients with brain metastases treated with trastuzumab, it may be due to improved extracranial disease control (88, 89). Pertuzumab showed promising clinical activity when added to a regimen containing trastuzumab in various clinical settings (90, 91). Clinical evidence of CNS penetration of pertuzumab was demonstrated in a demonstrating prolongation of the interval from treatment to development of CNS metastases, which was 15.0 months in the pertuzumab-treated population compared to 11.9 months (92). Lapatinib is a small molecule TKI inhibiting EGFR and HER2 receptor activation. In the absence of CNS metastases, lapatinib has an intracranial concentration of 3%, which increases to 25% in the presence of brain metastases (93). This is change in intracranial concentration has been attributed to altered blood brain barrier by brain metastases. In a phase 2 study, 39 patients with HER2 overexpressing breast cancer and measurable brain metastases who progressed on trastuzumab were treated with lapatinib and results showed only one partial response (94). In a multicenter single arm study of lapatinib in combination with capecitabine (a nucleoside inhibitor), 29 of 45 patients (66%) had a partial response (95). The combination of lapatinib and topotecan (a topoisomerase I inhibitor) failed to improve response rates compared to lapatinib and capecitabine (96). A combination of lapatinib and cabazitaxel (a microtubule inhibitor) has also been safely combined in brain metastases patients and the results of the phase 2 study have not been published (97). Neratinib, a newer HER2 targeting TKI approved for adjuvant treatment of breast cancer patients with HER2 overexpression was evaluated in HER2 overexpressing breast cancer brain metastases, the majority of which had progressed after WBRT (98), with an overall response of only 8%. The combination of neratinib plus capecitabine was recently evaluated in a phase 2 clinical trial with encouraging preliminary results showing a 12-month survival of 63% in 39 patients. Tesevatinib is another TKI which has shown safety and preliminary efficacy in brain metastases from breast and lung cancer patients (99, 100).

The antibody drug conjugate trastuzumab-emtansine (T-DM1) is an approved second line treatment option for metastatic HER2 overexpressing tumors after trastuzumab (101). Patients with brain metastases treated in the registration trial had improved survival with T-DM1 compared to lapatinib plus capecitabine (102).

IMMUNOTHERAPY

Monoclonal antibodies targeting immune-checkpoints (CTLA-4 and PD-1/PDL-1) have revolutionized the management of several advanced malignancies, particularly melanoma and NSCLC. Initial studies with ipilimumab, a CTLA-4 antibody, in melanoma patients with brain metastases showed modest responses, which was largely impacted by use of dexamethasone (103). A recent open label, multiinstituitional phase 2 study evaluated the combination of ipilimumab and nivolumab (anti PD-1 antibody) in melanoma patients with asymptomatic untreated brain metastases (104). The primary endpoint for this study was intracranial benefit rate, defined by stable disease for 6 months, or response to treatment. Ninety four patients were enrolled in the trial, and the results were impressive with 57% patients meeting the primary end-point while 26% had complete response. Pembrolizumab is another anti PD-1 antibody which was studied in a single center phase 2 clinical trial of patients with brain metastases from melanoma or NSCLC (105). The melanoma arm accrued 23 patients and 6 of them had intracranial response with a median OS of 17 months (106). An interim analysis for 18 NSCLC patients reported an intracranial response rate of 33%. These studies provide early but encouraging evidence for intracranial activity with these agents. An important limitation for immunotherapy is the use of dexamethasone for symptomatic brain metastases, and during radiation therapy.

VEGF (VASCULAR ENDOTHELIAL GROWTH FACTOR) PATHWAY

Angiogenesis and neovascularization play a critical role in the development of brain metastases, thus anti-angiogenic therapy could be a promising strategy. Bevacizumab is a monoclonal antibody which has an established track record of anti-VEGF activity. Preliminary results from a phase 2 trial of the combination of bevacizumab and carboplatin in breast cancer patients with brain metastases showed a response rate of 45% (107). The favorable changes in MRI appearance is likely

TABLE 1 | Summary of selected studies of targeted therapies in brain metastases.

Targeted therapy	Primary malignancy	Study design	Number of patients with brain metastases	Outcomes
ALK DIRECTED THERAPY				
Crizotinib (29)	NSCLC	Subgroup analysis of a phase 3 trial	• 79 patients with stable BM • 39 treated with crizotinib • 40 treated with standard chemotherapy	12 week DCR 85% in the crizotinib group compared to 45% in the chemotherapy group
Ceritinib (32)	NSCLC	Subgroup analysis of a phase 2 trial	• 100 patients had asymptomatic BM • 20 had measurable BM	IC-RR: 45%
Alectinib (35)	NSCLC	Pooled analysis of two phase 2 trials	136 patients with BM who had progressed on crizotinib	IC-RR: 64%
Brigatinib (38)	NSCLC	Subgroup analysis of phase 2 trial	40 patients in the brigatinib group and 41 patients in the crizotinib had brain metastases	IC-RR: 78% in the brigatinib group compared to 29% in the crizotinib group
BRAF-MEK DIRECTED THERAPY				
Vemurafenib (52)	Melanoma	Phase 2 trial	• 90 patients with previously untreated BM	IC-RR: 18%
Dabrafenib (54)	Melanoma	Phase 2 trial	• 172 patients with BRAF mutant melanoma and BM	IC-RR of 40% in treatment naïve and 30% in previously treated patients
Dabrafenib and trametinib (57)	Melanoma	Multicenter, multicohort phase 2 trial	• Cohort A: 76 patients with $BRAF^{V600E}$ mutation, good PS, asymptomatic and newly diagnosed BM • Cohort B: 16 patients with $BRAF^{V600E}$, good PS, asymptomatic but progressive BM • Cohort C: 16 patients, asymptomatic, good PS, $BRAF^{V600D/K/R}$ • Cohort D: 17 patients, symptomatic, $BRAF^{V600E/D/K/R}$	IC-RR in Cohort A: 58% IC-RR in Cohort B: 56% IC-RR in Cohort C: 44% IC-RR in Cohort D: 59%
EGFR DIRECTED THERAPY				
Erlotinib (67)	NSCLC	Phase 2 trial	• 48 patients with progressive BM	IC-PFS: 10.1 months
Erlotinib (68)	NSCLC	Phase 2 trial	• 40 patients with progressive BM, concurrent with radiation	IC-RR: 60%
Erlotinib (66)	NSCLC	Phase 3 trial	• 41 patients treated with WBRT/SRS plus erlotinib	MST: 6.1 months 6 month IC-DCR: 10%
Osimertinib (75)	NSCLC	Phase 3 trial	• 61 patients treated with osimertinib 67 patients treated with standard EGFR-TKI	PFS at 6 months: 87% vs. 71%. PFS at 18 months: 58% vs. 40%
HER2 DIRECTED THERAPY				
Lapatinib plus capecitabine (95)	Breast cancer	Phase 2 trial	• 45 patients with BM	IC-RR: 66%
Neratinib plus capecitabine (98)	Breast cancer	Phase 2 trial	• 39 patients with BM	12 month OS: 63%
IMMUNOTHERAPY				
Ipilimumab plus nivolumab (104)	Melanoma	Phase 2 trial	• 94 patients with BM	IC benefit: 57%
Pembrolizumab (105, 106)	Melanoma NSCLC	Phase 2 trial	• 23 patients with BM 18 patients with BM	IC-RR: 26% IC-RR: 33%

NSCLC, Non-small cell lung cancer; BM, brain metastases; DCR, disease control rate; IC-RR, Intracranial response rate; MST, median survival time; OS, overall survival; PFS, progression free survival; IC benefit, 6 month stable disease, complete or partial response.

secondary to decreased inflammation from alteration of blood vessels by bevacizumab.

CONCLUSION

The management of CNS metastatic disease remains challenging. Surgery and radiation are still the most common approaches to the management of brain metastases. The minimal progress in the management of brain metastases can be attributed to the unique challenges in drug delivery to the CNS, and the limited understanding of the genetic heterogeneity in brain metastases compared to primary tumors. Furthermore, most clinical trials have historically excluded patients with CNS disease. Our knowledge of the genetics of brain metastases is increasing and new targeted therapies with improved CNS penetration are in development. Finally, clinical trials dedicated to patients with brain metastases in all malignancies with an emphasis on translational science will provide insight and therapeutic options for this patient population. **Table 1** provides a summary of clinical trials with targeted agents for brain metastases.

FUTURE DIRECTIONS

A multi-disciplinary approach including primary medical oncologists, radiation oncologists, neuro-oncologists, and neurosurgeons is critical in the management patients with brain metastases. Histology and molecular profiling should guide treatment options. For specific malignancies such as melanoma and NSCLC, immune checkpoint inhibitiors have durable responses with and without radiation or surgery. Furthermore, patients with targetable driver mutations can be treated with novel systemic targeted agents with better CNS penetration than previously used chemotherapy. Dedicated clinical trials, brain metastases consortiums and a personalized approach to this patient population will focus on many remaining unanswered questions.

AUTHOR CONTRIBUTIONS

VV, JC, and PB were involved in the initial planning, writing, and editing the manuscript.

REFERENCES

1. Meert AP, Paesmans M, Berghmans T, Martin B, Mascaux C, Vallot F, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer*. (2001) 1:5. doi: 10.1186/1471-2407-1-5
2. Venur VA, Leone JP. Targeted therapies for brain metastases from breast cancer. *Int J Mol Sci*. (2016) 17: 1543. doi: 10.3390/ijms17091543
3. Venur VA, Funchain P, Kotecha R, Chao ST, Ahluwalia MS. Changing treatment paradigms for brain metastases from melanoma-part 1: diagnosis, prognosis, symptom control, and local treatment. *Oncology*. (2017) 31:602–6.
4. Gupta GP, Massagué J. Cancer metastasis: building a framework. *Cell*. (2006) 127:679–95. doi: 10.1016/j.cell.2006.11.001
5. Cooper JB, Ronecker JS, Tobias ME, Mohan AL, Hillard V, Murali R, et al. Molecular sequence of events and signaling pathways in cerebral metastases. *Anticancer Res*. (2018) 38:1859–77. doi: 10.21873/anticanres.12424
6. Tam WL, Weinberg RA. The epigenetics of epithelial-mesenchymal plasticity in cancer. *Nat Med*. (2013) 19:1438–49. doi: 10.1038/nm.3336
7. Xu J, Lamouille S, Derynck R. TGF-beta-induced epithelial to mesenchymal transition. *Cell Re*. (2009) 19:156–72. doi: 10.1038/cr.2009.5
8. Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. *Nature*. (2003) 425:577–84. doi: 10.1038/nature02006
9. Gründe M, Franzen A, Karlsson JO, Ericson LE, Heldin NE, Nilsson M. Transforming growth factor-β and epidermal growth factor synergistically stimulate epithelial to mesenchymal transition (EMT) through a MEK-dependent mechanism in primary cultured pig thyrocytes. *J Cell Sci*. (2002) 115:4227–36. doi: 10.1242/jcs.00091
10. Davies MJ. The oxidative environment and protein damage. *Biochim et Biophys Acta*. (2005) 1703:93–109. doi: 10.1016/j.bbapap.2004.08.007
11. Bakin AV, Tomlinson AK, Bhowmick NA, Moses HL, Arteaga CL. Phosphatidylinositol 3-kinase function is required for transforming growth factor beta-mediated epithelial to mesenchymal transition and cell migration. *J Biol Chem*. (2000) 275:36803–10. doi: 10.1074/jbc.M005912200
12. Wilhelm I, Molnár J, Fazakas C, Haskó J, Krizbai IA. Role of the blood-brain barrier in the formation of brain metastases. *Int J Mol Sci*. (2013) 14:1383–411. doi: 10.3390/ijms14011383
13. Eichler AF, Chung E, Kodack DP, Loeffler JS, Fukumura D, Jain RK. The biology of brain metastases-translation to new therapies. *Nat Rev Clinical Oncol*. (2011) 8:344–56. doi: 10.1038/nrclinonc.2011.58
14. Osswald M, Blaes J, Liao Y, Solecki G, Gömmel M, Berghoff AS, et al. Impact of blood-brain barrier integrity on tumor growth and therapy response in brain metastases. *Clin Cancer Res*. (2016) 22:6078–87. doi: 10.1158/1078-0432.ccr-16-1327
15. Lockman PR, Mittapalli RK, Taskar KS, Rudraraju V, Gril B, Bohn KA, et al. Heterogeneous blood–tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. *Clin Cancer Res*. (2010) 16:5664–78. doi: 10.1158/1078-0432.ccr-10-1564
16. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin Oncol*. (2004) 22:3608–17. doi: 10.1200/jco.2004.01.175
17. de Vries NA, Beijnen JH, Boogerd W, van Tellingen O. Blood-brain barrier and chemotherapeutic treatment of brain tumors. *Expert Rev Neurotherapeut*. (2006) 6:1199–209. doi: 10.1586/14737175.6.8.1199
18. Steeg PS, Zimmer A, Gril B. Therapeutics for brain metastases, v3. *Clin Cancer Res*. (2016) 22:1–3. doi: 10.1158/1078-0432.ccr-16-2035
19. Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discovery*. (2015) 5:1164–77. doi: 10.1158/2159-8290.cd-15-0369
20. Chen G, Chakravarti N, Aardalen K, Lazar AJ, Tetzlaff MT, Wubbenhorst B, et al. Molecular profiling of patient-matched brain and extracranial melanoma metastases implicates the pi3k pathway as a therapeutic target. *Clin Cancer Res*. (2014) 20:5537–46. doi: 10.1158/1078-0432.CCR-13-3003
21. Ferguson SD, Zheng S, Xiu J, Zhou S, Khasraw M, Brastianos PK, et al. Profiles of brain metastases: prioritization of therapeutic targets. *Int J Cancer*. (2018) 143:3019–26. doi: 10.1002/ijc.31624
22. Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science*. (1994) 263:1281–4.
23. Shaw AT, Engelman JA. ALK in Lung cancer: past, present, and future. *J Clin Oncol*. (2013) 31:1105–11. doi: 10.1200/jco.2012.44.5353
24. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. (2007) 448:561–6. doi: 10.1038/nature05945
25. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer*. (2015) 88:108–11. doi: 10.1016/j.lungcan.2015.01.020
26. Metro G, Lunardi G, Floridi P, Pascali JP, Marcomigni L, Chiari R, et al. CSF concentration of crizotinib in Two ALK-Positive non-small-cell lung cancer

patients with cns metastases deriving clinical benefit from treatment. *J Thor Oncol*. (2015) 10:e26–7. doi: 10.1097/jto.0000000000000468
27. Costa DB, Kobayashi S, Pandya SS, Yeo WL, Shen Z, Tan W, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol*. (2011) 29:e443–5. doi: 10.1200/jco.2010.34.1313
28. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. (2014) 371:2167–77. doi: 10.1056/NEJMoa1408440
29. Solomon BJ, Cappuzzo F, Felip E, Blackhall FH, Costa DB, Kim DW, et al. Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non-small-cell lung cancer: results from PROFILE 1014. *J Clin Oncol*. (2016) 34:2858–65. doi: 10.1200/jco.2015.63.5888
30. Costa DB, Shaw AT, Ou SH, Solomon BJ, Riely GJ, Ahn MJ, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. *J Clin Oncol*. (2015) 33:1881–8. doi: 10.1200/jco.2014.59.0539
31. Shaw A, Mehra R, Tan DSW, Felip E, Chow LQW, Camidge DR, et al. BM-32 Ceritinib (LDK378) for treatment of patients with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) and brain metastases (BM) in the ASCEND-1 trial. *Neuro-oncology*. (2014) 16 (Suppl. 5):v39. doi: 10.1093/neuonc/nou240.32
32. Crinò L, Ahn MJ, De Marinis F, Groen HJ, Wakelee H, Hida T, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non–small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. *J Clin Oncol*. (2016) 34:2866–73. doi: 10.1200/jco.2015.65.5936
33. Nishio M, Nakagawa K, Mitsudomi T, Yamamoto N, Tanaka T, Kuriki H, et al. Analysis of central nervous system efficacy in the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer*. (2018) 121:37–40. doi: 10.1016/j.lungcan.2018.04.015
34. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. (2017) 377:829–38. doi: 10.1056/NEJMoa1704795
35. Gadgeel SM, Shaw AT, Govindan R, Gandhi L, Socinski MA, Camidge DR, et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non–small-cell lung cancer. *J Clin Oncol*. (2016) 34:4079–85. doi: 10.1200/JCO.2016.68.4639
36. Gettinger S, Kim D-W, Tiseo M, Langer C, Ahn MJ, Shaw A, et al. OA08.06 brigatinib activity in patients with ALK+ NSCLC and intracranial CNS metastases in two clinical trials. *J Thor Oncol*. (2017) 12:S273–S74. doi: 10.1016/j.jtho.2016.11.271
37. Camidge DR, Kim DW, Tiseo M, Langer CJ, Ahn MJ, Shaw AT, et al. Exploratory analysis of brigatinib activity in patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer and brain metastases in two clinical trials. *J Clin Oncol*. (2018) 36:2693–701. doi: 10.1200/jco.2017.77.5841
38. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. (2018) 379:2027–39. doi: 10.1056/NEJMoa1810171
39. Acquaviva J, Wong R, Charest A. The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer. *Biochim et Biophys Acta*. (2009) 1795:37–52. doi: 10.1016/j.bbcan.2008.07.006
40. Gainor JF, Tseng D, Yoda S, Dagogo-Jack I, Friboulet L, Lin JJ, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis Oncol*. (2017) 2017. doi: 10.1200/po.17.00063
41. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. (2014) 371:1963–71. doi: 10.1056/NEJMoa1406766
42. Drilon AE, Subbiah V, Oxnard GR, Bauer TM, Velcheti V, Lakhani NJ, et al. A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. *J Clin Oncol*. (2018) 36 (Suppl. 15):102–02. doi: 10.1200/JCO.2018.36.15_suppl.102
43. Khotskaya YB, Holla VR, Farago AF, Mills Shaw KR, Meric-Bernstam F, Hong DS. Targeting TRK family proteins in cancer. *Pharmacol. Therap*. (2017) 173:58–66. doi: 10.1016/j.pharmthera.2017.02.006
44. Drilon A, Siena S, Ou SI, Patel M, Ahn MJ, Lee J, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov*. (2017) 7:400–9. doi: 10.1158/2159-8290.cd-16-1237
45. Hong DS, Dowlati A, Burris HA III, Lee MS, Brose MS, Farago TM, et al. Clinical safety and activity from a phase 1 study of LOXO-101, a selective TRKA/B/C inhibitor, in solid-tumor patients with NTRK gene fusions. *Eur J Cancer*. (2017) 72:S148. doi: 10.1016/S0959-8049(17)30561-0
46. Velcheti V, Bauer T, Subbiah V, Cabanillias M, Lakhani L, Wirth G, et al. OA 12.07 LOXO-292, a potent, highly selective RET inhibitor, in MKI-resistant RET fusion-positive lung cancer patients with and without brain metastases. *J Thor Oncol*. (2017) 12:S1778. doi: 10.1016/j.jtho.2017.09.399
47. Subbiah V, Gainor JF, Rahal R, Brubaker JD, Kim JL, Maynard M, et al. Precision targeted therapy with BLU-667 for RET-driven cancers. *Cancer Discov*. (2018) 8:836–49. doi: 10.1158/2159-8290.cd-18-0338
48. Garnett MJ, Marais R. Guilty as charged: B-RAF is a human oncogene. *Cancer Cell*. (2004) 6:313–9. doi: 10.1016/j.ccr.2004.09.022
49. Cantwell-Dorris ER, O'Leary JJ, Sheils OM. $BRAF^{V600E}$: implications for carcinogenesis and molecular therapy. *Mol Cancer Therap*. (2011) 10:385–94. doi: 10.1158/1535-7163.mct-10-0799
50. Cheng L, Lopez-Beltran A, Massari F, MacLennan GT, Montironi R. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. *Modern Pathol*. (2018) 31:24–38. doi: 10.1038/modpathol.2017.104
51. Long GV, Margolin KA. Multidisciplinary approach to brain metastasis from melanoma: the emerging role of systemic therapies. *Am Soc Clin Oncol Educ Book*. (2013) 31:393–8. doi: 10.1200/EdBook_AM.2013.33.393
52. Dummer R, Goldinger SM, Turtschi CP, Eggmann NB, Michielin O, Mitchell L, et al. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. *Eur J Cancer*. (2014) 50:611–21. doi: 10.1016/j.ejca.2013.11.002
53. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet*. (2012) 379:1893–901. doi: 10.1016/s0140-6736(12)60398-5
54. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. (2012) 13:1087–95. doi: 10.1016/s1470-2045(12)70431-x
55. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. (2014) 371:1867–76. doi: 10.1056/NEJMoa1408868
56. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. (2015) 372:30–39. doi: 10.1056/NEJMoa1412690
57. Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol*. (2017) 18:863–73. doi: 10.1016/s1470-2045(17)30429-1
58. Yee MK, Lin Y, Gorantla VC, Butterfield LH, Kluger HM, Chapman PB, et al. Phase 2 study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (coBRIM-B). *J Clin Oncol*. (2015) 33 (Suppl. 15):TPS9088–88. doi: 10.1200/jco.2015.33.15_suppl.tps9088
59. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. (2018) 19:603–15. doi: 10.1016/s1470-2045(18)30142-6
60. Baik CS, Myall NJ, Wakelee HA. Targeting BRAF-mutant non-small cell lung cancer: from molecular profiling to rationally designed therapy. *Oncologist*. (2017) 22:786–69. doi: 10.1634/theoncologist.2016-0458
61. Asghar U, Witkiewicz AK, Turner NC, Knudsen ES. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nat Rev Drug Discov*. (2015) 14:130–46. doi: 10.1038/nrd4504
62. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European

patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. (2012) 13:239–46. doi: 10.1016/S1470-2045(11)70393-X
63. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. *N Engl J Med*. (2010) 362:2380–88. doi: 10.1056/NEJMoa0909530
64. Chamberlain MC, Baik CS, Gadi VK, Bhatia S, Chow LQ. Systemic therapy of brain metastases: non–small cell lung cancer, breast cancer, and melanoma. *Neuro-oncology*. (2017) 19:i1–i24. doi: 10.1093/neuonc/now197
65. Togashi Y, Masago K, Fukudo M, Terada T, Fujita S, Irisa K, et al. Cerebrospinal fluid concentration of erlotinib and its active metabolite OSI-420 in patients with central nervous system metastases of non-small cell lung cancer. *J Thor Oncol*. (2010) 5:950–5. doi: 10.1097/JTO.0b013e3181e2138b
66. Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Rad Oncol Biol Phy*. (2013) 85:1312–8. doi: 10.1016/j.ijrobp.2012.11.042
67. Wu YL, Zhou C, Cheng Y, Lu S, Chen GY, Huang C, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). *Ann Oncol*. (2013) 24:993–9. doi: 10.1093/annonc/mds529
68. Welsh JW, Komaki R, Amini A, Munsell MF, Unger W, Allen PK, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol*. (2013) 31:895–902. doi: 10.1200/jco.2011.40.1174
69. Yu HA, Sima CS, Reales D, Jordan S, Rudin CM, Kris MG, et al. A phase I study of twice weekly pulse dose and daily low dose erlotinib as initial treatment for patients (pts) with EGFR-mutant lung cancers. *J Clin Oncol*. (2015) 33 (Suppl. 15):8017–17. doi: 10.1200/jco.2015.33.15_suppl.8017
70. Togashi Y, Masago K, Fukudo M, Tsuchido Y, Okuda C, Kim YH, et al. Efficacy of increased-dose erlotinib for central nervous system metastases in non-small cell lung cancer patients with epidermal growth factor receptor mutation. *Cancer Chemother Pharmacol*. (2011) 68:1089–92. doi: 10.1007/s00280-011-1691-z
71. Jackman DM, Mach SL, Heng JC, Rabin MS, Barbie DA, Gandhi L, et al. Pulsed dosing of erlotinib for central nervous system (CNS) progression in EGFR-mutant non-small cell lung cancer (NSCLC). *J Clin Oncol*. (2013) 31 (Suppl. 15):8116–16. doi: 10.1200/jco.2013.31.15_suppl.8116
72. Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crinò L, Villa E. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol*. (2004) 15:1042–7. doi: 10.1093/annonc/mdh276
73. Pesce GA, Klingbiel D, Ribi K, Zouhair A, von Moos R, Schlaeppi M, et al. Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). *Eur J Cancer*. (2012) 48:377–84. [published Online First: 2011/11/19] doi: 10.1016/j.ejca.2011.10.016
74. Goss G, Tsai CM, Shepherd FA, Ahn MJ, Bazhenova L, Crinò L, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. *Ann Oncol*. (2018) 29:687–93. doi: 10.1093/annonc/mdx820
75. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol*. (2018) 36:3290–3297. doi: 10.1200/jco.2018.78.3118
76. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med*. (2018) 378:113–25. doi: 10.1056/NEJMoa1713137
77. Cho BC, Ahn M-J, Lee J-S, Kim D-W, Kim S-W, John T, et al. Phase I study (BLOOM) of AZD3759, a BBB penetrable EGFR inhibitor, in EGFRm NSCLC patients with leptomeningeal metastasis (LM) who progressed after other anti-cancer therapy. *J Clin Oncol*. (2017) 35(Suppl. 15):2069–69. doi: 10.1200/JCO.2017.35.15_suppl.2069
78. Schettini F, Buono G, Cardalesi C, Desideri I, De Placido S, Del Mastro L. Hormone receptor/human epidermal growth factor receptor 2-positive breast cancer: where we are now and where we are going. *Cancer Treat Rev*. (2016) 46:20–6. doi: 10.1016/j.ctrv.2016.03.012
79. Gingras I, Gebhart G, de Azambuja E, Piccart-Gebhart M. HER2-positive breast cancer is lost in translation: time for patient-centered research. *Nat Rev Clin Oncol*. (2017) 14:669. doi: 10.1038/nrclinonc.2017.96
80. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal cancer. *Nat Rev Dis Prim*. (2017) 3:17048. doi: 10.1038/nrdp.2017.48
81. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. (2005) 353:1659–72. doi: 10.1056/NEJMoa052306
82. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. (2001) 344:783–92. doi: 10.1056/nejm200103153441101
83. Lin NU, Gaspar LE, Soffietti R. Breast cancer in the central nervous system: multidisciplinary considerations and management. *Am Soc Clin Oncol Edu Book*. (2017) 37:45–56. doi: 10.14694/edbk_175338
84. Pestalozzi BC, Brignoli S. Trastuzumab in CSF. *J Clin Oncol*. (2000) 18:2349–51. doi: 10.1200/JCO.2000.18.11.2349
85. Stemmler HJ, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. *Anti-Cancer Drugs*. (2007) 18:23–8. doi: 10.1097/01.cad.0000236313.50833.ee
86. Dijkers EC, Oude Munnink TH, Kosterink JG, Brouwers AH, Jager PL, de Jong JR, et al. Biodistribution of 89Zr-trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. *Clin Pharmacol Therap*. (2010) 87:586–92. doi: 10.1038/clpt.2010.12
87. Tamura K, Kurihara H, Yonemori K, Tsuda H, Suzuki J, Kono Y, et al. 64Cu-DOTA-trastuzumab PET imaging in patients with HER2-positive breast cancer. *J Nuclear Med*. (2013) 54:1869–75. doi: 10.2967/jnumed.112.118612
88. Le Scodan R, Jouanneau L, Massard C, Gutierrez M, Kirova Y, Cherel P, et al. Brain metastases from breast cancer: prognostic significance of HER-2 overexpression, effect of trastuzumab and cause of death. *BMC Cancer*. (2011) 11:395. doi: 10.1186/1471-2407-11-395
89. Park IH, Ro J, Lee KS, Nam BH, Kwon Y, Shin KH. Trastuzumab treatment beyond brain progression in HER2-positive metastatic breast cancer. *Ann Oncol*. (2009) 20:56–62. doi: 10.1093/annonc/mdn539
90. Baselga J, Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer. *Clin Breast Cancer*. (2010) 10:489–91. doi: 10.3816/CBC.2010.n.065
91. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. (2017) 377:122–31. doi: 10.1056/NEJMoa1703643
92. Swain SM, Baselga J, Miles D, Im YH, Quah C, Lee LF, et al. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA. *Ann Oncol*. (2014) 25:1116–21. doi: 10.1093/annonc/mdu133
93. Taskar KS, Rudraraju V, Mittapalli RK, Samala R, Thorsheim HR, Lockman J, et al. Lapatinib distribution in HER2 overexpressing experimental brain metastases of breast cancer. *Pharma Res*. (2012) 29:770–81. doi: 10.1007/s11095-011-0601-8
94. Lin NU, Carey LA, Liu MC, Younger J, Come SE, Ewend M, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. (2008) 26:1993–9. doi: 10.1200/jco.2007.12.3588
95. Bachelot T, Romieu G, Campone M, Diéras V, Cropet C, Dalenc F, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol*. (2013) 14:64–71. doi: 10.1016/s1470-2045(12)70432-1

96. Lin NU, Eierman W, Greil R, Campone M, Kaufman B, Steplewski K, et al. Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. *J Neuro-Oncology*. (2011) 105:613–20. doi: 10.1007/s11060-011-0629-y
97. Yardley DA, Hart LL, Ward PJ, Wright GL, Shastry M, Finney L, et al. Cabazitaxel plus lapatinib as therapy for HER2+ metastatic breast cancer with intracranial metastases: results of a dose-finding study. *Clin Breast Cancer*. (2018) 18:e781–7. doi: 10.1016/j.clbc.2018.03.004
98. Freedman R, Gelman R, Melisko M, Anders C, Moy B, Blackwell K, et al. TBCRC 022: Phase II trial of neratinib + capecitabine for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM). *J Clin Oncol*. (2017) 35:1005. doi: 10.1200/JCO.2017.35.15_suppl.1005
99. Berz D, Subrananiam D, Tonra J, Berger M, Ross Camidge D. P2.03b-016 tesevatinib in NSCLC patients with EGFR activating mutations and brain metastases (BM) or leptomeningeal metastases (LM). *J Thor Oncol*. (2017) 12:S942–S43. doi: 10.1016/j.jtho.2016.11.1297
100. Lin NU, Freedman RA, Miller K, Jhaveri KL, Eiznhamer DA, Berger MS, et al. Determination of the maximum tolerated dose (MTD) of the CNS penetrant tyrosine kinase inhibitor (TKI) tesevatinib administered in combination with trastuzumab in HER2+ patients with metastatic breast cancer (BC). *J Clin Oncol*. (2016) 34 (Suppl. 15):514. doi: 10.1200/JCO.2016.34.15_suppl.514
101. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. (2012) 367:1783–91. doi: 10.1056/NEJMoa1209124
102. Krop IE, Lin NU, Blackwell K, Guardino E, Huober J, Lu M, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol*. (2015) 26:113–9. doi: 10.1093/annonc/mdu486
103. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. (2012) 13:459–65. doi: 10.1016/s1470-2045(12)70090-6
104. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. (2018) 379:722–30. doi: 10.1056/NEJMoa1805453
105. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. (2016) 17:976–83. doi: 10.1016/s1470-2045(16)30053-5
106. Kluger HM, Chiang V, Mahajan A, Zito CR, Sznol M, Tran T, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. *J Clin Oncol*. (2019) 37:52–60. doi: 10.1200/jco.18.00204
107. Lin NU, Gelman RS, Younger WJ, Sohi J, Freedman RA, Gregory Sorensen A, et al. Phase II trial of carboplatin (C) and bevacizumab (BEV) in patients (pts) with breast cancer brain metastases (BCBM). *J Clin Oncol*. (2013) 31 (Suppl. 15):513. doi: 10.1200/jco.2013.31.15_suppl.513

Conflict of Interest Statement: PB has received speaker's honorarium from Genentech, and Merck and is a consultant for Lilly, Tesaro, Angiochem and Genentech-Roche. PB has also received grant support to MGH from Merck, BMS and Pfizer. VV received honorarium from Elsevier. JC is a consultant for Sanofi-Genzyme.

Copyright © 2019 Venur, Cohen and Brastianos. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

PERSPECTIVE
published: 23 August 2019
doi: 10.3389/fonc.2019.00797

The Impact of Targeted Therapy on Intracranial Metastatic Disease Incidence and Survival

Anders W. Erickson[1] *and Sunit Das*[2,3]*

[1] Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [2] Division of Neurosurgery, University of Toronto, Toronto, ON, Canada, [3] Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

Intracranial metastatic disease (IMD) is a common and severe complication of primary cancers. Current treatment options for IMD include surgical resection and radiation therapy, although there has been recent interest in targeted therapy in the management of IMD. As of yet, insufficient data exist to support the recommendation of targeted therapies in the treatment of IMD. Paradoxically, targeted therapy has been hypothesized to play a role in the development of IMD in patients with primary cancers. This is based on the observations that patients who receive targeted therapy for primary cancer experience prolonged survival, and that prolonged survival has been associated with increased incidence of IMD. Few data exist to clarify if treatment of primary cancers with targeted therapies influences IMD incidence. Here, we discuss the role of targeted therapy in IMD management, review the current literature on IMD incidence and targeted therapy use in primary cancer, and propose the need for future studies to inform physicians in choosing treatment options and counseling patients.

Keywords: intracranial metastatic disease (IMD), brain metastases, targeted therapy, survival, incidence

OPEN ACCESS

Edited by:
Sandro M. Krieg, Technical University of Munich, Germany

Reviewed by:
Riccardo Soffietti, University of Turin, Italy
Sumit Mukherjee, Icahn School of Medicine at Mount Sinai, United States

***Correspondence:**
Sunit Das
sunit.das@utoronto.ca

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *21 June 2019*
Accepted: *06 August 2019*
Published: *23 August 2019*

Citation:
Erickson AW and Das S (2019) The Impact of Targeted Therapy on Intracranial Metastatic Disease Incidence and Survival. Front. Oncol. 9:797. doi: 10.3389/fonc.2019.00797

INTRODUCTION

The development of intracranial metastatic disease (IMD) complicates the course of approximately 20% of patients with cancer, with the highest frequency of brain metastases arising in patients with melanoma (7–16%), breast cancer (5–20%), and lung cancer (20–56%) (1–3). The consequences of IMD are severe: across all cancers, patients with IMD have a 2-year survival of 8.1% (1). Prognosis is informed by patient age, Karnofksy performance status, extent of disease, and in recent years, molecular marker status, such as HER2/neu in breast cancer and EGFR in non-small cell lung cancer (4). Importantly, molecular marker status has also opened up the possibility for treatment of brain metastases with targeted therapies.

Targeted therapies are medications that inhibit cancer-specific driver mutations. For example, vemurafenib is a small molecule inhibitor of the B-raf/MEK pathway specific for cells possessing the V600E BRAF mutation. The B-raf/MEK pathway is a driver of cancer cell proliferation and survival in BRAF-mutant melanoma; inhibition of this pathway with vemurafenib results in programmed cell death in these melanoma cells (5). The arrival of targeted therapies has revolutionized cancer treatment and improved outcomes for many patients with cancer. However, little is known about role of targeted therapies in the treatment of patients with IMD, or if targeted therapies modify the risk of development of IMD in patients with systemic cancer. Some targeted therapies have been shown to improve survival in patients with brain metastases, a cohort deemed previously to harbor a uniformly poor survival (1).

Targeted Therapies and Survivorship in IMD

The therapeutic options that have historically been considered for treatment of IMD include surgical resection and radiation therapy; chemotherapies have not generally been useful in the treatment of brain metastases (6). Surgical resection has historically been reserved for patients with good Karnofsky performance status (KPS >70), well-controlled systemic disease, and a single or few accessible tumors (1, 7). Stereotactic radiosurgery (SRS), a therapy previously recommended for treating patients with up to four brain metastases (or >4 with cumulative volume <7 mL), is broadening its scope, and is now in clinical trial for patients with up to 20 brain metastases (NCT03075072) (8). Whole brain radiation therapy (WBRT) has historically been used as frontline therapy in patients with multiple brain metastases, but has been associated with neurocognitive decline in areas of episodic memory, executive function, processing speed, and fine motor control (6, 9, 10). Neuroprotective strategies adjunct to WBRT, such as memantine administration and hippocampal sparing, have been shown to reduce some of the deleterious neurocognitive effects of WBRT (6, 9, 10). Interest therefore exists in augmenting the treatment landscape, and replacing or delaying upfront radiotherapy with another treatment modality, such as targeted therapies (11).

Unfortunately, the data available in the literature on survival in patients with IMD treated with targeted therapies are limited and mixed. Existing studies support the hypothesis that patients who receive targeted therapies for the treatment of IMD experience prolonged survival (11–15). However, these studies have been limited by including only single study arms or too few patients, and have largely restricted their focus to IMD arising from single primary cancer subtypes. Some contradictory data also exist suggesting decreased overall survival (OS) with the use of targeted therapy for patients with IMD (16). Additionally, new-generation targeted therapies, such as alectinib and osimertinib, have been approved in only the last few years, and little is known about their outcomes on a population scale, although trial data suggest CNS efficacy (17, 18). At this time, the 2019 guidelines from the Congress of Neurological Surgeons cite insufficient evidence to recommend targeted therapies in treating IMD (19).

Targeted Therapies and IMD Incidence

One factor of import in addition to considering the effect of targeted therapies on survival in patients with IMD is the effect of these drugs on patient survival independent of the development of IMD. Targeted therapies have been shown to improve systemic disease control and prolong OS in patients with multiple cancer subtypes (20–23). Some literature supports the hypothesis that prolonged survival in patients with cancer is associated with increased incidence of IMD (3, 24, 25). In other words, targeted therapies for primary cancer may paradoxically be associated with increased incidence of brain metastases by extending patient survival through improved control of systemic disease, while relegating the brain as a "sanctuary" site in which undetected intracranial micrometastases are sheltered from systemic treatment that is unable to penetrate the "sanctuary" of the blood-brain barrier (BBB) (14, 24–29). For example, a meta-analysis of three randomized trials found that patients taking trastuzumab for HER2/neu-positive breast cancer had improved OS, but were 1.82 times more likely to develop IMD than non-trastuzumab comparators (29). Similarly, in patients with BRAF-mutant melanoma, one retrospective study found that 90 patients taking BRAF inhibitors were 30% more likely than a chemotherapy comparator group to develop IMD, although these results were not significant ($p = 0.5129$), nor did the study report data comparing OS in patients without IMD (14). In patients with EGFR-mutant non-small cell lung cancer, patients receiving first-line EGFR-targeted therapies had improved OS, but were 1.35 times more likely to develop IMD compared with patients receiving other therapies (28), although other analyses suggest the same first-line EGFR-targeted therapies decrease the incidence of IMD (30, 31).

Conversely, some have postulated that newer targeted therapies that are capable of crossing the BBB may *decrease* the incidence of IMD by overcoming the sanctuary effect. A randomized controlled trial of alectinib (BBB-penetrant) vs. crizotinib (less BBB-penetrant) for ALK-positive non-small cell lung cancer showed 12-month cumulative incidences of central nervous system progression of 9.4 and 41.4%, respectively (18, 32). Importantly, alectinib did not offer these patients a survival benefit beyond that gained by therapy with crizotinib: the 12-month survival rate was 84.3% (95% CI 78.4–90.2) for patients receiving alectinib, and 82.5% (95% CI 76.1–88.9) for patients receiving crizotinib. In contrast, targeted therapies for renal cell carcinoma (RCC) have been reported to decrease incidence of IMD compared to chemotherapy, despite minimal BBB penetration of these therapies due to active efflux by transporters P-glycoprotein and breast cancer resistance protein (33).

A snapshot of the current literature reveals that knowledge of the impact of targeted therapy on IMD incidence is sparse (**Table 1**, **Figure 1**, Appendix 1 in **Supplementary Material**). Few studies address the question of IMD incidence following targeted therapy in comparison to the volume of literature on IMD *survival* with targeted therapy. Notably, there appear to be more studies on IMD incidence from breast cancer and non-small cell lung cancer in comparison to melanoma, RCC, and hepatocellular carcinoma (HCC). This may be because targeted therapies for breast cancer and non-small cell lung cancer have existed longer, and in greater number, than for melanoma, RCC, and HCC. This is also consistent with the observed distribution of primary cancers that contribute to IMD prevalence, which attributes 56% of IMD cases to lung and breast cancers (**Figure 2**) (52). Regardless of primary disease type, most of the literature is comprised of retrospective cohort studies at single institutions, limited to several hundred patients, or lacking controls. Some studies are prospective or meta-analyses, but these form the minority.

The current literature is also mixed on whether targeted therapies increase, decrease, or have any impact on the incidence of IMD incidence. Many studies report insignificant differences in IMD incidence between patients receiving a targeted therapy vs. a conventional chemotherapy (14, 34, 35, 39, 48). In

TABLE 1 | Select studies reporting on IMD incidence in patients receiving targeted therapy.

Disease	References	Therapy	Study type	Patients (*n*)	IMD incidence with targeted therapy	Findings
Breast Cancer	Berghoff et al. (34)	Trastuzumab, lapatinib	Retrospective cohort	201	—	IMD incidence trended toward lower in trastuzumab (38.2%) vs. no trastuzumab (57.1%, $p = 0.058$). IMD incidence trended toward lower in lapatinib (30.8%) vs. no lapatinib (39.6%, $p = 0.530$).
	Swain et al. (35)	Pertuzumab vs. placebo (each with trastuzumab + docetaxel)	RCT	808	—	IMD incidence trended toward higher in pertuzumab arm (13.7%) vs. placebo arm (12.6%). But, median time-to-CNS-metastasis greater in pertuzumab arm (15.0 months) vs. placebo arm (12.9 months; HR, 0.58; 95% CI 0.39–0.85; $p = 0.0049$).
	Viani et al. (29)*	Trastuzumab vs. no trastuzumab	Meta-analysis	6,738	Higher	IMD incidence higher in trastuzumab arms by 1.82-fold (95% CI 1.89–3.16; $p = 0.009$).
	Bria et al. (36)*	Trastuzumab vs. no trastuzumab	Meta-analysis	6,738	Higher	IMD incidence higher in trastuzumab arms (RR, 1.57; 95% CI 1.03–2.37; $p = 0.033$).
	Okines et al. (37)	Ado-trastuzumab emtansine	Retrospective cohort	39	—	IMD incidence 18% in patients receiving ado-trastuzumab emtansine, with median time-to-IMD 7.5 months (95% CI 3.8–9.6). No control.
	Musolino et al. (38)	Trastuzumab vs. no trastuzumab	Retrospective cohort	1,429	Higher	IMD incidence higher in patients receiving trastuzumab (10.5%) vs. no trastuzumab (2.9%). HER2+ status and trastuzumab, together, predictive for CNS events (HR, 4.3; 95% CI 1.5–11.8; $p = 0.005$).
	Yau et al. (39)	Trastuzumab	Retrospective cohort	87	—	IMD risk not observed to be higher than disease-free population (RR, 1.0; 95% CI 0.4–2.2; $p = 0.09$). No control.
Melanoma	Sloot et al. (14)	BRAF/MEK inhibitor vs. chemo	Retrospective cohort	610	—	IMD incidence not higher in BRAF inhibitor vs. chemotherapy (OR, 1.3; 95% CI 0.6–2.49; $p = 0.5129$).
	Peuvrel et al. (40)	Vemurafenib	Retrospective cohort	86	—	IMD incidence 20% in patients receiving vemurafenib, with median time-to-IMD 5.3 months (±4.3). No control.
NSCLC	Heon et al. (31)	EGFR inhibitor	Retrospective cohort	81	Lower	IMD incidence lower in EGFR inhibitor arms (25% at 42 months) vs. historical comparators (40–55% at 35–37 months). No study control.
	Wang et al. (28)	EGFR inhibitor vs. other therapy	Retrospective cohort	1,254	Higher	IMD incidence higher in EGFR inhibitor vs. other therapy (HR,1.36; 95% CI 1.14–1.64; $p = 0.001$).
	Su et al. (41)	Gefitinib vs. Erlotinib vs. afatinib	Retrospective cohort	219	—	IMD incidences at 24 months for gefitinib (13.9%), erlotinib (9.3%), and afatinib (28.3%) were not significantly different ($p = 0.80$). Hazard ratio for IMD in afatinib vs. gefitinib 0.49 (95% CI 0.34–0.71; $p = 0.001$)
	Fu et al. (42)	Bevacizumab + chemo vs. chemo	Retrospective cohort	159	Lower	IMD incidence at 24 months lower in the bevacizumab + chemo arm (14.0%) vs. chemo arm (31%, $p<0.01$).
	Ilhan-Mutlu et al. (43)	Bevacizumab vs. chemo	Retrospective cohort	1,043	Lower	IMD incidence at 24 months lower for bevacizumab (2.6%) vs. chemo (5.8%, $p = 0.01$; HR, 0.36; 95% CI 0.19–0.68; $p = 0.001$).

(Continued)

TABLE 1 | Continued

Disease	References	Therapy	Study type	Patients (*n*)	IMD incidence with targeted therapy	Findings
	Gadgeel et al. (18)	Crizotinib vs. alectinib	RCT	181	—	IMD incidence at 12 months lower for alectinib (4.6%; 95% CI 1.5–10.6%) vs. crizotinib (31.5%; 95% CI 22.1–41.3%). Time-to-CNS progression longer in alectinib vs. crizotinib (csHR, 0.14; 95% CI 0.06–0.33; $p < 0.0001$).
	Nishio et al. (44)	Crizotonib vs. alectinib	Retrospective cohort	164	—	Time-to-CNS progression longer in alectinib vs. crizotinib (HR, 0.19; 95% CI: 0.07–0.53; $p = 0.0004$).
	Zhao et al. (45)	Icotinib vs. chemo	Retrospective cohort	396	Lower	IMD incidence at 24 months lower for icotinib (10.2%) vs. chemotherapy (32.1%). Hazard ratio for IMD in chemotherapy vs. icotinib 3.32 (95% CI 1.89–5.82; $p < 0.001$).
RCC	Verma et al. (46)	TKI vs. no TKI	Retrospective cohort	338	Lower	IMD incidence lower in TKI vs. no TKI (HR, 0.39; 95% CI 0.21–0.73; $p = 0.003$).
	Dudek et al. (33)	TKI vs. no TKI	Retrospective cohort	92	Lower	IMD incidence lower in TKI vs. no TKI (per month incidence rate ratio 1.568; 95% CI 1.06–2.33).
	Massard et al. (47)	Sorafenib vs. placebo	Retrospective cohort	139	Lower	IMD incidence lower in sorafenib (3%) vs. placebo (12%, $p < 0.05$).
	Vanhuyse et al. (48)	Antiangiogenic** vs. other therapy	Retrospective cohort	199	—	IMD incidence in targeted therapy group (15.7%) lower than non-targeted therapy group (18.2%). However, targeted therapy was not associated with a lower cumulative rate of brain metastases (HR, 0.58; 95% CI 0.26–1.30; $p = 0.18$).
HCC	Shao et al. (49)	Antiangiogenic therapy ***	Retrospective cohort	158	Higher	IMD incidence 7% in patients receiving antiangiogenic targeted therapies vs. 0.2–2.2% in historical comparators. Median time-to-IMD 9.6 months.

- Incidence trends marked with a dash if study reports 1) insignificant results, 2) only comparison between multiple targeted therapies, or 3) no control.

**Both Viani et al. and Bria et al. report on the same datasets.*

***Antiangiogenic therapies in Vanhuyse et al. study = sorafenib, sunitinib, bevacizumab, temsirolimus, or everolimus.*

****Antiangiogenic therapies in Shao et al. study = sorafenib, sorafenib plus tegafur/uracil, sunitinib, bevacizumab plus capecitabine, bevacizumab plus erlotinib, or thalidomide plus tegafur/uracil.*

(cs)HR, (cause-specific) hazard ratio; RR, relative risk; RCT, randomized controlled trial; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor (sorafenib or sunitinib); EGFR inhibitor, gefitinib or erlotinib; BRAF/MEK inhibitor, BRAF, vemurafenib or dabrafenib; MEK, cobimetinib or trametinib.

breast cancer, most studies indicate that targeted therapy is associated with increase in IMD incidence (29, 35, 38). One study reports a prolonged median time-to-IMD in patients receiving targeted therapy vs. other therapies, supporting the "sanctuary" hypothesis that prolonged survival due to systemic disease control increases IMD risk (35). In RCC, targeted therapy is associated with a decrease in IMD incidence (33, 46, 47). In non-small cell lung cancer, some studies report an increase in IMD incidence with use of a targeted therapy, while others report an associated decrease (28, 31, 42, 43). One hypothesis to explain these differences between primary disease types is that the targeted therapies studied in breast cancer, such as the 140kDa+ monoclonal antibodies trastuzumab and pertuzumab, are less BBB-penetrant than available targeted therapies in RCC, such as the small molecule kinase inhibitors sunitinib and sorafenib, while there is a range of BBB-penetrability among the therapies used in non-small cell lung cancer. However, the arrival of novel BBB-penetrant agents may be anticipated to disrupt these trends.

FUTURE DIRECTIONS

The questions of IMD incidence and survival are relevant today because the frequency of IMD is rising, while prognosis remains poor (3). As improvements are made in the early detection of IMD and the management of systemic disease, more clinicians will counsel patients on the risk and management of IMD. Additionally, the use of targeted therapies is expected to increase as the management of both primary systemic disease and IMD moves toward precision

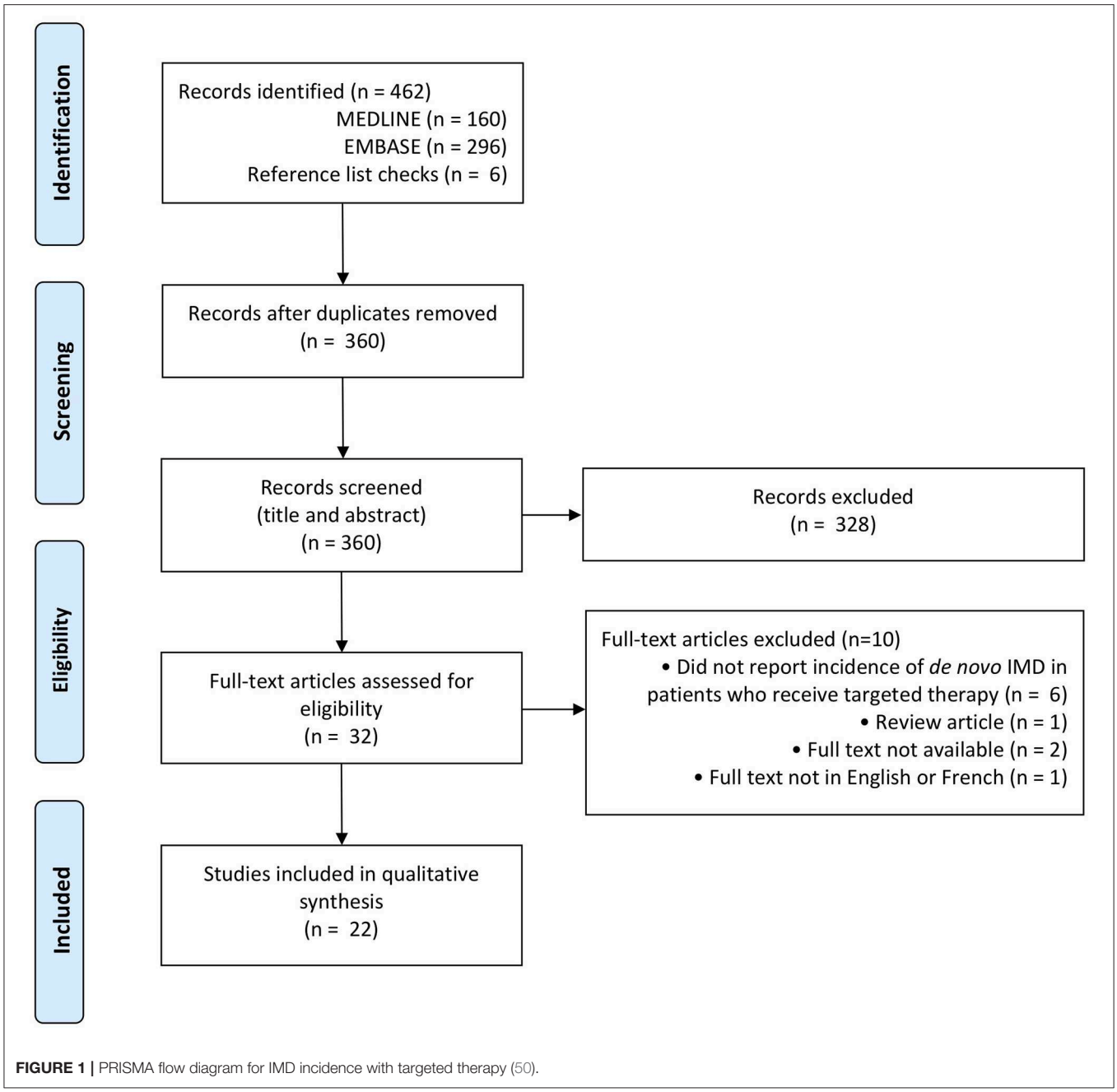


FIGURE 1 | PRISMA flow diagram for IMD incidence with targeted therapy (50).

methods, raising the question of the impact of targeted therapies on IMD incidence and survival (11). Formal appraisal to date has found insufficient evidence for the use of targeted therapies in the treatment of IMD, and the question of IMD incidence following targeted therapy remains debated (19).

Future studies may address these gaps from multiple approaches. Trials of targeted therapies have historically excluded patients with baseline IMD, but more recent studies have done so, beginning the process of clarifying the role of targeted therapy in the management of this disease. Prospective collection of data on intracranial outcomes in patients treated with a targeted therapy will elucidate the risk of IMD and provide insight on the role of targeted therapy in treating IMD. Future retrospective studies interested in the question of IMD incidence may examine larger populations to more finely control for covariates like cancer mutation status, or compare the effects of targeted therapies across primary disease types. Meta-analyses will benefit from broader reporting of IMD incidence stratified by status of baseline CNS disease, and database studies will allow observation of longer-term outcomes across institutions as survival with IMD improves.

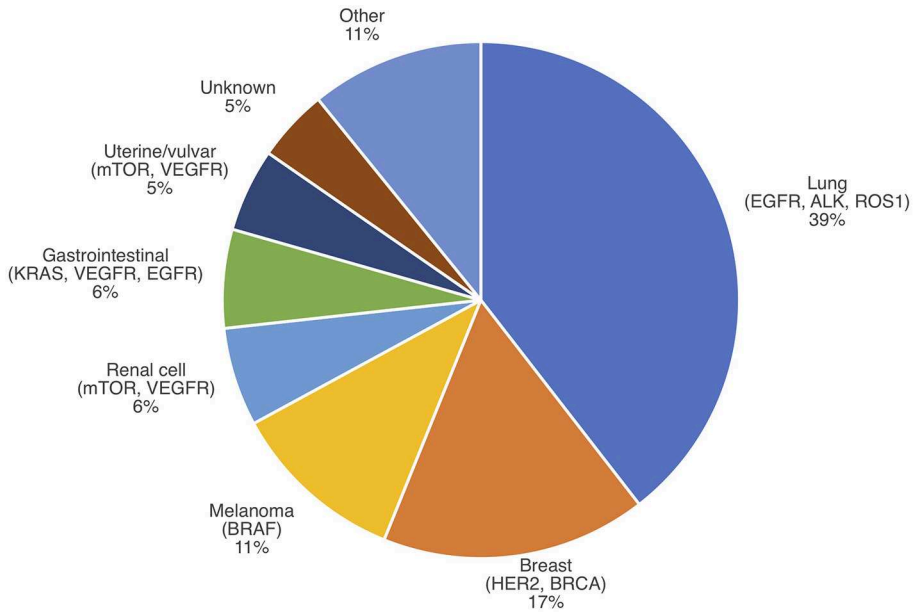


FIGURE 2 | IMD incidence by primary cancer type with select actionable mutations. Modified from Nussbaum et al. (51).

While the 2019 guidelines from the Congress of Neurological Surgeons do not make recommendations on the use of targeted therapy in the management of IMD, they note in their evidence review that therapies and studies since 2015 were not considered. Yet, targeted therapies in the field of IMD have undergone explosive development since that time, with new approvals in breast cancer, non-small cell lung cancer, melanoma, and RCC. New data will clarify the role of targeted therapy in the initial treatment of IMD, and clinicians will be required to make complex management decisions considering treatment sequencing, multimodal strategies with radiation and surgery, and weighing survival and quality of life for their patients with IMD. As survivorship in primary disease improves, more physicians may expect to discuss IMD risk with patients receiving targeted therapy, or to consider the implementation of focused surveillance imaging. Targeted therapy may replace the frontline modalities in the management of IMD, or it may occupy a prophylactic role for patients with primary disease. More immediately, targeted therapy may fill adjuvant or neoadjuvant roles alongside the current standard IMD treatments, and may vary between primary disease types.

CONCLUSION

Targeted therapies are emerging onto a dynamic treatment landscape for IMD, and future work will elucidate their place among current standards. Present data are few on IMD incidence among patients receiving targeted therapies for primary cancers, often limited to studies with single arms or small sample sizes. Future studies will stratify IMD incidence according to the BBB penetrance of targeted therapies in order to clarify the role of targeted therapies in preventing—or facilitating—the development of IMD. There is also a need for larger studies with higher power to elucidate the impact of targeted therapy on both incidence and survival in IMD. As more novel agents are developed, and the management of systemic disease improves, the treatment landscape for IMD may be expected to change, and physicians may anticipate considering IMD risk as they create management plans and counsel patients.

AUTHOR CONTRIBUTIONS

AE and SD wrote and revised the manuscript. AE was responsible for review of the literature and drawing the table and figures. SD designed the article.

FUNDING

SD is supported by an Early Researcher Award from the Province of Ontario. AE is supported by the Graduate Diploma in Health Research program at the University of Toronto.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00797/full#supplementary-material

REFERENCES

1. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, et al. Brain metastases. *Nat Rev Dis Primers.* (2019) 5:5. doi: 10.1038/s41572-018-0055-y
2. Cagney DN, Martin AM, Catalano PJ, Redig AJ, Lin NU, Lee EQ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol.* (2017) 19:1511–21. doi: 10.1093/neuonc/nox077
3. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol.* (2004) 22:2865–72. doi: 10.1200/JCO.2004.12.149
4. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol.* (2012) 30:419–25. doi: 10.1200/JCO.2011.38.0527
5. Ascierto PA, Kirkwood JM, Grob JJ, Simeone E, Grimaldi AM, Maio M, et al. The role of BRAF V600 mutation in melanoma. *J Transl Med.* (2012) 10:85. doi: 10.1186/1479-5876-10-85
6. Kotecha R, Gondi V, Ahluwalia MS, Brastianos PK, Mehta MP. Recent advances in managing brain metastasis. (2018) 7:F1000Res. doi: 10.12688/f1000research.15903.1
7. Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). *Neuro Oncol.* (2017) 19:162–74. doi: 10.1093/neuonc/now241
8. Graber JJ, Cobbs CS, Olson JJ. Congress of neurological surgeons systematic review and evidence-based guidelines on the use of stereotactic radiosurgery in the treatment of adults with metastatic brain tumors. *Neurosurgery.* (2019) 84:E168–70. doi: 10.1093/neuros/nyy543
9. Tsao MN, Xu W, Wong RK, Lloyd N, Laperriere N, Sahgal A, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev.* (2018) 1:CD003869. doi: 10.1002/14651858.CD003869.pub4
10. Gaspar LE, Prabhu RS, Hdeib A, McCracken DJ, Lasker GF, McDermott MW, et al. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of whole brain radiation therapy in adults with newly diagnosed metastatic brain tumors. *Neurosurgery.* (2019) 84:E159–62. doi: 10.1093/neuros/nyy541
11. Martinez P, Mak RH, Oxnard GR. Targeted therapy as an alternative to whole-brain radiotherapy in EGFR-mutant or ALK-positive non-small-cell lung cancer with brain metastases. *JAMA Oncol.* (2017) 3:1274–5. doi: 10.1001/jamaoncol.2017.1047
12. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol.* (2017) 3:827–31. doi: 10.1001/jamaoncol.2016.3834
13. Juloori A, Miller JA, Parsai S, Kotecha R, Ahluwalia MS, Mohammadi AM, et al. Overall survival and response to radiation and targeted therapies among patients with renal cell carcinoma brain metastases. *J Neurosurg.* (2019) 18:1–9. doi: 10.3171/2018.8.JNS182100
14. Sloot S, Chen YA, Zhao X, Weber JL, Benedict JJ, Mule JJ, et al. Improved survival of patients with melanoma brain metastases in the era of targeted BRAF and immune checkpoint therapies. *Cancer.* (2018) 124:297–305. doi: 10.1002/cncr.30946
15. Ha FJ, Spain L, Dowling A, Kwan EM, Pezaro C, Day D, et al. Timing of brain metastases development in metastatic renal cell cancer patients treated with targeted therapies and survival outcomes: an Australian multicenter study. *Asia Pac J Clin Oncol.* (2019). doi: 10.1111/ajco.13109. [Epub ahead of print].
16. Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys.* (2013) 85:1312–8. doi: 10.1016/j.ijrobp.2012.11.042
17. Goss G, Tsai CM, Shepherd FA, Ahn MJ, Bazhenova L, Crino L, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. *Ann Oncol.* (2018) 29:687–93. doi: 10.1093/annonc/mdx820
18. Gadgeel S, Peters S, Mok T, Shaw AT, Kim DW, Ou SI, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol.* (2018) 29:2214–22. doi: 10.1093/annonc/mdy405
19. Elder JB, Nahed BV, Linskey ME, Olson JJ. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of emerging and investigational therapies for the treatment of adults with metastatic brain tumors. *Neurosurgery.* (2019) 84:E201–E3. doi: 10.1093/neuros/nyy547
20. Coppin C, Kollmannsberger C, Le L, Porzsolt F, Wilt TJ. Targeted therapy for advanced renal cell cancer (RCC): a Cochrane systematic review of published randomised trials. *BJU Int.* (2011) 108:1556–63. doi: 10.1111/j.1464-410X.2011.10629.x
21. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev.* (2012) 4:CD006243. doi: 10.1002/14651858.CD006243.pub2
22. Nguyen KS, Neal JW, Wakelee H. Review of the current targeted therapies for non-small-cell lung cancer. *World J Clin Oncol.* (2014) 5:576–87. doi: 10.5306/wjco.v5.i4.576
23. Eggermont AMM, Robert C, Ribas A. The new era of adjuvant therapies for melanoma. *Nat Rev Clin Oncol.* (2018) 15:535–6. doi: 10.1038/s41571-018-0048-5
24. Gampa G, Vaidhyanathan S, Resman BW, Parrish KE, Markovic SN, Sarkaria JN, et al. Challenges in the delivery of therapies to melanoma brain metastases. *Curr Pharmacol Rep.* (2016) 2:309–25. doi: 10.1007/s40495-016-0072-z
25. Bartsch R, Berghoff A, Pluschnig U, Bago-Horvath Z, Dubsky P, Rottenfusser A, et al. Impact of anti-HER2 therapy on overall survival in HER2–overexpressing breast cancer patients with brain metastases. *Br J Cancer.* (2012) 106:25–31. doi: 10.1038/bjc.2011.531
26. Puhalla S, Elmquist W, Freyer D, Kleinberg L, Adkins C, Lockman P, et al. Unsanctifying the sanctuary: challenges and opportunities with brain metastases. *Neuro Oncol.* (2015) 17:639–51. doi: 10.1093/neuonc/nov023
27. Nolan C, Deangelis LM. Overview of metastatic disease of the central nervous system. *Handb Clin Neurol.* (2018) 149:3–23. doi: 10.1016/B978-0-12-811161-1.00001-3
28. Wang BX, Ou W, Mao XY, Liu Z, Wu HQ, Wang SY. Impacts of EGFR mutation and EGFR-TKIs on incidence of brain metastases in advanced non-squamous NSCLC. *Clin Neurol Neurosurg.* (2017) 160:96–100. doi: 10.1016/j.clineuro.2017.06.022
29. Viani GA, Afonso SL, Stefano EJ, De Fendi LI, Soares FV. Adjuvant trastuzumab in the treatment of her-2–positive early breast cancer: a meta-analysis of published randomized trials. *BMC Cancer.* (2007) 7:153. doi: 10.1186/1471-2407-7-153
30. Heon S, Yeap BY, Lindeman NI, Joshi VA, Butaney M, Britt GJ, et al. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. *Clin Cancer Res.* (2012) 18:4406–14. doi: 10.1158/1078-0432.CCR-12-0357
31. Heon S, Yeap BY, Britt GJ, Costa DB, Rabin MS, Jackman DM, et al. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. *Clin Cancer Res.* (2010) 16:5873–82. doi: 10.1158/1078-0432.CCR-10-1588
32. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med.* (2017) 377:829–38. doi: 10.1056/NEJMoa1704795
33. Dudek AZ, Raza A, Chi M, Singhal M, Oberoi R, Mittapalli RK, et al. Brain metastases from renal cell carcinoma in the era of tyrosine kinase inhibitors. *Clin Genitourin Cancer.* (2013) 11:155–60. doi: 10.1016/j.clgc.2012.11.001
34. Berghoff AS, Bago-Horvath Z, Dubsky P, Rudas M, Pluschnig U, Wiltschke C, et al. Impact of HER-2–targeted therapy on overall survival in patients with HER-2 positive metastatic breast cancer. *Breast J.* (2013) 19:149–55. doi: 10.1111/tbj.12070

35. Swain SM, Baselga J, Miles D, Im YH, Quah C, Lee LF, et al. Incidence of central nervous system metastases in patients with HER2–positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA. *Ann Oncol.* (2014) 25:1116–21. doi: 10.1093/annonc/mdu133
36. Bria E, Cuppone F, Fornier M, Nisticò C, Carlini P, Milella M, et al. Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomized trials. *Breast Cancer Res Treat.* (2008) 109:231–9. doi: 10.1007/s10549-007-9663-z
37. Okines A, Irfan T, Khabra K, Smith I, O'Brien M, Parton M, et al. Development and responses of brain metastases during treatment with trastuzumab emtansine (T-DM1) for HER2 positive advanced breast cancer: A single institution experience. *Breast J.* (2018) 24:253–9. doi: 10.1111/tbj.12906
38. Musolino A, Ciccolallo L, Panebianco M, Fontana E, Zanoni D, Bozzetti C, et al. Multifactorial central nervous system recurrence susceptibility in patients with HER2–positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. *Cancer.* (2011) 117:1837–46. doi: 10.1002/cncr.25771
39. Yau T, Swanton C, Chua S, Sue A, Walsh G, Rostom A, et al. Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab. *Acta Oncol.* (2006) 45:196–201. doi: 10.1080/02841860500486630
40. Peuvrel L, Saint-Jean M, Quéreux G, Brocard A, Khammari A, Knol AC, et al. Incidence and characteristics of melanoma brain metastases developing during treatment with vemurafenib. *J Neurooncol.* (2014) 120:147–54. doi: 10.1007/s11060-014-1533-z
41. Su PL, Wu YL, Chang WY, Ho CL, Tseng YL, Lai WW, et al. Preventing and treating brain metastases with three first-line EGFR-tyrosine kinase inhibitors in patients with EGFR mutation-positive advanced non-small cell lung cancer. *Ther Adv Med Oncol.* (2018) 10:1758835918797589. doi: 10.1177/1758835918797589
42. Fu Y, Hu J, Du N, Jiao S, Li F, Li X, et al. Bevacizumab plus chemotherapy versus chemotherapy alone for preventing brain metastasis derived from advanced lung cancer. *J Chemother.* (2016) 28:218–24. doi: 10.1179/1973947815Y.0000000045
43. Ilhan-Mutlu A, Osswald M, Liao Y, Gommel M, Reck M, Miles D, et al. Bevacizumab prevents brain metastases formation in lung adenocarcinoma. *Mol Cancer Ther.* (2016) 15:702–10. doi: 10.1158/1535-7163.MCT-15-0582
44. Nishio M, Nakagawa K, Mitsudomi T, Yamamoto N, Tanaka T, Kuriki H, et al. Analysis of central nervous system efficacy in the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer.* (2018) 121:37–40. doi: 10.1016/j.lungcan.2018.04.015
45. Zhao X, Zhu G, Chen H, Yang P, Li F, Du N. Efficacy of icotinib versus traditional chemotherapy as first-line treatment for preventing brain metastasis from advanced lung adenocarcinoma in patients with epidermal growth factor receptor-sensitive mutation. *J Cancer Res Ther.* (2014) 10(Suppl.):C155–9. doi: 10.4103/0973-1482.145851
46. Verma J, Jonasch E, Allen P, Tannir N, Mahajan A. Impact of tyrosine kinase inhibitors on the incidence of brain metastasis in metastatic renal cell carcinoma. *Cancer.* (2011) 117:4958–65. doi: 10.1002/cncr.26138
47. Massard C, Zonierek J, Gross-Goupil M, Fizazi K, Szczylik C, Escudier B. Incidence of brain metastases in renal cell carcinoma treated with sorafenib. *Ann Oncol.* (2010) 21:1027–31. doi: 10.1093/annonc/mdp411
48. Vanhuyse M, Penel N, Caty A, Fumagalli I, Alt M, Zini L, et al. Do anti-angiogenic therapies prevent brain metastases in advanced renal cell carcinoma? *Bull Cancer.* (2012) 99:100–6. doi: 10.1684/bdc.2012.1672
49. Shao YY, Lu LC, Cheng AL, Hsu CH. Increasing incidence of brain metastasis in patients with advanced hepatocellular carcinoma in the era of antiangiogenic targeted therapy. *Oncologist.* (2011) 16:82–6. doi: 10.1634/theoncologist.2010-0272
50. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* (2009) 62:1006–12. doi: 10.1016/j.jclinepi.2009.06.005
51. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer.* (1996) 78:1781–8.
52. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer.* (1996) 78:1781–8. doi: 10.1002/(SICI)1097-0142(19961015)78:8<1781::AID-CNCR19>3.0.CO;2-U

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Erickson and Das. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 27 September 2018
doi: 10.3389/fonc.2018.00414

Immune Checkpoint Inhibitors for the Treatment of Central Nervous System (CNS) Metastatic Disease

Suneel D. Kamath[1,2]* *and Priya U. Kumthekar*[2,3]

[1] Northwestern Medicine, Chicago, IL, United States, [2] Feinberg School of Medicine, Northwestern University, Chicago, IL, United States, [3] Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, United States

While the CNS has long been viewed as an immune-privileged environment, a paradigm shift in neuro-immunology has elevated the role of systemic immunotherapy for the treatment of metastatic disease. Increasing knowledge regarding the presence of a CNS lymphatic system and the physical and biochemical alteration of the blood brain barrier (BBB) by the tumor microenvironment suggests immune cell trafficking in and out of the CNS is possible. Emerging clinical data suggest immune checkpoint inhibitors (ICIs) can stimulate T cells peripherally to in turn have anti-tumor effects in the CNS. For example, anti-programmed cell death-1 (PD-1) monotherapy with pembrolizumab has shown intracranial response rates of 20–30% in patients with melanoma or non-small cell lung cancer (NSCLC) brain metastases. The combination of nivolumab and ipilimumab [anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)] showed an intracranial response rate of 55% in patients with melanoma brain metastases. More data are needed to confirm these response rates and to determine mechanisms of efficacy and resistance. While local therapies such as stereotactic radiosurgery (SRS), whole-brain radiation therapy (WBRT), and surgery remain current mainstays, ICIS offer potential decreased neurotoxicity. This review summarizes the biological rationale for systemic immunotherapy to treat CNS metastatic disease, existing clinical data on ICIs in this setting and ongoing clinical trials exploring areas of unmet need.

Keywords: immunotherapy, brain metastasis, CNS metastasis, checkpoint inhibitors, PD-1, pembrolizumab, nivolumab, ipilimumab

OPEN ACCESS

Edited by:
Sunit Das,
St. Michael's Hospital, Canada

Reviewed by:
David M. Peereboom,
Cleveland Clinic Lerner College of Medicine, United States
Seunggu Jude Han,
Oregon Health & Science University, United States

***Correspondence:**
Suneel D. Kamath
suneel.kamath@northwestern.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *31 July 2018*
Accepted: *07 September 2018*
Published: *27 September 2018*

Citation:
Kamath SD and Kumthekar PU (2018) Immune Checkpoint Inhibitors for the Treatment of Central Nervous System (CNS) Metastatic Disease. Front. Oncol. 8:414. doi: 10.3389/fonc.2018.00414

INTRODUCTION

Despite recent advances in cancer therapy, CNS metastasis remains a devastating complication for many solid organ cancer patients. Brain metastases occur in up to 20% of adults with systemic malignancies, most commonly in lung cancer, melanoma, and breast cancer (1). The incidence is increasing in many histologies, in part due to improved detection by magnetic resonance imaging (MRI) and with prolonged survival from improved systemic therapies (2). To date, local therapies such as SRS, WBRT, and surgical resection have been the mainstays. These modalities can cause significant complications and morbidity (stroke, radiation necrosis, cognitive deficits) with only a modest benefit in overall survival (3).

Systemic immunotherapy has shown promising early results in treating brain metastases and has altered the traditional immune-privileged paradigm of the brain. The immune system plays an important role in clearance of oncogenic clones through antigen-presenting cell (APC) recognition

of tumor cell antigens, T cell activation by APCs and subsequent T cell cytotoxicity (4, 5). Conversely, tumor cells can evade immune destruction through expression of various immune checkpoints that promote self-tolerance and suppress effector T cell function and proliferation (6, 7). The most clinically relevant immune checkpoints are programmed cell death protein 1 and its ligand (PD-1 and PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4). PD-L1 is expressed on the tumor cell surface and through interaction with PD-1 on T cells causes apoptosis of cytotoxic T cells while inhibiting apoptosis of regulatory T cells (8). CTLA4 is a co-stimulatory pathway protein that interacts with HLA-B7-1 and HLA-B7-2 on T cells and delivers an inhibitory signal to effector T cells while promoting inhibitory function of regulatory T cells (6–8). In net, these pathways promote tumor cell survival and proliferation through immune evasion.

While normal brain parenchyma and primary CNS tumors have immunoregulatory environments with rare lymphocytes, brain metastases have been shown to have significant tumor-infiltrating lymphocytes (TILs). One series of 116 patients with brain metastases specimens showed that CD3+ TILs were present in 115/116 (99.1%) specimens and 56% had dense or very dense TIL infiltration (9). 112/116 (96.6%) tumor specimens had CD8+ T cell infiltration while 19/67 (28.4%) of specimens evaluated for PD-L1 expression had > 5% membranous expression. The highest density of CD3+ TILs, CD8+ TILs, and PD-1-expressing T cells was found in melanoma brain metastases. High density of CD3+ TILs was associated with longer median overall survival (OS) regardless of primary tumor site compared to low CD3+ TIL density (15 months vs. 6 months, respectively) (9). It has previously been demonstrated that higher density of TILs, CD8+ T cells, and CD45RO+ memory T cells in the primary tumor is associated with longer disease-free survival and OS in various solid tumor cancers (4). The concordance of higher TIL density and improved OS in both primary tumors and brain metastases supports the use of immune checkpoint inhibition to treat both systemic and CNS metastatic disease. Given that the brain is no longer a strict "immune privileged" environment and brain metastases can disrupt the blood brain barrier, there have been several trials of ICIs with promising results that are summarized herein.

CLINICAL DATA

Ipilimumab

The anti-CTLA4 monoclonal antibody ipilimumab was the first ICI to show efficacy in treating brain metastases. This CNS activity was discovered incidentally in the original trials establishing its efficacy in metastatic melanoma when patients with brain metastases also showed durable CNS responses (10). This was confirmed in a subsequent phase II study of 72 patients with melanoma brain metastases treated with ipilimumab 10 mg/kg every 3 weeks (11). Of 51 patients with asymptomatic brain metastases, 16% showed an objective response in the CNS with a median CNS progression-free survival (PFS) of 1.5 months. Of 21 patients with symptomatic brain metastases or those that required steroids, the objective response rate (ORR) was 5% with median CNS PFS of 1.2 months. CNS disease control was achieved in 24% of asymptomatic patients and 10% of symptomatic patients (11). A second phase II trial (NIBIT-M1 trial) of ipilimumab 10 mg/kg combined with fotemustine in metastatic melanoma showed a 40% CNS response rate, though only 20 patients with brain metastases were included in this trial. Two patients achieved a CNS complete response (CR) and 50% of patients achieved CNS disease control (12). OS at 3 years was 27.8%, suggesting that responses and disease control were durable in this population as has been observed in other immunotherapy trials (13).

An expanded access program in the United States that included 165 patients with melanoma brain metastases treated with ipilimumab demonstrated a 20% rate of OS at 1 year (14). Another expanded access program in Italy that included 146 patients with melanoma brain metastases treated with ipilimumab demonstrated an ORR of 12% and disease control rate of 27%. This included 4 patients who achieved a CR (15). Of note, these trials used high-dose ipilimumab, which is associated with a higher rate of severe colitis and treatment-related mortality (16, 17). As a result, the 10 mg/kg dose is uncommon in more recent clinical trials, especially when dual immunotherapy is used, where the 1–3 mg/kg doses are often used (18, 19). Overall, these data were the first to establish efficacy and durability of ICIs for the treatment of CNS metastatic disease and paved the way for anti-PD-1 therapy in this setting.

Pembrolizumab

The anti-PD-1 monoclonal antibody pembrolizumab was the first PD-1 inhibitor that clearly demonstrated efficacy against untreated brain metastases in melanoma and non-small cell lung cancer (NSCLC). The original trial was a single-institution, phase II trial that included 2 cohorts of patients with untreated or progressive brain metastases, one for melanoma and one for NSCLC (17). All levels of PD-L1 expression were included in the melanoma cohort and a cutoff of $\geq$ 1% was used in the NSCLC cohort. In the 18 patients with melanoma brain metastases, 4 (22%) patients experienced an objective response, 2 CRs and 2 partial responses (PRs). An additional 4 patients had stable disease. In the NSCLC cohort of 18 patients, 6 (33%) had an objective response, which included 4 CRs and 2 PRs. One patient achieved stable disease as the best response (17).

There was strong concordance between CNS response and systemic response as 8/9 (88%) of patients with a confirmed systemic response also had a CNS response. After 11.6 months of follow up, median OS in the melanoma cohort was not reached and was 7.7 months in the NSCLC cohort. The toxicity profile was similar to other trials of pembrolizumab across disease types and importantly, there were no treatment-related deaths. Of note, pembrolizumab was given as 10 mg/kg every 2 weeks in this trial as opposed to the fixed dose of 200 mg every 3 weeks that is FDA-approved now (17).

An update of data for the NSCLC cohort presented at the ASCO 2018 annual meeting showed a CNS response rate of 29.4% in the 34 patients enrolled (20). Median OS was 8.9 months with 31% of patients living more than 2 years. Discordance between CNS and systemic responses was seen in 7 patients (21%, 4

with CNS disease progression but PR systemically and 3 with CNS response but systemic disease progression). An additional 5 patients with PD-L1 negative or unevaluable tumors were included, though there were no CNS responses in this subgroup (20).

Nivolumab

The anti-PD-1 monoclonal antibody nivolumab has shown similar efficacy to pembrolizumab for untreated melanoma brain metastases. In the monotherapy arm of the randomized phase II ABC study, patients with asymptomatic melanoma brain metastases treated with nivolumab 3 mg/kg every 2 weeks showed a 20% CNS response rate (21). Median intracranial PFS and OS were 2.5 and 18.5 months, respectively. In a cohort of patients with symptomatic brain metastases, leptomeningeal disease or failure of local radiotherapy, a 6% CNS response rate was observed (21).

Additional data supporting nivolumab for untreated brain metastases comes from an Italian expanded-access program of 372 patients with advanced squamous NSCLC, 38 of whom had asymptomatic brain metastases (22). The disease control rate was 47.3% in this cohort, comprising of one CR, six PRs and 11 patients with stable disease. Four patients were treated beyond progression. The median PFS and OS were 5.5 and 6.5 months, respectively and only 1 patient discontinued therapy due to adverse events (22). Another small series of 5 patients with asymptomatic NSCLC brain metastases treated with nivolumab showed activity in 3 patients: 1 CR, 1 PR, and 1 with stable disease for 10 weeks. Both responses were durable beyond 6 months (23).

Another Italian expanded access program for nivolumab in metastatic renal cell carcinoma (RCC) included 389 patients, 32 with brain metastases. The CNS response rate was 18.7% with a disease control rate of 53.1%. This included 1 CR, 5 PRs, and 11 with stable disease. The CNS response rate was similar to the systemic response rate of 23.2%. The 1 year OS rate was 63.1% and in a univariate analysis, CNS metastasis was not associated with inferior OS (24).

Nivolumab and Ipilimumab

The combination of nivolumab and ipilimumab has shown the most impressive CNS response rates to immunotherapy. The phase II CheckMate 204 study of nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks was the first to demonstrate efficacy of combination immunotherapy for patients with untreated melanoma brain metastases (25). An updated analysis of CheckMate 204 with 94 enrolled patients showed a 52% CNS response rate, including 24 (26%) intracranial CRs (26). The intracranial clinical benefit rate was 57%. The systemic ORR was 47% with high concordance between systemic and CNS responses. Only 5 patients (5%) discontinued therapy due to immune-related neurologic adverse events, though there was one death due to immunotherapy-related myocarditis.

These results were confirmed in the randomized phase II ABC study comparing nivolumab 3 mg/kg every 2 weeks alone vs. combination therapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks (21). This study showed a CNS response rate of 46% with the combination of nivolumab and ipilimumab vs. 20% with nivolumab alone. This included CNS complete response rates of 17 and 12%, respectively. Median intracranial PFS and median OS were both not reached in the combination therapy arm after a median follow up of 14 months (21).

The combination of nivolumab and ipilimumab was significantly more toxic than nivolumab alone. Grade 3 or higher adverse events were observed in 63% of patients receiving the combination vs. 16% receiving nivolumab alone and were mainly systemic. There was only one grade 3 CNS adverse event that was more common with combination therapy vs. nivolumab monotherapy, which was headache (20 vs. 6%). There were no treatment-related deaths in this trial (21).

Overall, these data demonstrate that the combination of anti-PD-1 and anti-CTLA4 therapy has significant activity for CNS metastatic disease with a relatively low rate of serious CNS-specific toxicity. Larger randomized clinical trials are needed to confirm these findings and to identify predictive biomarkers for CNS response. One such study, the phase III NIBIT-M2 study randomizing patients with melanoma brain metastases to fotemustine, fotemustine, and ipilimumab or ipilimumab and nivolumab, is ongoing (27).

A table summarizing the clinical trials discussed is shown in **Table 1**.

Additional Case Series

There are several single-institution series of ICIs for patients with CNS metastatic disease. One series from Cleveland Clinic included 128 patients with brain metastases from NSCLC (94 patients), RCC (15 patients), or melanoma (19 patients) who were treated with either pembrolizumab, nivolumab, ipilimumab, or a combination. Patients could also receive WBRT or SRS. While the authors did not report on CNS response or disease control rates, they reported 1 year survival rates of 48.3, 54.5, and 55.4% in patients with NSCLC, melanoma, and RCC, respectively (28).

Another single-institution series from the University of Cincinnati identified 51 patients with brain metastases from NSCLC, small cell lung cancer (SCLC), melanoma and head, and neck squamous cell carcinoma (HNSCC). Thirty patients had symptomatic brain metastases. Patients were treated with either atezolizumab, durvalumab, pembrolizumab, nivolumab, ipilimumab, or a combination. They could also receive concurrent radiation. The authors did not report CNS response or disease control rates, but reported median OS after the start of immunotherapy of 7.6, 7.2, 6.2, and 4 months for patients with melanoma, NSCLC, SCLC, and HNSCC, respectively. They also found that patients treated with immunotherapy alone had worse survival compared to combined modality therapy with radiation or surgery (29).

Future Directions and Challenges

Immunotherapy in neuro-oncology is an active area of investigation given its potential efficacy and clinical impact. Since most patients with brain metastases receive radiation therapy at some point, understanding the interplay of radiation with immunotherapy is of particular interest. Historically, radiation was considered to be immunosuppressive due to peripheral blood lymphodepletion (30). More recent pre-clinical work

TABLE 1 | Summary of immunotherapy trials for CNS metastatic disease.

Trial	Drug(s)	Phase	*N* (ITT)	Disease	PD-L1 status	CNS ORR	Median CNS PFS (months)	Median PFS (months)	Median OS (months)
NCT00623766	Ipilimumab 10 mg/kg q3W × 4 doses, then 10 mg/kg q12W	2	51	Melanoma (asymptomatic BMs)	NA	16% (8/51)	1.5	1.4	7
			21	Melanoma (symptomatic BMs or on steroids)	NA	5% (1/21)	1.2	1.2	3.7
NIBIT-M1	Ipilimumab 10 mg/kg q3W × 4 doses, then 10 mg/kg q12W + fotemustine 100 mg/m2 q3W	2	20	Melanoma (asymptomatic BMs)	NA	40% (8/20)	3	4.5	13.4
NCT02085070	Pembrolizumab 10 mg/kg q2W	2	18	Melanoma	Any	22% (4/18)	not reported	not reported	NR
			18	NSCLC	≥ 1%	33% (6/18)	not reported	not reported	7.7
CheckMate 204	Nivolumab 1 mg/kg q3W + Ipilimumab 3 mg/kg q3W	2	75	Melanoma	Any	56% (42/75)	not reported	not reported	not reported
NCT02374242	Nivolumab 1 mg/kg q3W + Ipilimumab 3 mg/kg q3W	2	35	Melanoma (asymptomatic BMs)	Any	46% (16/35)	NR	13.8	NR
	Nivolumab 3 mg/kg q2W		25	Melanoma (asymptomatic BMs)	Any	20% (5/25)	2.5	2.6	18.5
	Nivolumab 3 mg/kg q2W		16	Melanoma (symptomatic BMs, failed local therapy)	Any	6% (1/16)	2.3	2.6	5.1

N, number; ITT, intention to treat; W, week; NA, not applicable; BMs, brain metastases; NR, not reached.

has shown that radiation can augment anti-tumor immune responses through several mechanisms. First, radiation-induced tumor cell necrosis increases the release of tumor neoantigens and increases tumor mutational burden (TMB) (31). This also triggers the release of immune-stimulatory damage-associated molecular patterns (DAMPs), including high-mobility group protein B1 (HMGB1) and calreticulin (32, 33). These promote APC recruitment to the tumor microenvironment and antigen uptake and presentation to cytotoxic T cells. Radiation primes CD8 T cells by stimulating IFN-γ production and increasing tumor cell MHC class I and Fas expression (34). Radiation also increases PD-L1 expression, creating an opportunity for synergy with anti-PD-1 therapy (31, 35).

Small series have shown synergy between ipilimumab and SRS. One series of 70 patients with melanoma brain metastases showed improved median OS in 37 patients who received ipilimumab and SRS vs. the 33 patients who received SRS alone (18.3 months vs. 5.3 months) (36). Another series of 77 patients (27 received ipilimumab and SRS, 50 received SRS alone) also showed improved median OS of 21 months vs. 5 months, respectively (37). It appears that concurrent radiation with checkpoint inhibition is more effective than sequential treatment and high-dose, hypofractionated radiation is best, but this must be confirmed with more clinical data (31, 38). Steroid administration during SRS can negatively impact response to ICIs and must be considered only when clinically necessary (39).

Radiation delivered to a local site has been shown to cause regression of distant metastatic sites outside of the radiation field, a phenomenon known as the abscopal effect (32, 40). Activated cytotoxic T lymphocytes from increased tumor antigen stimulation and presentation at a local tumor site are thought to mediate the effect seen at distant tumor locations (32, 34, 40). Immune checkpoint inhibition dramatically improves the abscopal effect of radiation in pre-clinical models (32, 34). There are also two case reports (one NSCLC and one melanoma) of patients who achieved durable systemic complete responses at all tumor sites for 1 year with concurrent ipilimumab and local site stereotactic body radiation therapy (41, 42).

Based on these promising results, there are numerous ongoing clinical trials combining ICIs and brain radiation (NCT03104439, NCT02608385, NCT02730130, NCT03453164, NCT02444741), (NCT02696993).

Despite the fact the CNS is no longer considered an immune privileged site, it remains at least an immune deficient environment. While TILs have clearly been identified in CNS metastases, they are in lower number than in systemic tumors and the ratio of effector T cells to regulatory T cells remains unknown (9, 43). T cell and APC trafficking into and out of the CNS is more strictly regulated than in other tissues (9, 44). The degree of blood brain and blood tumor barrier disruption is variable between diseases, patients and even individual lesions in the same patient (45–47).

Patients with brain metastases frequently require steroids for symptomatic control, which has been found to negate the mechanisms of immunotherapy. In a series of 244 metastatic NSCLC patients, the use of steroids at > 20 mg/day of prednisone was associated with worse median PFS (1 month vs. 3 months) and median OS (3 months vs. 10 months) (48). Only 19 patients

received > 20 mg/day of prednisone and it remains unclear if high-dose steroids truly blunt the effect of immunotherapy or simply select for a population with worse overall prognosis (48).

A substantial number of patients do not respond systemically or in the CNS to existing immunotherapy drugs, creating a tremendous unmet need. The combination of pembrolizumab and bevacizumab is being studied in a phase II clinical trial in patients with untreated NSCLC and melanoma brain metastases (NCT02681549). The anti-PD-L1 drug atezolizumab is also being studied in combination with bevacizumab for untreated melanoma brain metastases (BEAT-MBM study; NCT03175432). This study includes a cohort with symptomatic brain metastases or those who require corticosteroids. Indoleamine (2,3)-dioxygenase (IDO) has emerged as another immune checkpoint that can be combined with anti-PD-1 therapy. There is an ongoing phase II study evaluating the IDO inhibitor BMS-986205 in combination with nivolumab for untreated melanoma brain metastases. A phase II trial evaluating pembrolizumab for patients with leptomeningeal carcinomatosis is ongoing, but to date, there have been no completed randomized trials in this population (49). Data from these trials and others may further expand the role of immunotherapy for the treatment of CNS metastatic disease.

There is also a significant need to identify more predictive immune biomarkers in the CNS. Many series have shown increased density and/or number of CD3+ and/or CD8+ TILs in brain tumor specimens is correlated with improved survival (9, 43, 50, 51). It is important to note that TIL density is lower in general in brain metastases and discordance in TIL density between primary tumors and brain metastases may be as high as 48% (51, 52). PD-L1 expression ($\geq$ 1%) is present in $\sim$ 25–30% of brain tumor specimens in some series, but it may be discordant from primary tumors in 30% of cases (9, 51, 53). Discordance in TIL density or PD-L1 expression can be partially explained by temporal and spatial heterogeneity from biopsies taken at different time points and from different sites (51). The predictive value of PD-L1 expression was shown in one series in which NSCLC patients with PD-L1+ brain metastases had a 29% intracranial response rate, while those with PD-L1- negative brain metastases had no responses (54). However, the data overall are very limited and prospective validation is still required. High TMB in brain metastases has been reported in 39% of cases and was more common than in primary tumors in one series (55). This may emerge as a clinically useful biomarker in the future.

As evidenced by the trials reviewed herein, there are disparate primary outcomes and disease measures, creating a need for consistent and clear CNS-specific endpoints in these studies. For example, the phenomenon of pseudo-response seen with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab may alter a study whose primary outcome is response rate (56). Furthermore, response is seen less often in the brain than systemically and using clinical benefit as an endpoint might be more accurate. These are all considerations that need to be unified across brain metastases clinical trials (56, 57).

CONCLUSIONS

Patients with brain metastases have traditionally been excluded from clinical trials, which is a detriment to our understanding of systemic therapies for CNS metastatic disease. A 2014 systematic analysis of interventional drug trials in advanced NSCLC listed on www.ClinicalTrials.gov showed that only 26% allowed for patients with untreated brain metastases (58). An ongoing analysis of currently available trials for advanced NSCLC showed only 27.7% specifically allowed enrollment of patients with untreated asymptomatic brain metastases and only 3.7% included patients with symptomatic or progressive brain metastases. While these patients have often been excluded because of lacking pre-clinical data or concerns about worsening outcome measures, it is important that we include these patients as they are more representative of the real-world disease population (59).

While there are legitimate barriers for clinical trial design and patient enrollment, the early data for immunotherapy in CNS metastatic disease show some promise and necessitate more studies where brain metastases are not exclusionary criteria. This viewpoint is further supported by the American Society of Clinical Oncology—Friends of Cancer Research Brain Metastases Working Group recommendation statement from November 2017 (59). Their recommendations provide a clear and practical framework to improve clinical trial eligibility criteria for patients with brain metastases without compromising good scientific trial design.

As systemic therapies improve and patients live longer with metastatic disease, the number of patients with CNS metastases will grow, creating a larger unmet need for cancer patients. The existing evidence of the efficacy of systemic immunotherapy for untreated brain metastases is promising and supports increased enrollment of patients with brain metastases in immunotherapy clinical trials.

AUTHOR CONTRIBUTIONS

SK and PK both contributed equally to the conception, design, writing, and editing of this manuscript as well as the selection and construction of its figures/tables.

REFERENCES

1. Johnson JD, Young B. Demographics of brain metastasis. *Neurosurg Clin N Am*. (1996) 7:337–44. doi: 10.1016/S1042-3680(18)30365-6
2. Gavrilovic IT, Posner JB, Brain metastases: epidemiology and pathophysiology. *J Neurooncol*. (2005) 75:5–14. doi: 10.1007/s11060-004-8093-6
3. Jindal V, Gupta S. Expected paradigm shift in brain metastases therapy-immune checkpoint inhibitors. *Mol Neurobiol*. (2018) 55:7072–8. doi: 10.1007/s12035-018-0905-3
4. Fridman WH, Pages F, Sautes-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. *Nat Rev Cancer* (2012) 12:298–306. doi: 10.1038/nrc3245

5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* (2011) 144:646–74. doi: 10.1016/j.cell.2011.02.013
6. Herbst RS, Soria, JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* (2014) 515:563–7. doi: 10.1038/nature14011
7. Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer 2014; preclinical background: CTLA-4 and PD-1 Blockade. *Semin Oncol*. (2010) 37:430–9. doi: 10.1053/j.seminoncol.2010.09.005
8. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev*. (2010) 236:219–42. doi: 10.1111/j.1600-065X.2010.00923.x
9. Berghoff AS, Fuchs E, Ricken G, Mlecnik B, Bindea G, Spanberger T, et al. Density of tumor-infiltrating lymphocytes correlates with extent of brain edema and overall survival time in patients with brain metastases. *Oncoimmunology* (2016) 5:e1057388. doi: 10.1080/2162402X.2015.1057388
10. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Eng J Med*. (2010) 363:711–23. doi: 10.1056/NEJMoa1003466
11. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. (2012) 13:459–65. doi: 10.1016/S1470-2045(12)70090-6
12. Di Giacomo AM, Ascierto PA, Pilla L, Santinami M, Ferrucci PF, Giannarelli D, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. *Lancet Oncol.* (2012) 13:879–86. doi: 10.1016/S1470-2045(12)70324-8
13. Di Giacomo AM, Ascierto PA, Queirolo P, Pilla L, Ridolfi R, Santinami M, et al. Three-year follow-up of advanced melanoma patients who received ipilimumab plus fotemustine in the Italian Network for Tumor Biotherapy (NIBIT)-M1 phase II study. *Ann Oncol*. (2015) 26:798–803. doi: 10.1093/annonc/mdu577
14. Heller KN, Pavlick AC, Hodi FS, Thompson JA, Margolin KA, Lawrence DP, et al. Safety and survival analysis of ipilimumab therapy in patients with stable asymptomatic brain metastases. *J Clin Oncol*. (2011) 29:8581. doi: 10.1200/jco.2011.29.15_suppl.8581
15. Queirolo P, Spagnolo F, Ascierto PA, Simeone E, Marchetti P, Scoppola A, et al. Efficacy and safety of ipilimumab in patients with advanced melanoma and brain metastases. *J Neuro-Oncol*. (2014) 118:109–16. doi: 10.1007/s11060-014-1400-y
16. Eggermont AM, Chiarion-Sileni V, Grob, JJ, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Eng J Med*. (2016) 375:1845–55. doi: 10.1056/NEJMoa1611299
17. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. (2016) 17:976–83. doi: 10.1016/S1470-2045(16)30053-5
18. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Eng J Med*. (2018) 378:1277–90. doi: 10.1056/NEJMoa1712126
19. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob, JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Eng J Med*. (2017) 377:1345–56. doi: 10.1056/NEJMoa1709684
20. Goldberg S, Mahajan A, Herbst R, Chiang A, Lilenbaum R, Jilaveanu L et al. Durability of brain metastasis response and overall survival in patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab. In: *ASCO Annual Meeting* (2018) Available online at: http://abstracts.asco.org/214/AbstView_214_228899.html
21. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol*. (2018) 19:672–81. doi: 10.1016/S1470-2045(18)30139-6
22. Bidoli P, Chiari R, Catino A, Grossi F, Noberasco C, Gelsomino F, et al. Efficacy and safety data from patients with advanced squamous NSCLC and brain metastases participating in the nivolumab Expanded Access Programme (EAP) in Italy. *Ann Oncol*. (2016) 27:1228P. doi: 10.1093/annonc/mdw383.28
23. Dudnik E, Yust-Katz S, Nechushtan H, Goldstein DA, Zer A, Flex D, et al. Intracranial response to nivolumab in NSCLC patients with untreated or progressing CNS metastases. *Lung Cancer* (2016) 98:114–7. doi: 10.1016/j.lungcan.2016.05.031
24. De Giorgi U, Carteni G, Giannarelli D, Basso U, Galli L, Cortesi E, et al. Safety and efficacy of nivolumab for metastatic renal cell carcinoma: real-world results from an expanded access programme. *BJU Int*. (2018). doi: 10.1111/bju.14461. [Epub ahead of print].
25. Tawbi HAH, Forsyth PAJ, Algazi AP, Hamid O, Hodi FS, Moschos SJ, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204. *J Clin Oncol*. (2017) 35:9507. doi: 10.1200/JCO.2017.35.15_suppl.9507
26. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. (2018) 379:722–30. doi: 10.1056/NEJMoa1805453
27. Di Giacomo AM, Annesi D, Ascierto PA, Calabrò L, Chiarion-Sileni V, Danielli R, et al. A randomized, phase III study of fotemustine versus the combination of fotemustine and ipilimumab or the combination of ipilimumab and nivolumab in patients with metastatic melanoma with brain metastasis: the NIBIT-M2 trial. *J Clin Oncol*. (2015) 33:TPS9090. doi: 10.1200/jco.2015.33.15_suppl.tps9090
28. Lauko A, Thapa B, Jia X, Ahluwalia MS. Efficacy of immune checkpoint inhibitors in patients with brain metastasis from NSCLC, RCC, and melanoma. *J Clin Oncol*. (2018) 36:214. doi: 10.1200/JCO.2018.36.5_suppl.214
29. Karivedu V, Jandarov R, Wise-Draper TM. Brain metastases treated with immune checkpoint inhibitors: a single center experience. *J Clin Oncol*. (2018) 36:e14012. doi: 10.1200/JCO.2018.36.15_suppl.e14012
30. Piotrowski AF, Nirschl TR, Velarde E, Blosser L, Ganguly S, Burns KH, et al. Systemic depletion of lymphocytes following focal radiation to the brain in a murine model. *Oncoimmunology* (2018) 7:e1445951. doi: 10.1080/2162402X.2018.1445951
31. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res*. (2014) 74:5458–68. doi: 10.1158/0008-5472.CAN-14-1258
32. Hodge JW, Guha C, Neefjes J, Gulley JL. Synergizing radiation therapy and immunotherapy for curing incurable cancers. Opportunities and challenges. *Oncology* (2008) 22:1064–70.
33. Weichselbaum RR, Liang H, Deng L, Fu YX, Radiotherapy and immunotherapy: a beneficial liaison? *Nat Rev Clin Oncol*. (2017) 14:365–79. doi: 10.1038/nrclinonc.2016.211
34. Tang C, Wang X, Soh H, Seyedin S, Cortez MA, Krishnan S, et al. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? *Cancer Immunol Res*. (2014) 2:831–8. doi: 10.1158/2326-6066.CIR-14-0069
35. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest*. (2014) 124:687–95. doi: 10.1172/JCI67313
36. Silk AW, Bassetti MF, West BT, Tsien CI, Lao CD. Ipilimumab and radiation therapy for melanoma brain metastases. *Cancer Med* (2013) 2:899–906. doi: 10.1002/cam4.140
37. Knisely JP, Yu JB, Flanigan J, Sznol M, Kluger HM, Chiang VL. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. *J Neurosurg*. (2012) 117:227–33. doi: 10.3171/2012.5.JNS111929
38. Demaria S, Formenti SC. Radiation as an immunological adjuvant: current evidence on dose and fractionation. *Front Oncol*. (2012) 2:153. doi: 10.3389/fonc.2012.00153
39. Schoenfeld JD, Mahadevan A, Floyd SR, Dyer MA, Catalano PJ, Alexander BM, et al. Ipilmumab and cranial radiation in metastatic melanoma patients: a case series and review. *J Immunother Cancer* (2015) 3:50. doi: 10.1186/s40425-015-0095-8
40. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med*. (2012) 366:925–31. doi: 10.1056/NEJMoa1112824
41. Hiniker SM, Chen DS, Reddy S, Chang DT, Jones JC, Mollick JA, et al. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. *Transl Oncol*. (2012) 5:404–7. doi: 10.1593/tlo.12280

42. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non–small cell lung cancer. *Cancer Immunol Res.* (2013) 1:365–72. doi: 10.1158/2326-6066.CIR-13-0115
43. Berghoff AS, Inan C, Ricken G, Widhalm G, Dieckmann K, Birner P, et al. 1324PTUMOR-Infiltrating lymphocytes (TILS) and PD-L1 expression in non-small cell lung cancer brain metastases (BM) and matched primary tumors (PT). *Ann Oncol.* (2014) 25:iv465–6. doi: 10.1093/annonc/mdu349.103
44. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* (2015) 523:337–41. doi: 10.1038/nature14432
45. Lockman PR, Mittapalli RK, Taskar KS, Rudraraju V, Gril B, Bohn KA, et al. Heterogeneous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. *Clin Cancer Res.* (2010) 16:5664–78. doi: 10.1158/1078-0432.CCR-10-1564
46. Lampson LA, Monoclonal antibodies in neuro-oncology: getting past the blood-brain barrier. *MAbs* (2011) 3:153–60. doi: 10.4161/mabs.3.2.14239
47. Donelli MG, Zucchetti M, D'Incalci M. Do anticancer agents reach the tumor target in the human brain? *Cancer Chemother Pharmacol.* (1992) 30:251–60. doi: 10.1007/BF00686291
48. Martínez Bernal G, Mezquita L, Auclin E, Ferrara R, Planchard D, Remon Masip J, et al. 1323PBaseline corticosteroids (CS) could be associated with absence of benefit to immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (NSCLC) patients. *Ann Oncol.* (2017) 28:mdx380.025. doi: 10.1093/annonc/mdx380.025
49. Brastianos PK, Prakadan S, Alvarez-Breckenridge C, Lee EQ, Tolaney SM, Nayak L, et al. Phase II study of pembrolizumab in leptomeningeal carcinomatosis. *J Clin Oncol.* (2018) 36:2007. doi: 10.1200/JCO.2018.36.15_suppl.2007
50. Zakaria R, Platt-Higgins A, Rathi N, Radon M, Das S, Das K, et al. T cell densities in brain metastases are associated with patient survival times and diffusion tensor MRI changes. *Cancer Res. (*2017) 78:610–16. doi: 10.1158/0008-5472.CAN-17-1720
51. Zhou J, Gong Z, Jia Q, Wu Y, Yang ZZ, Zhu B. Programmed death ligand 1 expression and CD8(+) tumor-infiltrating lymphocyte density differences between paired primary and brain metastatic lesions in non-small cell lung cancer. *Biochem Biophys Res Commun.* (2018) 498:751–7. doi: 10.1016/j.bbrc.2018.03.053
52. Lu BY, Gupta R, Ribeiro M, Stewart T, Chiang V, Contessa JN, et al. PD-L1 expression and tumor-infiltrating lymphocytes in lung cancer brain metastases. *J Clin Oncol.* (2018) 36:e24116. doi: 10.1200/JCO.2018.36.15_suppl.e24116
53. Takamori S, Toyokawa G, Okamoto I, Takada K, Kinoshita F, Kozuma Y, et al. Clinical significance of PD-L1 expression in brain metastases from non-small cell lung cancer. *Anticancer Res.* (2018) 38:553–7. doi: 10.21873/anticanres.12653
54. Goldberg SB, Gettinger SN, Mahajan A, Herbst RS, Chiang AC, Lilenbaum R, et al. Durability of brain metastasis response and overall survival in patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab. *J Clin Oncol.* (2018) 36:2009. doi: 10.1200/JCO.2018.36.15_suppl.2009
55. Stein MK, Martin MG, Xiu J, Mittal S, Phuphanich S, Provenzano AP, et al. Mutational complexity increases in lung adenocarcinoma (LADC) with the development of brain metastasis (BM). *J Clin Oncol.* (2018) 36:2067. doi: 10.1200/JCO.2018.36.15_suppl.2067
56. Taylor JW, Molinaro AM, Butowski N, Prados M. Clinical trial endpoints for patients with gliomas. *Neuro-Oncol Pract.* (2017) 4:201–8. doi: 10.1093/nop/npw034
57. Camidge DR, Lee EQ, Lin NU, Margolin K, Ahluwalia MS, Bendszus M, et al. Clinical trial design for systemic agents in patients with brain metastases from solid tumours: a guideline by the Response Assessment in Neuro-Oncology Brain Metastases Working Group. *Lancet Oncol.* (2018) 19:e20–32. doi: 10.1016/S1470-2045(17)30693-9
58. McCoach CE, Berge EM, Lu X, Baron AE, Camidge DR. A brief report of the status of central nervous system metastasis enrollment criteria for advanced non-small cell lung cancer clinical trials: a review of the clinicaltrials.gov trial registry. *J Thorac Oncol.* (2016) 11:407–13. doi: 10.1016/j.jtho.2015.10.024
59. Lin NU, Prowell T, Tan AR, Kozak M, Rosen O, Amiri-Kordestani L, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology–friends of cancer research brain metastases working group. *J Clin Oncol.* (2017) 35:3760–73. doi: 10.1200/JCO.2017.74.0761

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Kamath and Kumthekar. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 28 August 2018
doi: 10.3389/fonc.2018.00338

Low-Intensity MR-Guided Focused Ultrasound Mediated Disruption of the Blood-Brain Barrier for Intracranial Metastatic Diseases

Ying Meng[1,2], *Suganth Suppiah*[1], *Shanan Surendrakumar*[2], *Luca Bigioni*[2] *and Nir Lipsman*[1,2]*

[1] Division of Neurosurgery, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2] Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, Toronto, ON, Canada

OPEN ACCESS

Edited by:
John S. Kuo,
Dell Medical School, The University of Texas at Austin, United States

Reviewed by:
Volodymyr Nahirnyak,
Bukovinian State Medical University, Ukraine
Hao-Li Liu,
Chang Gung University, Taiwan
Benjamin J. Umlauf,
University of Wisconsin-Madison, United States
Seunggu Jude Han,
Oregon Health & Science University, United States

***Correspondence:**
Nir Lipsman
nir.lipsman@utoronto.ca

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 23 June 2018
Accepted: 03 August 2018
Published: 28 August 2018

Citation:
Meng Y, Suppiah S, Surendrakumar S, Bigioni L and Lipsman N (2018) Low-Intensity MR-Guided Focused Ultrasound Mediated Disruption of the Blood-Brain Barrier for Intracranial Metastatic Diseases. Front. Oncol. 8:338. doi: 10.3389/fonc.2018.00338

Low-intensity MR-guided focused ultrasound in combination with intravenously injected microbubbles is a promising platform for drug delivery to the central nervous system past the blood-brain barrier. The blood-brain barrier is a key bottleneck for cancer therapeutics via limited inter- and intracellular transport. Further, drugs that cross the blood-brain barrier when delivered in a spatially nonspecific way, result in adverse effects on normal brain tissue, or at high concentrations, result in increasing risks to peripheral organs. As such, various anti-cancer drugs that have been developed or to be developed in the future would benefit from a noninvasive, temporary, and repeatable method of targeted opening of the blood-brain barrier to treat metastatic brain diseases. MR-guided focused ultrasound is a potential solution to these design requirements. The safety, feasibility and preliminary efficacy of MRgFUS aided delivery have been demonstrated in various animal models. In this review, we discuss this preclinical evidence, mechanisms of focused ultrasound mediated blood-brain barrier opening, and translational efforts to neuro-oncology patients.

Keywords: focused ultrasound (MRgFUS), blood brain barrier (BBB) disruption, neuro-oncology–surgical, intracranial metastatic disease, drug deliver-system

INTRODUCTION

Intracranial metastatic disease (IMD) is the most common type of brain tumors (1, 2) with over 20% of all oncology patients expected to have a metastatic brain lesion, and an annual incidence of 170,000 in the United States alone (1, 3–6). The rates of IMD are on the rise, which may be partially explained by improved imaging modalities facilitating earlier detection and prolonged survival of cancer patients due to advances in oncological care (7). Primary lung, breast and melanoma cancers are the most likely to metastasize to the brain, accounting for 67–80% of all brain metastases (3).

Surgery and radiation therapy are the cornerstones for management of IMD, with most intracranial metastases considered chemo-resistant (8, 9). The median survival period of untreated patients runs from the order of weeks to a few months, and can be prolonged to 4–6 months with the use of whole brain radiation therapy (WBRT) (10). For patients with a single brain metastasis <3 cm in size, surgical resection or stereotactic radiosurgery (SRS) have shown survival benefit (11–14). The evidence and indications for surgical resection in patients with multiple brain metastases are much less established. Radiosurgery is favored for treatment of multiple lesions and,

historically, patients with more than 4 lesions were treated with WBRT (15). However, SRS has become a viable option in this setting, as WBRT is associated with greater neurocognitive adverse effects (e.g., immediate memory, delayed memory, attention, and executive functions), and without significant added benefit in overall survival (16–21).

Chemotherapies that effectively treat the primary cancer and extracranial metastases remain largely ineffective for treatment of IMD (22). The function of the blood-brain barrier (BBB) and efflux transporters play a major role in suppressing the effectiveness of chemotherapies in the brain. The BBB excludes many chemotherapeutic agents from access to the brain, and the drugs that are able to penetrate may do so in insufficient concentrations. Another potential explanation for the ineffectiveness of chemotherapies in the brain is that IMD arises from chemoresistant clones (23). The primary cancer is often treated with chemotherapeutic agents, and thus only the chemoresistant clones metastasize to the brain. However, patients with IMD and are naive to chemotherapeutic agents continue to demonstrate decreased intracranial response rates compared to extracranial response rates, suggesting that chemoresistant clones alone do not explain this phenomena (23, 24). The BBB is, also, thought to confer an immune privileged microenvironment in the central nervous system, preventing access of surveilling immune cells to the tumor cells (25).

The BBB is a highly selective semi-permeable membrane formed by tight junctions between endothelial cells that primarily separates the circulating blood from the central nervous system (CNS). In addition to endothelial cells, the BBB is augmented by pericytes, astrocyte projections (also known as glia limitans), and neurons to provide biochemical support (26). The BBB is largely permeable to lipophilic compounds smaller than ∼400 Da. The BBB is essential in protecting the CNS from circulating pathogens. At the same time, it is a key impediment for cancer therapeutics to effectively treat IMD. For example, doxorubicin, a common chemotherapeutic, is ∼540 Da in size, albumin is 66.5 kDa in size, and most targeted or immunotherapies are of even larger size, such as trastuzumab at 148 kDa. These agents would have difficulty traversing a normal BBB. In addition, the penetration of therapeutics into the parenchyma is limited by the presence of p-glycoprotein 1 (P-gp) bound to the surface of endothelial cells. P-gp is responsible for efflux of chemotherapeutic agents, and is particularly abundant in cancerous tissue (27, 28). Thus, the BBB substantially limits the bioavailability of chemotherapies in treating IMD.

There is a pressing need for improved therapeutic delivery or effective circumvention of the BBB to improve the management of IMD with therapies that have been effective against the primary lesion. Existing methods to circumvent the BBB include convection enhanced therapy with intracranial injections or modification of the drug such as with nanoparticles to help penetrate the BBB. Convection enhanced delivery, however, requires implantation of intracranial catheter and results still in limited diffusion of drug from the catheter tip (29). Current nanoparticles and therapeutic modifications may also result in peripheral toxicity, such as unwanted accumulation in other end organs (30). The BBB permeability is also known to be increased by radiation therapy. In such a case it improves effectiveness of concurrent chemotherapy (31, 32). However, this approach is limited by the unpredictable temporal characteristics of radiation-induced BBB disruption and a radiation-induced injury to the surrounding normal brain tissue such as gliosis, necrosis, or demyelination (31). Furthermore, drugs that are delivered across the BBB in a spatially nonspecific manner can increase the risk to normal brain tissue.

Accordingly, a non-invasive, temporally, and spatially controlled BBB opening that is repeatable could significantly improve the management of IMD. Low-intensity MR-guided focused ultrasound (MRgFUS), in combination with intravenously injected microbubbles, fulfill these design requirements. In this review, we discuss the preclinical evidence of the circumvention of the BBB with low-intensity MRgFUS. Recent translational efforts and potential applications, along with critical areas for improvement.

FOCUSED ULTRASOUND

Transcranial MRgFUS is an emerging image-guided, surgical modality that enables accurate steering of ultrasound energy into discrete targets within the brain. This technology utilizes a phased array of transducers to exert either thermal or mechanical effects on target tissue depending on the acoustic parameters, with higher intensity and frequency settings used for thermal effects. Currently, high-intensity MRgFUS operating at 650 kHz is approved by US Food and Drug Administration (FDA) for thalamotomy, an option for patients with essential tremor. At these parameters, ultrasound sonications rapidly result in temperature rise above 56°C, and well-circumscribed coagulative necrosis in the targeted region (33). In addition, sonications at the sub-lesional temperatures can result in transient neurological effects, to ensure accurate target selection.

Historically, Patrick et al. first found BBB disruption in the periphery of high-intensity focused ultrasound (FUS) lesions (34), with subsequent studies demonstrating BBB opening induced by low intensity protocols without damage to surrounding neuronal structures (35–37). Currently, clinical studies are conducted using a MRgFUS device operating at 220 kHz. MRgFUS opens the BBB primarily through two mechanisms: (1) disruption of the tight junction and (2) induced transcytosis. Cavitation, a biological effect of ultrasound, occurs through oscillation of gas bubbles formed within vessels after exposure to ultrasound energy, resulting into disruption of the tight junctions between endothelial cells, which has been shown via immunoelectron microscopy. This disruption is temporary and is restored after ∼4 h (38). It permits the paracellular passage of molecules (38). There is also the evidence that the physical stress on the vessels leads to cellular changes that increase paracellular and transcellular transport of molecules across the BBB (38, 39), along with increased caveolins, an integral membrane proteins involved in receptor-independent endocytosis, and decreased P-gp visualized after FUS (38, 40, 41).

To further augment the cavitation process, exogenous microbubbles can be introduced into the blood system by

intravenous administration ahead of sonication. The addition of exogenous microbubbles has been found to reduce the energy required to initiate cavitation by 100-fold, and increase the permeability lasting ~6–8 h. Sonications are typically initiated within half a minute of injection to allow sufficient circulation of the microbubbles (42). Consequently, ultrasound sonication can be made safer with a minimal injury to the surrounding tissue. The most commonly studied molecules are gadolinium-based contrast agents, which makes it easy to confirm the successful BBB opening using MR imaging due to the gadolinium now crossing the BBB and to assess the size of treated region (36, 43, 44) (**Figure 1**). Serial gadolinium scans showcased full closures of the BBB in 90% of cases at the 6-h mark post treatment, while the remaining rats displayed considerable decrease in the enhancement of the BBB opening and complete resolution at the 24-h mark post procedure (46).

Although overly high sonication powers can result in inertial cavitation and capillary damage, BBB opening is inducible at lower settings, at which results have been shown to be reproducible in large animal models (e.g., nonhuman primates) without any significant adverse events (47, 48). Successful weekly whole-hemisphere BBB openings for 4 weeks in elderly beagles was demonstrated using MRgFUS (49). This group, according to neuroimaging and histology analysis, reported no significant or enduring damage to any brain tissue targeted by MRgFUS. This discovery is significant evidence to support the safety of FUS administered treatments for brain metastases, as clinical utilization commonly requires several BBB openings for treatment. These MRgFUS parameters and study findings indicate its application-based significance that is capable of being translated to future clinical studies.

MRgFUS holds numerous benefits over other methods of drug delivery system. Paired with MRI guidance, FUS is capable of millimeter spatial accuracy of targeted regions within the brain, including the brain stem region (50). This precision allows targeted delivery of cytotoxic drugs only to abnormal tissue or specific areas in the tumor, which advanced imaging techniques can further help identify (51). Additionally, MRgFUS permits uniform delivery, in contrast to other intracranial treatments, such as convection-enhanced delivery. Lastly, the parameters of BBB opening can be adjusted by modulating ultrasound parameters to further customize treatment.

CHEMOTHERAPIES

Traditional chemotherapies for extracranial cancers have not generally been effective for brain tumors. A possible exception is temozolomide which is used for treatment of glioblastoma due to its limited side effect profile and central nervous system bioavailability. This is demonstrated by a group that used FUS-aided BBB disruption in a rat model to enhance temozolomide delivery to treat glioblastoma (52). In addition, another study displayed similar effects to improve drug delivery of temozolomide to treat a glioma in a mice model (53). Doxorubicin, an inhibitor of topoisomerase II, blocks DNA and RNA synthesis, and is effective in treatment of a broad range of tumors (54). Doxorubicin cannot cross the BBB to any appreciable extent and, as a result, demonstrates little effectiveness in treating CNS malignancies when administered systemically (55, 56). Further dose escalation is limited by cardiac toxicity. In preclinical studies, doxorubicin is effective against glial tumors *in vitro* and in animal models, and when administered intratumorally to patients via an Ommaya reservoir (57). While doxorubicin with FUS has predominantly been investigated in an animal model of malignant glioma, the results of significantly improved tissue concentration (e.g., 21 times in one study) and antineoplastic effects show promise for IMDs (58, 59). Further supportive survival data from the same group has recently been published and demonstrated a significant survival advantage in a rat glioblastoma model when using doxorubicin in combination with ultrasound-mediated BBB disruption. Delivery of doxorubicin to a brainstem was also recently shown to be feasible and safe for animals after histological and behavioral tests (50). Other chemotherapies investigated in conjunction

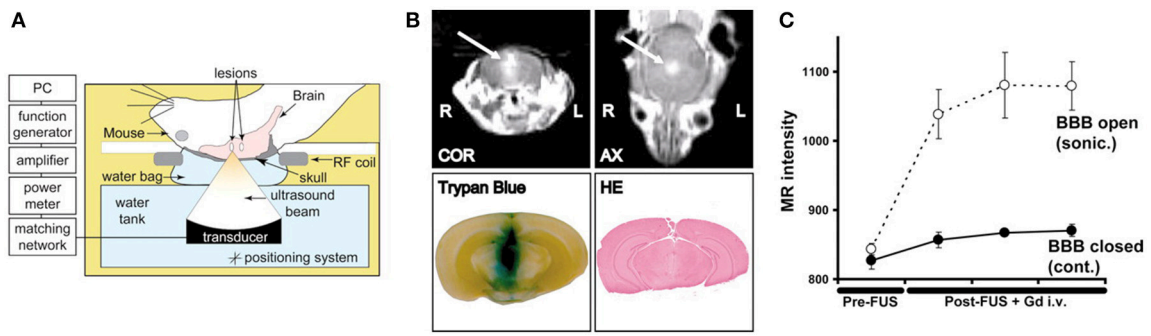


FIGURE 1 | Demonstration of MR-guided focused ultrasound mediated blood-brain barrier opening in an animal model of intracranial breast metastasis. **(A)** Diagram of experimental set-up shows administration of ultrasound through the intact skull. **(B)** Representative example of focused ultrasound induced blood-brain barrier opening, as demonstrated by increased gadolinium (arrow) and tryphan blue extravasation. Hematoxylin and eosin stained tissue demonstrated preservation of gross tissue integrity and lack of macroscopic hemorrhage. COR, coronal scan; AX, axial scan; HE, hematoxylin and eosin. **(C)** The change in MR image intensity over time in the sonicated vs. non-sonicated regions. Bars represent standard deviation. Reprinted with permission from Kinoshita et al. PNAS 2006 (45), copyright 2006 National Academy of Sciences.

with MRgFUS BBB opening in small (e.g., rat, rabbit) to large (e.g., nonhuman primates) animals include paclitaxel (60), methotrexate (61, 62), doxorubicin (50, 63, 64), cisplatin (65), bevacizumab (66), and carmustine (67) (**Table 1**).

TARGETED THERAPY

Technological advances and greater understanding of molecular biology have made an increased number of targeted therapies a standard of care for cancer patients. Targeted therapies address specific molecular aspects of cancer biology. Human epidermal growth factor 180 receptor 2 (HER2) is addressed when trastuzumab has been administered, and specific inhibition of mutated BRAF, a proto-oncogene is addressed when vemurafenib is administered. Trastuzumab has been found to be highly effective in controlling local and distal breast cancer lesions (45, 69, 70). BRAF inhibitors such as vemurafenib and dabrafenib are effective in extending the progression free survival of BRAF-mutant melanomas which are present in 50% of melanomas and is associated with significantly higher incidence of CNS involvement (71). The development of targeted therapies has been the cornerstone of precision medicine. Many targeted therapies have been approved for clinical use and may be used in combination to inhibit simultaneously multiple pathways which are important for tumor growth.

Trastuzumab is ∼150 kDa in size, which makes it too large to pass through the BBB. In a rodent study, the tissue concentration of trastuzumab after systemic administration was undetectable (< 780 ng/g), whereas after sonication, the concentration increased to 3257 ng/g of tissue (45). This significant increase in trastuzumab concentration in tissue using FUS was further corroborated in a xenograft rodent model (70). Notably repeated dose of FUS greatly increased the concentration yield (70). In another HER2/neu-positive human breast cancer xenograft model, 6 weekly treatment of FUS plus trastuzumab led to what appeared to be complete resolution on MRI (69). The group where trastuzumab was administered along with FUS had significantly slower growth rate than controls. In another study of HER2-positive cells derived from cancer patients, 6 weekly treatments of trastuzumab and pertuzumab along with FUS led to a response in 4 out of 10 rats compared to none in the antibodies only group (72). These studies have paved the way for clinical translation in MRgFUS mediated BBB opening for patients with IMD.

TABLE 1 | Representative change in therapeutic's concentration in tumor in sonicated relative to non-sonicated regions after systemic administration of therapeutic.

Therapeutic	References	Approximate relative change
Doxorubicin	Treat et al. (58)	21 x
Liposomal paclitaxel	Shen et al. (60)	2 x
Cisplatin-loaded BPN	Timbie et al. (65)	30 x
Liposomal methotrexate	Wang et al. (62)	9 x
Trastuzumab	Kinoshita et al. (45)	2 x
Interleukin-12	Chen et al. (68)	2 x
Bevacizumab	Liu et al. (66)	Range 5.7 x-56.7 x
Carmustine	Liu et al. (67)	2 x

BPN, brain penetrating nanoparticles.

IMMUNOTHERAPY

Immunotherapy directly helps or stimulates the patient's immune system to treat cancer. For instance, checkpoint inhibitors support T-cell surface receptor recognition and activation against cancer cells. Other types of immunotherapy include immunization, cytokines (e.g., interleukins), and cell therapy (e.g., CAR T-cell therapy) (68, 73, 74). Ipilimumab, a monoclonal antibody to T-lymphocyte-associated protein 4 (CTLA-4), another checkpoint in the immune system, is used in the treatment of unresectable and metastatic melanomas. These drugs have shown some preliminary efficacy in phase II studies in patients with IMD from lung cancer and melanoma, with ∼20–30% 1-year survival rate. Several animal studies have established the safety and feasibility of delivering both cell-based (e.g., NK-92 cells) and cytokine (e.g., IL-12) in rodent models, with preliminary evidence of efficacy. Specifically, a repeated, biweekly treatment paradigm of NK-92 cells administered by MRgFUS BBB opening, resulted in long-term survival in 50% of animals injected with HER2 amplified tumors.

CARRIERS

Once the delivered drug therapies have penetrated the BBB they are confronted by the extracellular space (ECS) of the brain, which extensively dictates and restricts the movement of the therapeutics in the brain. The ECS consist of mixed hydrophobic and electrostatically charged areas that comprises about 15–20% of the entire brain volume. Initially to penetrate the targeted brain parenchyma and deliver the appropriate drugs, brain-penetrating nanoparticles (BPNs) coated densely with poly(ethylene-co-glycol) (PEG) was explored, which has superior stability in the bloodstream (75). However, PEGylated BPNs results in reduced cell absorption or exchange through the BBB. Although it may potentially be used in combination with MRgFUS BBB opening.

A research group had recently explored this concept in rodents and reported the evidence of the successful first time use of MRgFUS and microbubbles with a biodegradable BPN platform which could penetrate and effectively transport therapeutic agents within the targeted areas of the CNS (76). It was also discovered that higher pressures of FUS modify the dispersal of the BPNs in the CNS, permitting more coverage and improving further the penetration within the targeted regions of the brain. Another study in rodent model of the breast IMD demonstrated substantial growth inhibition after one treatment of intravenously delivered PEGylated liposomal doxorubicin nanoparticles

with FUS-induced hyperthermia without BBB opening (76). We may conclude that, the addition of carriers to existing therapeutic agents delivered through a BBB opening may provide some additional advantages for drug distribution in the parenchyma.

Other Applications of Focused Ultrasound

FUS creates a transient, targeted opening of the BBB that allows bidirectional communication between the systemic circulation and the central nervous system milieu. Shedding cancerous cells or cells' components is another possible result of the application of FUS. Blood-based analysis of circulating tumor cells, DNA, micro RNA, and extracellular vesicles hold the promise of improving upon histopathologic examinations or obviating the need for tissue biopsy (77). However, the challenges in these approaches lie in their uniform lack of sensitivity, with tumor DNA representing <1% of total circulating DNA, and significant advance technology required for analysis (78). A proof of concept study in rat glioma model using fluorescent markers shows promise, but it remains to be demonstrated how this may be clinically applied (79). Finally, non-thermal ablation of tumor tissue using low-intensity focused ultrasound is being developed as a viable alternative to high-intensity focused ultrasound, where energy required to ablate large tissue volumes limits its safety and feasibility (80–82).

CLINICAL APPLICATIONS AND LIMITATIONS OF FUS IN IMD

The feasibility and preliminary efficacy of focused ultrasound-assisted targeted delivery of cancer therapeutics have been demonstrated in various animal models. Clinically, there is now preliminary data regarding safety and feasibility of focused ultrasound BBB opening with co-administration of carboplatin in patients with gliomas (83). Doxorubicin and temozolomide delivery studies using MRgFUS are underway for neuro-oncology patients (NCT02343991, NCT03322813). For other neurological disorders, a pilot study of MRgFUS BBB opening in patients with Alzheimer's disease (84) was recently reported to have demonstrated safety and feasibility. Finally, a study for patients with amyotrophic lateral sclerosis is also underway (NCT03321487).

Notwithstanding the potential advantages to MRgFUS for therapeutic delivery for patients with IMD, there are important limitations. They include the need for pre-procedural removal of hair, the substantial operating time of the procedure, and the use of a stereotactic frame, which may represent limitations for widespread utilization and tolerability. In addition, clinical experience with MRgFUS induced BBB opening is preliminary with side effect profile (e.g., microhemorrhage, ischemia) in human subjects still to be characterized. Furthermore, essential technical data is urgently needed regarding the feasibility in tissues of various interstitial pressures, tissue, and vascular properties, and pathologies, such as in the case of peritumor edema. Future modifications of this technique may include controller based on acoustic feedback will likely significantly shorten operating time while preserving the uniformity of BBB opening (85). Finally, the specific treatment protocol and dosing remain to be elucidated for each anti-neoplastic agent. MRgFUS will most likely be most beneficial for patients with IMD and relatively well controlled systemic disease burden. MRgFUS is a drug delivery platform, where in the age of precision medicine and with the increasing availability of advanced imaging, it opens up exciting opportunities for induction of the precisely targeted delivery of drugs to the brain. Although still in the early investigational stages, this minimally invasive technology for targeted BBB opening has the potential to revolutionize the care of neuro-oncology patients.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. Epidemiology of metastatic brain tumors. *Neurosurg Clin N Am.* (2011) 22:1–6. doi: 10.1016/j.nec.2010.08.007
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin.* (2008) 58:71–96. doi: 10.3322/CA.2007.0010
3. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep.* (2012) 14:48–54. doi: 10.1007/s11912-011-0203-y
4. Nathoo N, Chahlavi A, Barnett GH, Toms SA. Pathobiology of brain metastases. *J Clin Pathol.* (2005) 58:237–42. doi: 10.1136/jcp.2003.013623
5. Davis FG, Dolecek TA, McCarthy BJ, Villano JL. Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data. *Neuro-Oncol.* (2012) 14:1171–7. doi: 10.1093/neuonc/nos152
6. Fidler IJ. The biology of brain metastasis: challenges for therapy. *Cancer J.* (2015) 21:284. doi: 10.1097/PPO.0000000000000126
7. Rostami R, Mittal S, Rostami P, Tavassoli F, Jabbari B. Brain metastasis in breast cancer: a comprehensive literature review. *J Neurooncol.* (2016) 127:407–14. doi: 10.1007/s11060-016-2075-3
8. Peak S, Abrey LE. Chemotherapy and the treatment of brain metastases. *Hematol Oncol Clin North Am.* (2006) 20:1287–95. doi: 10.1016/j.hoc.2006.09.007
9. Fabi A, Felici A, Metro G, Mirri A, Bria E, Telera S, et al. Brain metastases from solid tumors: disease outcome according to type of treatment and therapeutic resources of the treating center. *J Exp Clin Cancer Res.* (2011) 30:10. doi: 10.1186/1756-9966-30-10
10. Mehta MP, Rodrigus P, Terhaard CHJ, Rao A, Suh J, Roa W, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol Off J Am Soc Clin Oncol.* (2003) 21:2529–36. doi: 10.1200/JCO.2003.12.122
11. Selek U, Chang EL, Hassenbusch SJ, Shiu AS, Lang FF, Allen P, et al. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. *Int J Radiat Oncol Biol Phys.* (2004) 59:1097–106. doi: 10.1016/j.ijrobp.2003.12.037
12. Hasegawa T, Kondziolka D, Flickinger JC, Germanwala A, Lunsford LD. Brain metastases treated with radiosurgery alone: an alternative to whole brain radiotherapy? *Neurosurgery* (2003) 52:1318–26, discussion:1326. doi: 10.1227/01.NEU.0000117126.32806.A5a

13. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol.* (1993) 33:583–90. doi: 10.1002/ana.410330605
14. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* (1990) 322:494–500. doi: 10.1056/NEJM199002223220802
15. Ferguson SD, Wagner KM, Prabhu SS, McAleer MF, McCutcheon IE, Sawaya R. Neurosurgical management of brain metastases. *Clin Exp Metastasis* (2017) 34:377–89. doi: 10.1007/s10585-017-9860-z
16. Serizawa T, Iuchi T, Ono J, Saeki N, Osato K, Odaki M, et al. Gamma knife treatment for multiple metastatic brain tumors compared with whole-brain radiation therapy. *J Neurosurg.* (2000) 93(Suppl. 3):32–6. doi: 10.3171/jns.2000.93.supplement
17. Park S-H, Hwang S-K, Kang D-H, Lee S-H, Park J, Hwang J-H, et al. Gamma knife radiosurgery for multiple brain metastases from lung cancer. *J Clin Neurosci Off J Neurosurg Soc Aust.* (2009) 16:626–9. doi: 10.1016/j.jocn.2008.08.003
18. Raldow AC, Chiang VL, Knisely JP, Yu JB. Survival and intracranial control of patients with 5 or more brain metastases treated with gamma knife stereotactic radiosurgery. *Am J Clin Oncol.* (2013) 36:486–90. doi: 10.1097/COC.0b013e31825494ef
19. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* (2009) 10:1037–44. doi: 10.1016/S1470-2045(09)70263-3
20. Onodera S, Aoyama H, Tha KK, Hashimoto N, Toyomaki A, Terae S, Shirato H. The value of 4-month neurocognitive function as an endpoint in brain metastases trials. *J Neurooncol.* (2014) 120:311–9. doi: 10.1007/s11060-014-1550-y
21. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi: 10.1001/jama.2016.9839
22. Mehta MP, Paleologos NA, Mikkelsen T, Robinson PD, Ammirati M, Andrews DW, et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* (2010) 96:71–83. doi: 10.1007/s11060-009-0062-7
23. Chamberlain MC, Baik CS, Gadi VK, Bhatia S, Chow LQM. Systemic therapy of brain metastases: non-small cell lung cancer, breast cancer, and melanoma. *Neuro-Oncol.* (2017) 19:i1–24. doi: 10.1093/neuonc/now197
24. Seute T, Leffers P, Wilmink JT, ten Velde GPM, Twijnstra A. Response of asymptomatic brain metastases from small-cell lung cancer to systemic first-line chemotherapy. *J Clin Oncol.* (2006) 24:2079–83. doi: 10.1200/JCO.2005.03.2946
25. Ameratunga M, Coleman N, Welsh L, Saran F, Lopez J. CNS cancer immunity cycle and strategies to target this for glioblastoma. *Oncotarget* (2018) 9:22802–16. doi: 10.18632/oncotarget.24896
26. Pardridge WM. CSF, blood-brain barrier, and brain drug delivery. *Expert Opin Drug Deliv.* (2016) 13:963–75. doi: 10.1517/17425247.2016.1171315
27. Adkins CE, Mittapalli RK, Manda VK, Nounou MI, Mohammad AS, Terrell TB, et al. P-glycoprotein mediated efflux limits substrate and drug uptake in a preclinical brain metastases of breast cancer model. *Front Pharmacol.* (2013) 4:136. doi: 10.3389/fphar.2013.00136
28. Cordon-Cardo C, O'Brien JP, Boccia J, Casals D, Bertino JR, Melamed MR. Expression of the multidrug resistance gene product (P-glycoprotein) in human normal and tumor tissues. *J Histochem Cytochem.* (1990) 38:1277–87. doi: 10.1177/38.9.1974900
29. Salvatore MF, Ai Y, Fischer B, Zhang AM, Grondin RC, Zhang Z, et al. Point source concentration of GDNF may explain failure of phase II clinical trial. *Exp Neurol.* (2006) 202:497–505. doi: 10.1016/j.expneurol.2006.07.015
30. Appelboom G, Detappe A, LoPresti M, Kunjachan S, Mitrasinovic S, Goldman S, et al. Stereotactic modulation of blood-brain barrier permeability to enhance drug delivery. *Neuro-Oncol.* (2016) 18:1601–9. doi: 10.1093/neuonc/now137
31. Rubin P, Gash DM, Hansen JT, Nelson DF, Williams JP. Disruption of the blood-brain barrier as the primary effect of CNS irradiation. *Radiother Oncol.* (1994) 31:51–60. doi: 10.1016/0167-8140(94)90413-8
32. Lim WH, Choi SH, Yoo R-E, Kang KM, Yun TJ, Kim J-H, et al. Does radiation therapy increase gadolinium accumulation in the brain?: Quantitative analysis of T1 shortening using R1 relaxometry in glioblastoma multiforme patients. *PLoS ONE* (2018) 13:e0192838. doi: 10.1371/journal.pone.0192838
33. Meng Y, Suppiah S, Mithani K, Solomon B, Schwartz ML, Lipsman N. Current and emerging brain applications of MR-guided focused ultrasound. *J Ther Ultrasound* (2017) 5:26. doi: 10.1186/s40349-017-0105-z
34. Patrick JT, Nolting MN, Goss SA, Dines KA, Clendenon JL, Rea MA, et al. Ultrasound and the blood-brain barrier. *Adv Exp Med Biol.* (1990) 267:369–81. doi: 10.1007/978-1-4684-5766-7_36
35. Vykhodtseva NI, Hynynen K, Damianou C. Histologic effects of high intensity pulsed ultrasound exposure with subharmonic emission in rabbit brain *in vivo*. *Ultrasound Med Biol.* (1995) 21:969–79. doi: 10.1016/0301-5629(95)00038-S
36. Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. *Radiology* (2001) 220:640–6. doi: 10.1148/radiol.2202001804
37. Mesiwala AH, Farrell L, Wenzel HJ, Silbergeld DL, Crum LA, Winn HR, et al. High-intensity focused ultrasound selectively disrupts the blood-brain barrier *in vivo*. *Ultrasound Med Biol.* (2002) 28:389–400. doi: 10.1016/S0301-5629(01)00521-X
38. Sheikov N, McDannold N, Sharma S, Hynynen K. Effect of focused ultrasound applied with an ultrasound contrast agent on the tight junctional integrity of the brain microvascular endothelium. *Ultrasound Med Biol.* (2008) 34:1093–104. doi: 10.1016/j.ultrasmedbio.2007.12.015
39. Sheikov N, McDannold N, Vykhodtseva N, Jolesz F, Hynynen K. Cellular mechanisms of the blood-brain barrier opening induced by ultrasound in presence of microbubbles. *Ultrasound Med Biol.* (2004) 30:979–89. doi: 10.1016/j.ultrasmedbio.2004.04.010
40. Lionetti V, Fittipaldi A, Agostini S, Giacca M, Recchia FA, Picano E. Enhanced caveolae-mediated endocytosis by diagnostic ultrasound *in vitro*. *Ultrasound Med Biol.* (2009) 35:136–43. doi: 10.1016/j.ultrasmedbio.2008.07.011
41. Deng J, Huang Q, Wang F, Liu Y, Wang Z, Wang Z, et al. The role of Caveolin-1 in blood–brain barrier disruption induced by focused ultrasound combined with microbubbles. *J Mol Neurosci.* (2012) 46:677–87. doi: 10.1007/s12031-011-9629-9
42. Huang Y, Alkins R, Schwartz ML, Hynynen K. Opening the blood-brain barrier with MR imaging-guided focused ultrasound: preclinical testing on a trans-human skull porcine model. *Radiology* (2017) 282:123–30. doi: 10.1148/radiol.2016152154
43. Arvanitis CD, Livingstone MS, Vykhodtseva N, McDannold N. Controlled ultrasound-induced blood-brain barrier disruption using passive acoustic emissions monitoring. *PLoS ONE* (2012) 7:e45783. doi: 10.1371/journal.pone.0045783
44. Chu P-C, Chai W-Y, Hsieh H-Y, Wang J-J, Wey S-P, Huang C-Y, et al. Pharmacodynamic analysis of magnetic resonance imaging-monitored focused ultrasound-induced blood-brain barrier opening for drug delivery to brain tumors. *BioMed Res Int.* (2013) 2013:627496. doi: 10.1155/2013/627496
45. Kinoshita M, McDannold N, Jolesz FA, Hynynen K. Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood–brain barrier disruption. *Proc Natl Acad Sci USA.* (2006) 103:11719–23. doi: 10.1073/pnas.0604318103
46. O'Reilly MA, Hough O, Hynynen K. Blood-brain barrier closure time after controlled ultrasound-induced opening is independent of opening volume. *J Ultrasound Med Off J Am Inst Ultrasound Med.* (2017) 36:475–83. doi: 10.7863/ultra.16.02005
47. Downs ME, Buch A, Sierra C, Karakatsani ME, Chen S, Konofagou EE, et al. Long-term safety of repeated blood-brain barrier opening via focused ultrasound with microbubbles in non-human primates performing a cognitive task. *PLoS ONE* (2015) 10:e0125911. doi: 10.1371/journal.pone.0125911
48. McDannold N, Arvanitis CD, Vykhodtseva N, Livingstone MS. Temporary disruption of the blood-brain barrier by use of ultrasound and microbubbles: safety and efficacy evaluation in rhesus macaques. *Cancer Res.* (2012) 72:3652–63. doi: 10.1158/0008-5472.CAN-12-0128

49. O'Reilly MA, Jones RM, Barrett E, Schwab A, Head E, Hynynen K. Investigation of the safety of focused ultrasound-induced blood-brain barrier opening in a natural canine model of aging. *Theranostics* (2017) 7:3573–84. doi: 10.7150/thno.20621
50. Alli S, Figueiredo CA, Golbourn B, Sabha N, Wu MY, Bondoc A, et al. Brainstem blood brain barrier disruption using focused ultrasound: a demonstration of feasibility and enhanced doxorubicin delivery. *J Control Release Off J Control Release Soc.* (2018) 281:29–41. doi: 10.1016/j.jconrel.2018.05.005
51. Valentini MC, Mellai M, Annovazzi L, Melcarne A, Denysenko T, Cassoni P, et al. Comparison among conventional and advanced MRI, 18F-FDG PET/CT, phenotype and genotype in glioblastoma. *Oncotarget* (2017) 8:91636–53. doi: 10.18632/oncotarget.21482
52. Wei K-C, Chu P-C, Wang H-YJ, Huang C-Y, Chen P-Y, Tsai H-C, et al. Focused ultrasound-induced blood-brain barrier opening to enhance temozolomide delivery for glioblastoma treatment: a preclinical study. *PLoS ONE* (2013) 8:e58995. doi: 10.1371/journal.pone.0058995
53. Liu H-L, Huang C-Y, Chen J-Y, Wang H-YJ, Chen P-Y, Wei K-C. Pharmacodynamic and therapeutic investigation of focused ultrasound-induced blood-brain barrier opening for enhanced temozolomide delivery in glioma treatment. *PLoS ONE* (2014) 9:e114311. doi: 10.1371/journal.pone.0114311
54. Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE, et al. Doxorubicin pathways: pharmacodynamics and adverse effects. *Pharmacogenet Genomics* (2011) 21:440–6. doi: 10.1097/FPC.0b013e32833ffb56
55. Bao L, Haque A, Jackson K, Hazari S, Moroz K, Jetly R, et al. Increased expression of P-glycoprotein is associated with doxorubicin chemoresistance in the metastatic 4T1 breast cancer model. *Am J Pathol.* (2011) 178:838–52. doi: 10.1016/j.ajpath.2010.10.029
56. Lamsam L, Johnson E, Connolly ID, Wintermark M, Hayden Gephart M. A review of potential applications of MR-guided focused ultrasound for targeting brain tumor therapy. *Neurosurg Focus* (2018) 44:E10. doi: 10.3171/2017.11.FOCUS17620
57. Voulgaris S, Partheni M, Karamouzis M, Dimopoulos P, Papadakis N, Kalofonos HP. Intratumoral doxorubicin in patients with malignant brain gliomas. *Am J Clin Oncol.* (2002) 25:60–4. doi: 10.1097/00000421-200202000-00013
58. Treat LH, McDannold N, Vykhodtseva N, Zhang Y, Tam K, Hynynen K. Targeted delivery of doxorubicin to the rat brain at therapeutic levels using MRI-guided focused ultrasound. *Int J Cancer* (2007) 121:901–7. doi: 10.1002/ijc.22732
59. Treat LH, McDannold N, Zhang Y, Vykhodtseva N, Hynynen K. Improved anti-tumor effect of liposomal doxorubicin after targeted blood-brain barrier disruption by MRI-guided focused ultrasound in rat glioma. *Ultrasound Med Biol.* (2012) 38:1716–25. doi: 10.1016/j.ultrasmedbio.2012.04.015
60. Shen Y, Pi Z, Yan F, Yeh C-K, Zeng X, Diao X, et al. Enhanced delivery of paclitaxel liposomes using focused ultrasound with microbubbles for treating nude mice bearing intracranial glioblastoma xenografts. *Int J Nanomed.* (2017) 12:5613–29. doi: 10.2147/IJN.S136401
61. Mei J, Cheng Y, Song Y, Yang Y, Wang F, Liu Y, et al. Experimental study on targeted methotrexate delivery to the rabbit brain via magnetic resonance imaging-guided focused ultrasound. *J Ultrasound Med.* (2009) 28:871–80. doi: 10.7863/jum.2009.28.7.871
62. Wang X, Liu P, Yang W, Li L, Li P, Liu Z, et al. Microbubbles coupled to methotrexate-loaded liposomes for ultrasound-mediated delivery of methotrexate across the blood-brain barrier. *Int J Nanomed.* (2014) 9:4899–909. doi: 10.2147/IJN.S69845
63. Lin Y-L, Wu M-T, Yang F-Y. Pharmacokinetics of doxorubicin in glioblastoma multiforme following ultrasound-Induced blood-brain barrier disruption as determined by microdialysis. *J Pharm Biomed Anal.* (2018) 149:482–7. doi: 10.1016/j.jpba.2017.11.047
64. Park J, Aryal M, Vykhodtseva N, Zhang Y-Z, McDannold N. Evaluation of permeability, doxorubicin delivery, and drug retention in a rat brain tumor model after ultrasound-induced blood-tumor barrier disruption. *J Control Release Off J Control Release Soc.* (2017) 250:77–85. doi: 10.1016/j.jconrel.2016.10.011
65. Timbie KF, Afzal U, Date A, Zhang C, Song J, Wilson Miller G, et al. MR image-guided delivery of cisplatin-loaded brain-penetrating nanoparticles to invasive glioma with focused ultrasound. *J Control Release Off J Control Release Soc.* (2017) 263:120–31. doi: 10.1016/j.jconrel.2017.03.017
66. Liu H-L, Hsu P-H, Lin C-Y, Huang C-W, Chai W-Y, Chu P-C, et al. Focused ultrasound enhances central nervous system delivery of bevacizumab for malignant glioma treatment. *Radiology* (2016) 281:99–108. doi: 10.1148/radiol.2016152444
67. Liu H-L, Hua M-Y, Chen P-Y, Chu P-C, Pan C-H, Yang H-W, et al. Blood-brain barrier disruption with focused ultrasound enhances delivery of chemotherapeutic drugs for glioblastoma treatment. *Radiology* (2010) 255:415–25. doi: 10.1148/radiol.10090699
68. Chen P-Y, Hsieh H-Y, Huang C-Y, Lin C-Y, Wei K-C, Liu H-L. Focused ultrasound-induced blood–brain barrier opening to enhance interleukin-12 delivery for brain tumor immunotherapy: a preclinical feasibility study. *J Transl Med.* (2015) 13:93. doi: 10.1186/s12967-015-0451-y
69. Park E-J, Zhang Y-Z, Vykhodtseva N, McDannold N. Ultrasound-mediated blood-brain/blood-tumor barrier disruption improves outcomes with trastuzumab in a breast cancer brain metastasis model. *J Control Release* (2012) 163:277–84. doi: 10.1016/j.jconrel.2012.09.007
70. Centelles MN, Wright M, Gedroyc W, Thanou M. Focused ultrasound induced hyperthermia accelerates and increases the uptake of anti-HER-2 antibodies in a xenograft model. *Pharmacol Res* (2016) 114:144–51. doi: 10.1016/j.phrs.2016.10.017
71. Abate-Daga D, Ramello MC, Smalley I, Forsyth PA, Smalley KSM. The biology and therapeutic management of melanoma brain metastases. *Biochem Pharmacol.* (2018) 153:35–45. doi: 10.1016/j.bcp.2017.12.019
72. Kobus T, Zervantonakis IK, Zhang Y, McDannold NJ. Growth inhibition in a brain metastasis model by antibody delivery using focused ultrasound-mediated blood-brain barrier disruption. *J Control Release* (2016) 238:281–8. doi: 10.1016/j.jconrel.2016.08.001
73. Berghoff AS, Venur VA, Preusser M, Ahluwalia MS. Immune checkpoint inhibitors in brain metastases: from biology to treatment. *Am Soc Clin Oncol Educ Book* (2016) 36:e116–22. doi: 10.14694/EDBK_100005
74. Alkins R, Burgess A, Ganguly M, Francia G, Kerbel R, Wels WS, Hynynen K. Focused ultrasound delivers targeted immune cells to metastatic brain tumors. *Cancer Res.* (2013) 73:1892–9. doi: 10.1158/0008-5472.CAN-12-2609
75. Nance E, Timbie K, Miller GW, Song J, Louttit C, Klibanov AL, et al. Noninvasive delivery of stealth, brain-penetrating nanoparticles across the blood-brain barrier using MRI-guided focused ultrasound. *J Control Release* (2014) 189:123–32. doi: 10.1016/j.jconrel.2014.06.031
76. Wu S-K, Chiang C-F, Hsu Y-H, Lin T-H, Liou H-C, Fu W-M, et al. Short-time focused ultrasound hyperthermia enhances liposomal doxorubicin delivery and antitumor efficacy for brain metastasis of breast cancer. *Int J Nanomed.* (2014) 9:4485–94. doi: 10.2147/IJN.S68347
77. Zachariah MA, Oliveira-Costa JP, Carter BS, Stott SL, Nahed BV. Blood-based biomarkers for the diagnosis and monitoring of gliomas. *Neuro-Oncol.* (2018) 20:1155–61. doi: 10.1093/neuonc/noy074
78. Ossandon MR, Agrawal L, Bernhard EJ, Conley BA, Dey SM, Divi RL, et al. Circulating tumor DNA assays in clinical cancer research. *J Natl Cancer Inst.* doi: 10.1093/jnci/djy105. [Epub ahead of print].
79. Zhu L, Cheng G, Ye D, Nazeri A, Yue Y, Liu W, et al. Focused ultrasound-enabled brain tumor liquid biopsy. *Sci Rep.* (2018) 8:6553. doi: 10.1038/s41598-018-24516-7
80. McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging- guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery* (2010) 66:323–32, discussion:332. doi: 10.1227/01.NEU.0000360379.95800.2F
81. Quadri SA, Waqas M, Khan I, Khan MA, Suriya SS, Farooqui M, Fiani B. High-intensity focused ultrasound: past, present, and future in neurosurgery. *Neurosurg Focus* (2018) 44:E16. doi: 10.3171/2017.11.FOCUS17610
82. McDannold N, Zhang Y-Z, Power C, Jolesz F, Vykhodtseva N. Nonthermal ablation with microbubble-enhanced focused ultrasound close to the optic

tract without affecting nerve function: Laboratory investigation. *J Neurosurg.* (2013) 119:1208. doi: 10.3171/2013.8.JNS122387

83. Carpentier A, Canney M, Vignot A, Reina V, Beccaria K, Horodyckid C, et al. Clinical trial of blood-brain barrier disruption by pulsed ultrasound. *Sci Transl Med.* (2016) 8:343re2. doi: 10.1126/scitranslmed.aaf6086
84. Lipsman N, Meng Y, Bethune AJ, Huang Y, Lam B, Masellis M, et al. Blood–brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. *Nat Commun.* (2018) 9:2336. doi: 10.1038/s41467-018-04529-6
85. Kamimura HA, Flament J, Valette J, Cafarelli A, Aron Badin R, et al. Feedback control of microbubble cavitation for ultrasound-mediated blood-brain barrier disruption in non-human primates under magnetic resonance guidance. *J Cereb Blood Flow Metab.* (2018). doi: 10.1177/0271678X17753514. [Epub ahead of print].

Conflict of Interest Statement: NL has served as paid consultants on expert steering committees for the Focused Ultrasound Foundation.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Meng, Suppiah, Surendrakumar, Bigioni and Lipsman. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 28 November 2018
doi: 10.3389/fonc.2018.00558

Contemporary Surgical Management of Deep-Seated Metastatic Brain Tumors Using Minimally Invasive Approaches

*Lina Marenco-Hillembrand, Keila Alvarado-Estrada and Kaisorn L. Chaichana**

Department of Neurosurgery, Mayo Clinic, Jacksonville, FL, United States

A subset of metastatic brain tumors occurs in deep-seated locations. Accessing and resecting these lesions can be associated with significant morbidity because it involves large craniotomies, extensive white matter dissection, prolonged retraction, and risk of inadvertent tissue injury. As a result, only palliative treatment options are typically offered for these lesions including observation, needle biopsies, and/or radiation therapy. With the development of new surgical tools and techniques, minimally invasive techniques have allowed for the treatment of these lesions previously associated with significant morbidity. These minimally invasive techniques include laser interstitial thermal therapy and channel-based resections.

Keywords: brain metastases, laser, LITT, minimally invasive, tubular retractors

OPEN ACCESS

Edited by:
Sunit Das,
St. Michael's Hospital, Canada

Reviewed by:
Brad E. Zacharia,
Penn State Milton S. Hershey Medical Center, United States
Zachary Naren Litvack,
Swedish Medical Center, United States

****Correspondence:***
Kaisorn L. Chaichana
chaichana.kaisorn@mayo.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *16 August 2018*
Accepted: *09 November 2018*
Published: *28 November 2018*

Citation:
Marenco-Hillembrand L, Alvarado-Estrada K and Chaichana KL (2018) Contemporary Surgical Management of Deep-Seated Metastatic Brain Tumors Using Minimally Invasive Approaches. Front. Oncol. 8:558. doi: 10.3389/fonc.2018.00558

INTRODUCTION

Metastatic brain cancer (MBC) is the most common type of brain tumor in adults (1, 2). It is estimated that there will be more than 200,000 new cases each year in the United States alone (1, 2). The most common sources are the lung, breast, kidney, colon, and skin, where approximately 20–30% of patients with these primary cancers will develop a brain metastasis (1, 2). The treatment of primary cancers has improved; however, the ability to prevent MBC and prolong survival for patients who develop MBC has not (1, 2). The treatment options for patients with MBC include some combination of surgical resection, radiation therapy, and/or chemotherapy (1, 2). The goals of these therapies are to primarily prevent local tumor progression (3–6).

The majority of brain metastases occur at the gray-white junction (7, 8) These metastatic cancers are thought to breach the blood-brain barrier in areas of slow flow, which is typically in watershed regions and the ends of small perforating vessels (7, 8). As a result, most of these lesions are cortically based or in close juxtaposition to the cerebral cortex and/or cerebellar hemisphere (7, 8). When surgery is pursued for these typical lesions, the distance of brain parenchyma that must be traversed is relatively short (3–6). However, some metastases can occur in deep-seated, eloquent regions such as the thalamus, basal ganglia, and deep cerebellar nuclei (7, 8). When these deep-seated lesions occur, patients are typically symptomatic from mass effect and eloquent nuclei and white matter tract (WMT) involvement, and surgical treatment is more challenging because of the morbidity associated with accessing and resecting these lesions (9–12). In this review, we will discuss the use of contemporary surgical management of these lesions using minimally invasive approaches, namely laser interstitial thermal therapy (LITT) and channel-based resections (9–12).

SURGICAL INDICATIONS FOR BRAIN METASTASES

Patients who present with MBC can undergo various treatments including surgical resection, radiation therapy, and/or chemotherapy (1, 2, 13–17). The choice of therapies is typically predicated by an estimation of a patient's prognosis, where generally more localized (surgery, stereotactic radiosurgery) and aggressive therapies are offered to patient's with better prognoses (3, 18). In order to predict survival, there are several prognostic scoring systems that have been developed including the Recursive Partitioning Analysis (RPA), Score Index For Radiosurgery (SIR), Basic Score for Brain Metastases (BSBM), Rotterdam system (ROTTERDAM), Golden Grading System (GGS), Rades classification (RADES), and Graded Prognostic Assessment (GPA) classification systems.

In general, surgery for brain metastases are indicated for patients who possess good prognoses and accessible lesions with low potential associated morbidity (3–6). However, surgery is often pursued for large lesions (<3 cm), lesions with significant mass effect, and/or symptomatic lesions, even for palliative purposes (3–6). Lesions that are large and deep-seated, however, represent a surgical dilemma (10–12). For metastatic lesions that are small with minimal edema and mass effect, radiation therapy, namely stereotactic radiosurgery, is preferred (10–12). This is because historically accessing and resecting lesions has been associated with significant surgical morbidity (10–12). This morbidity is associated with accessing, visualizing, resecting, and achieving hemostasis (10–12). Deep-seated tumors have typically required large craniotomies and large dural openings to accommodate bladed retractor systems (10–12). These bladed retractor systems require a large footprint in order to be effective (10–12). In addition, the superficial cortex and overlying white matter have to be retracted to provide exposure of the underlying lesion (10–12). These retractor blades can induce significant damage by retractor-applied sheer forces, especially when multiple retractors are used, ischemia from contact pressure under the retractor blades, and potential tissue injury when left unprotected between the blades during repeated accessing the lesion with surgical instruments (10–12). As a result, offering surgery for deep-seated brain tumors has been limited. However, some deep-seated metastatic brain tumors are symptomatic and can have significant mass effect including hydrocephalus (10–12). In these cases, surgery is warranted because of the delayed effect of non-surgical options such as radiation therapy. There are, however, no clinical trials that specifically address surgery for deep-seated metastatic tumor, as they represent a smaller subset of metastatic tumors. The use of minimally invasive technique including LITT and channel-based retraction, however, have allowed for a potentially safer surgical options for these lesions (10–12).

LASER INTERSTITIAL THERAPY (LITT)

LITT is a minimally invasive technique that was initially used in the 1980s, and used to treat difficult to access lesions including malignant gliomas, radiation-resistant metastases, epileptic foci, and radiation necrosis (19–22). This involves making a burrhole over the intended trajectory, insertion of a skull bolt, and placement of a probe affixed with an optical fiber into the lesion through the bolt under stereotactic navigation (19–22). The optical fiber is used to heat the surrounding tissue causing coagulative necrosis, with the goal of sharp drop off in temperature effects to minimize damaging the surrounding peri-lesional tissue (19–22). The thermal effects of the interstitial laser can be measured with MR thermometry and cooled with carbon dioxide or saline (19–22). The lesion itself can enlarge from edema associated with cell swelling and necrosis from the thermal effects up to 1.5–5 times its original size and be enlarged for up to 40 days until there is resorption of the necrotic center (19–22). The resorption can take over 6 months (19–22). The advantages of LITT as opposed to standard craniotomies include smaller incision, less blood loss, less parenchymal manipulation, shorter hospital stay, and ability to perform adjuvant therapies sooner because of the lack of need for incisional healing with smaller incisions (19–22). The disadvantages include difficulty with treating large lesions, lesions with significant edema, and highly vascular lesions (19–22). The biggest concern is the transient volume increases in the immediate postoperative period that can lead to increased mass effect and neurological deficits, necessitating pharmacotherapy or surgical therapy (19–22).

There are two principle companies that provide LITT are Monteris™ (Neuroblate® and Medtronic™ (Visualase®) (19–22). The Neuroblate® system uses a CO_2 gas-cooled laser probe and has both side-firing and diffuse-tip laser applications (19–22). Similar, but different, the Visualase® system uses a diode laser generator and has a cooling catheter than contains a 1-cm-long fiberoptic applicator with a light-diffusing tip, where the catheter is connected to a peristaltic roller pump that circulates sterile saline to cool the probe tip and surrounding tissue (19–22). It also provides thermal delivery in an ellipsoid-cylindrical pattern (19–22). Both systems are connected to an MRI unit and computer workstation that allows robotic manipulation and real-time thermographic data, where predetermined peri-lesional thresholds can be pre-assigned (19–22).

The majority of studies on the use of LITT for metastatic brain tumors are small institutional series with <10 patients (19–22). Carpentier et al. reported the use of LITT in 7 patients with 15 metastatic lung and breast adenocarcinomas with lesion sizes ranging from 1 to 3 cm in diameter of unknown locations (19). All patients were discharged within 24 h, had no new deficits, and the median survival was 19.8 months (19). Hawasli and colleagues reported their institutional series of 17 LITT cases, where five had brain metastases and prior therapy including surgery and radiation therapy (21). The lesions ranged from 5.2 to 9.9 cm^3 and involved the WMT of the frontal, parietal, frontoparietal lobes and the insula (21). Two of the five patients had transient deficits including aphasia and hemiparesis (21). The median progression free and overall survival of these patients was 5.8 months (21). Eichberg et al. documented the use of LITT in four patients with recurrent cerebellar metastases, where the sizes ranged from 1.1 to 7.2 cm^3 and the postop volume ranged from

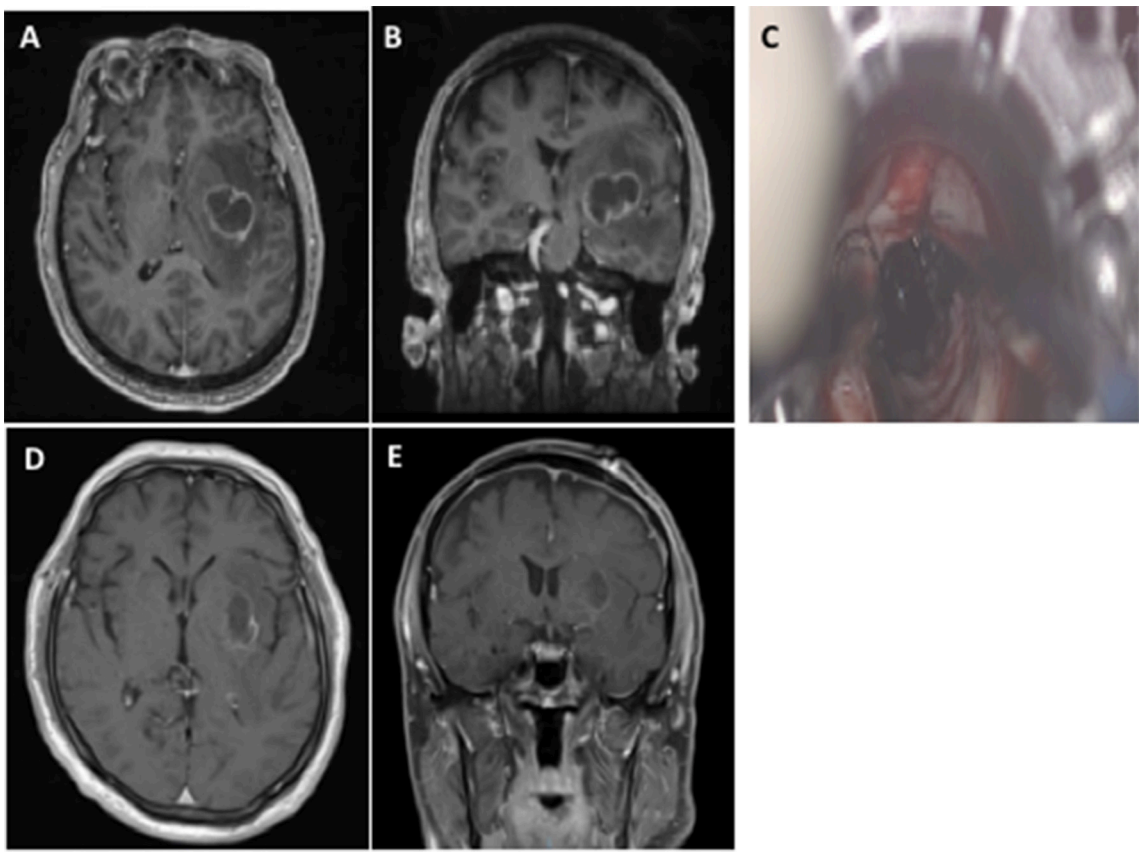


FIGURE 1 | The use of channel-based retractor of a left basal ganglia non-small cell lung cancer brain metastasis. Preoperative axial **(A)** and coronal **(B)** MRI with contrast demonstrating a deep-seated left basal ganglia brain metastasis. The use of a channel-based retractor to access the lesion **(C)**. Postoperative axial **(D)** and coronal **(E)** MRI with contrast demonstrating gross total resection and no superficial cortical and white matter changes.

0.5 to 7.6 cm^3, where lesion size increased by an average of 487% on postoperative day 1 and the time it took to shrink below initial volume was 295 days (20).

LITT is typically reserved for metastatic brain tumors that have failed radiation therapy (19–22). It provides a minimally invasive way to target both deep-seated and superficial metastatic lesions that have not responded to radiation therapy (19–22). Its use, however, is tempered by the transient increase in tumor volume that can persist for months (19–22). Therefore, the use of LITT is not typically used as the initial treatment of metastatic brain tumors and for lesions with significant mass effect and/or in close proximity to eloquent structures (19–22). Interestingly, in a recent study by Sloan and colleagues, they reported the use of LITT followed by transportal resection in 10 patients with brain tumors (1 MBC) (23). This use may expand the use of LITT therapy for MBC (23).

CHANNEL-BASED RESECTIONS

Tubular or channel-based retractors provide a means to access deep-seated lesions (9–12). The typical approach to deep-seated lesions involved large craniotomies, sizeable cortisectomies, extensive white matter dissections, and use of multiple bladed retractors to create a large enough corridor to provide visualization, access, and resection (24). This approach is associated with potential injury as a result of large exposures, prolonged retraction, and inadvertent tissue injury during access and resection (24). Channel-based retractors circumvent a lot of these limitations (9–12). In this approach, a circular channel is placed into the brain typically through a sulcus (9–12). This channel displaces rather than severs the WMT, provides a protected corridor for accessing and resecting the lesion, and creates equivalent, circumferential radial forces to minimize collateral injury (9–12). These retractors were first used in the 1980s, and their use has expanded to intracranial hemorrhages, gliomas, vascular lesions, and MBC, among others (9–12).

The most widely used channel-based retractors are peel-away catheters, oval-shaped retractors, and circular retractors (9–12). The peel-away catheters (Medtronic^{TM}) are similar to central line peel-away catheters whose diameters are typically measured in French (9–12). These catheters are typically limited to ventricular surgery as they require working channel endoscopes for visualization and resection and a clear fluid medium (9–12). The advantages are they are the least invasive,

can be used through burrholes, and the least disruptive for white matter tracts (9–12). The disadvantages are they are limited to clear fluid media, obviate bimanual techniques because require working-channel endoscopes, and hemostasis can be challenging (9–12). Oval-shaped retractors (Viewsite Brain Access System®, Vycor™) comes in a variety of lengths (30–70 mm) and widths (12–28 mm). The oval-shaped retractors can be applied to both deep-seated ventricular and parenchymal lesions (9–12). The advantages of oval-shaped retractors are they allow bimanual techniques and have greater widths for maneuverability, but the disadvantages are that they have inequivalent radial retraction because of the oval shape, can severe white matter tracts at wider widths, and are difficult to use through sulci because of the blunt tip (9–12). Circular shaped retractors (Brainpath®, Nico™) also come in a variety of lengths (50–95 mm) and widths (11.5–13.5 mm) and can also be applied to both deep-seated ventricular and parenchymal lesions (9–12). The advantages of circular retractors are they provide equivalent radial retraction, can be applied to the sulcal space, and allow bimanual techniques (9–12). The primary disadvantage of the circular retractors is they are narrower than the oval-shaped retractors with less maneuverability (9–12).

There are an expanding number of case series that have evaluated the use of these channel-based retractors for MBC **(Figure 1)** (9–12). Bakhsheshian et al. performed a multi-center study with 25 patients with metastatic brain tumors, where gross total resection was achieved in 80%, 1 (4%) had a new neurological deficit, and 19 (76%) had improved neurological symtpoms (9). These lesions were frontal ($n = 5$), parietal ($n = 8$), cerebellar ($n = 8$), occipital ($n = 3$), and splenium ($n = 1$) (9). Day reported a single surgeon experience with this approach in 20 metastatic brain tumors, where gross total resection was achieved in 19 (95%), postoperative hemorrhage in 1 (5%) that did not require evacuation, new deficit in 0, and perioperative mortality in 1 (5%) due to pulmonary complications (25). More recently, we reported our experience in 50 consecutive channel-based resection cases, where 14 had brain metastases (10). All of these patients underwent gross total resection and no patients had worsening neurological deficits (10).

Channel-based retractors allow a protected corridor for accessing and resecting deep-seated brain metastases that are at least below the deepest sulcal boundary (10–12). It provides a minimally invasive ability to access these lesions that previously were not resected, offered only needle biopsies, or offered surgery with significant risks (10–12). The tubular retractors, however, are narrow (approximately 13.5 mm in diameter), making it difficult to maneuver, establish hemostasis, and visualize feeding vessels (10–12). This narrow corridor also obviates certain instruments that are wide in caliber including an ultrasonic aspirator (10–12). The use of exoscopes helps minimize the obstruction due to the small corridor, and provides ergonomic surgical positioning for retractors placed at obtuse angles (10–12).

CONCLUSIONS

A subset of metastatic brain tumors occurs in deep-seated locations. Accessing and resecting these lesions can be associated with significant morbidity because it involves large craniotomies, extensive white matter dissection, prolonged retraction, and risk of inadvertent tissue injury. As a result, only palliative treatment options are typically offered for these lesions including observation, needle biopsies, and/or radiation therapy. With the development of new surgical tools and techniques, minimally invasive techniques have allowed for the treatment of these lesions previously associated with significant morbidity. These techniques include laser interstitial thermal therapy and channel-based resections.

AUTHOR CONTRIBUTIONS

LM-H played a role in manuscript preparation, manuscript revision, figure edits, and critical evaluation. KA-E played a role in manuscript preparation, manuscript revision, literature search. KC played a role in manuscript preparation, final approval, supervision.

REFERENCES

1. Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. *Oncologist* (2007) 12:884–98. doi: 10.1634/theoncologist.12-7-884
2. Ewend MG, Morris DE, Carey LA, Ladha AM, Brem S. Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. *J Natl Compr Cancer Netw.* (2008) 6:505–13. doi: 10.6004/jnccn.2008.0038
3. Chaichana KL, Acharya S, Flores M, Wijesekera O, Rigamonti D, Weingart JD, et al. Identifying better surgical candidates among RPA class 2 patients who underwent surgery for intracranial metastases. *World Neurosurg.* (2013) 82:e267–75. doi: 10.1016/j.wneu.2013.08.031
4. Chaichana KL, Gadkaree S, Rao K, Link T, Rigamonti D, Purtell M, et al. Patients undergoing surgery of intracranial metastases have different outcomes based on their primary pathology. *Neurol Res.* (2013) 35:1059–69. doi: 10.1179/1743132813Y.0000000253
5. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. *World Neurosurg.* (2010) 73:22–41. doi: 10.1016/j.surneu.2009.05.027
6. Chaichana KL, Rao K, Gadkaree S, Dangelmajer S, Bettegowda C, Rigamonti D, et al. Factors associated with survival and recurrence for patients undergoing surgery of cerebellar metastases. *Neurol Res.* (2014) 36:13–25. doi: 10.1179/1743132813Y.0000000260
7. Carbonell WS, Ansorge O, Sibson N, Muschel R. The vascular basement membrane as "soil" in brain metastasis. *PLoS ONE* (2009) 4:e5857. doi: 10.1371/journal.pone.0005857
8. Pompili A, Carapella CM, Cattani F, Fabi A, Giannarelli D, Giovannetti M, et al. Metastases to the cerebellum. Results and prognostic factors in a consecutive series of 44 operated patients. *J Neuro Oncol.* (2008) 88:331–7. doi: 10.1007/s11060-008-9572-y
9. Bakhsheshian J, Strickland BA, Jackson C, Chaichana KL, Young R, Pradilla G, et al. Multicenter investigation of channel-based subcortical trans-sulcal exoscopic resection of metastatic brain tumors: a retrospective case series. *Oper Neurosurg.* (2018) doi: 10.1093/ons/opy079

10. Gassie K, Wijesekera O, Chaichana KL. Minimally invasive tubular retractor-assisted biopsy and resection of subcortical intra-axial gliomas and other neoplasms. *J Neurosurg Sci*. (2018). doi: 10.23736/S0390-5616.18.04466-1. [Epub ahead of print].
11. Iyer R, Chaichana KL. Minimally invasive resection of deep-seated high-grade gliomas using tubular retractors and exoscopic visualization. *J Neurol Surg A Cent Eur Neurosurg*. (2018) 79:330–6. doi: 10.1055/s-0038-1641738
12. Jackson C, Gallia GL, Chaichana KL. Minimally invasive biopsies of deep-seated brain lesions using tubular retractors under exoscopic visualization. *J Neurol Surg A Cent Eur Neurosurg*. (2017) 78:588–94. doi: 10.1055/s-0037-1602698
13. Venur VA, Ahluwalia MS. Prognostic scores for brain metastasis patients: use in clinical practice and trial design. *Chin Clin Oncol*. (2015) 4:18. doi: 10.3978/j.issn.2304-3865.2015.06.01
14. Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. *J Neurosurg*. (1993) 79:210–6. doi: 10.3171/jns.1993.79.2.0210
15. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*. (1990) 322:494–500. doi: 10.1056/NEJM199002223220802
16. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* (1998) 280:1485–9. doi: 10.1001/jama.280.17.1485
17. Wronski M, Arbit E, McCormick B. Surgical treatment of 70 patients with brain metastases from breast carcinoma. *Cancer* (1997) 80:1746–54. doi: 10.1002/(SICI)1097-0142(19971101)80:9<1746::AID-CNCR8>3.0.CO;2-C
18. Barnholtz-Sloan JS, Yu C, Sloan AE, Vengoechea J, Wang M, Dignam JJ, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol*. (2012) 14:910–8. doi: 10.1093/neuonc/nos087
19. Carpentier A, McNichols RJ, Stafford RJ, Guichard JP, Reizine D, Delaloge S, et al. Laser thermal therapy: real-time MRI-guided and computer-controlled procedures for metastatic brain tumors. *Lasers Surg Med*. (2011) 43:943–50. doi: 10.1002/lsm.21138
20. Eichberg DG, VanDenBerg R, Komotar RJ, Ivan ME. Quantitative volumetric analysis following magnetic resonance-guided laser interstitial thermal ablation of cerebellar metastases. *World Neurosurg*. (2018) 110:e755–65. doi: 10.1016/j.wneu.2017.11.098
21. Hawasli AH, Bagade S, Shimony JS, Miller-Thomas M, Leuthardt EC. Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: single-institution series. *Neurosurgery* (2013) 73:1007–17. doi: 10.1227/NEU.0000000000000144
22. Missios S, Bekelis K, Barnett GH. Renaissance of laser interstitial thermal ablation. *Neurosurg Focus* (2015) 38:E13. doi: 10.3171/2014.12.FOCUS14762
23. Wright J, Chugh J, Wright CH, Alonso F, Hdeib A, Gittleman H, et al. Laser interstitial thermal therapy followed by minimal-access transsulcal resection for the treatment of large and difficult to access brain tumors. *Neurosurg Focus* (2016) 41:E14. doi: 10.3171/2016.8.FOCUS16233
24. Chaichana KL, Vivas-Buitrago T, Jackson C, Ehresman J, Olivi A, Bettegowda C, et al. The radiographic effects of surgical approach and use of retractors on the brain after anterior cranial fossa meningioma resection. *World Neurosurg*. (2018) 112:e505–13. doi: 10.1016/j.wneu.2018.01.069
25. Day JD. Transsulcal parafascicular surgery using brain path(R) for subcortical lesions. *Neurosurgery* (2017) 64:151–6. doi: 10.1093/neuros/nyx324

Conflict of Interest Statement: KC is a course lecturer for NICO Corporation.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Marenco-Hillembrand, Alvarado-Estrada and Chaichana. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

ORIGINAL RESEARCH
published: 31 October 2018
doi: 10.3389/fonc.2018.00499

Management of Intracranial Metastatic Disease With Laser Interstitial Thermal Therapy

*Afshin Salehi, Ashwin A. Kamath, Eric C. Leuthardt and Albert H. Kim**

Department of Neurological Surgery, Washington University School of Medicine, St. Louis, MO, United States

Treatment approaches for metastatic brain tumors continue to evolve, with increasing recent emphasis on focal therapies whenever possible. MRI-guided Laser Interstitial Thermal Therapy (LITT) is a minimally invasive surgical option that has broadened the capability of the neurosurgeon in treating difficult-to-treat intracranial lesions. This technology uses image-guided delivery of laser to the target lesion to generate heat and thereby ablate pathological tissue and has expanded the neurosurgical armamentarium for surgical treatment of brain metastases. In this study, we describe the indications for LITT in the management of intracranial metastatic disease and report our institutional experience with LITT.

Keywords: laser interstitial thermal therapy (LITT), intracranial metastatic disease, brain metastases, overall survival (OS), thermal-damage-threshold (TDT)

OPEN ACCESS

Edited by:
Arjun Sahgal,
University of Toronto, Canada

Reviewed by:
Brian Toyota,
University of British Columbia, Canada
Dimitris G. Placantonakis,
NYU School of Medicine,
United States

****Correspondence:***
Albert H. Kim
alberthkim@wustl.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *13 August 2018*
Accepted: *15 October 2018*
Published: *31 October 2018*

Citation:
Salehi A, Kamath AA, Leuthardt EC and Kim AH (2018) Management of Intracranial Metastatic Disease With Laser Interstitial Thermal Therapy. Front. Oncol. 8:499. doi: 10.3389/fonc.2018.00499

INTRODUCTION

Current strategies for the treatment of metastatic brain tumors include surgical resection or ablation, stereotactic radiosurgery, fractionated radiation therapy, whole brain radiation therapy (WBRT), and in select cases, targeted medical therapy. Recent data indicate that rather than performing WBRT, more focused and localized treatment of brain metastases using stereotactic radiosurgery (SRS) might be favorable due to cognitive issues associated with WBRT (1). These results also raise the general concept that focal therapies, where possible, should be preferentially considered for brain metastases. Additionally, due to advances in the treatment of systemic disease in this diverse group of patients, practitioners are encountering a growing number of patients with brain metastases (2) and particularly patients who fail first- and even second-line therapy for their intracranial disease.

Laser Interstitial Thermal Therapy (LITT) is a novel, highly focused, minimally invasive technique that can be used to treat a variety of solid organ tumors (3, 4). The development of complementary technologies, such as intraoperative magnetic resonance imaging (MRI) and real-time MRI thermometry has enabled LITT to enter the fields of neurosurgery and neuro-oncology (5–10). In recent years, LITT has been applied to intracranial lesions, including metastatic disease to the brain, and has yielded safe and satisfactory treatment results with significantly less morbidity (11) and shorter hospital stays than traditional open craniotomy (7).

Proper patient selection for the appropriate indication is of utmost importance in ensuring the success of LITT. Firstly, patients must be willing to undergo a surgical procedure and be able to medically tolerate general anesthesia. In general, the indications fall into the broad categories of LITT as salvage therapy or frontline therapy. LITT has been used as frontline therapy in surgically inaccessible tumors (12), such as thalamic or basal ganglia gliomas.

Other work has shown LITT to be effective in managing metastases that fail radiosurgery (13, 14) and in radiation necrosis (13, 15). Conveniently, in cases where the diagnosis is uncertain or would affect subsequent management, LITT can be performed subsequent to stereotactic needle biopsy during the same procedure.

LITT uses an MRI-compatible optical probe that transmits laser light through to a sapphire tip. The probe is inserted into the brain lesion with stereotactic guidance via a stab incision and a simple burr hole. The laser then produces a controlled thermal injury to the surrounding tissues. MRI thermometry allows for continuous monitoring of ablation in a controlled manner. The LITT procedure is generally well-tolerated with low operative morbidity (11), which is especially desirable in the treatment of cancer patients who often have significant systemic burden of disease. LITT therefore offers a promising treatment modality for intracranial metastatic disease. In this study, we describe our institutional series of 25 cases of intracranial metastatic disease treated with LITT.

METHODS

Study Design

Institutional review board approval was obtained for this research (IRB #201609152). A retrospective database of LITT patients was maintained and included demographics, age, sex, indications for LITT, lesion type/location/dimensions as well as operative data, such as procedure time, number of trajectories, post-operative complications and readmission rates. Patients were followed post-operatively. Overall survival was determined as time from surgery until the time of death or time of last visit. PFS was measured from the time of surgery until evidence of tumor progression, time of last stable image, or death.

Operative Technique

The LITT procedure at our institution has previously been described in detail (8, 9). In brief, for all procedures, Stealth navigation (Medtronic Inc., Minneapolis, MN, USA) was used for stereotaxy and trajectory planning. A registration error of less than 2 mm was used as a general goal. Intra-operative MRI (IMRIS Inc, Minnetonka, MN, USA) was used for real-time MRI thermography of the treatment zone. The planned trajectory was evaluated in detail to avoid sulci and blood vessels, and generally, the trajectory chosen was in line with the long axis of the lesion. All patients received advanced MR imaging, including diffusion tensor imaging (DTI), which was used to avoid passage through eloquent white matter. Earlier in our series, we tended to use the Monteris Axiis® frame while later in the series, most cases were performed with the Monteris® Mini-Bolt as the laser base, which has a low profile (142 mm with driver). Yet in instances with superficial lesions, the Axiis® frame is advantageous due to less artifact superficially in the cranium compared to the Mini-Bolt. Typically, the stereotactic trajectory was aligned using the Vertek® arm (Medtronic Inc). A handheld Stryker drill was used to generate a 4.5 mm burr hole, through which the Monteris® bolt was screwed into the skull. Either diffusion tip or a side-fire tip was inserted stereotactically into the tumor. Next, the intra-operative MRI was brought into the operative theater, and initial imaging obtained to confirm probe placement. The surgeon then delivered laser therapy to the lesion while monitoring real-time thermography via MRI to achieve appropriate heat dose delivery. Post-operatively, patients were treated with Keppra and a 2-to-3-weeks taper of dexamethasone.

Statistics

The Kaplan-Meier (KM) product limit method was used to estimate empirical survival probabilities, including overall survival and progression-free survival. Log-rank test was applied to compare survival between patient groups. KM curves were generated. Progression-free survival was determined as the time from surgery to recurrence, date of last stable scan, or death. Multivariate Cox proportional hazard model was applied to include multiple covariates for survival analysis. Hazard ratio (HR) with 95% confidence interval was calculated from Cox proportional hazard model.

RESULTS

Participants

A total of 25 LITT cases were performed for metastatic brain tumors on 24 patients between September 2010 to April 2016 at Washington University in St. Louis (**Table 1**). There were 15 males and 9 females with an average age of 59 years (range 38–74). Tumor types ranged from primary origin of lung ($n = 16$), melanoma ($n = 3$), followed by breast, colon, ovarian, and unknown primary. The majority of the lesions were frontal ($n = 11$) followed by parietal ($n = 8$) and other locations ($n = 6$) (**Table 1**). The mean follow-up period was 16.05 months (range 0.7–46.73).

Indications and Operative Details

LITT was chosen as the first-line therapy in only two cases for which "difficult to resect" location was the primary indication. For the rest of the cases ($n = 23$), it was chosen as a secondary or salvage therapy. In this latter group, surgeons indicated location as the primary reason for LITT in five of the cases, failure of prior treatments as the primary reason in 13 cases, and old age as well as poor functional status in the remaining 5 cases. Six patients had craniotomy and radiation therapy performed prior to LITT. Four patients had previous craniotomy and SRS/Gamma knife. Six patients had prior SRS and no craniotomies.

The average lesion volume was 7.32 cm^3 (range 1.00–24.59). Treatment areas were monitored via standard thermal dose threshold (TDT) lines, with yellow line signifying the thermal dose equivalent of 43°C for 2 min and the blue line 43°C for 10 min. TDT lines were not available for two of the cases. Of the remaining 23 cases, 12 (53%) and 6 (26%) achieved complete coverage of the contrast-enhancing lesion by the yellow and blue TDT lines, respectively, with average coverage in the overall cohort of 95% and 92% by the yellow and blue TDT lines. Complete coverage of the lesions was limited by ablation area encroaching on eloquent regions, presence of heat sinks, such as ventricles or blood vessels near the ablation area, or prohibitively

TABLE 1 | This table shows the demographic of the overall population.

Sex, *n* (%)	
Male	15 (62)
Female	9 (38)
Total	24
Average age, years	59 (38–74)
Primary tumor type, *n* (%)	
Lung	16 (64)
Melanoma	3 (12)
Breast	2 (8)
Colon	1 (4)
Ovarian	1 (4)
Unknown	2 (8)
Total cases	25
Location, *n* (%)	
Lobar	
Frontal	11 (44)
Parietal	8 (32)
Temporal	1 (4)
Occipital	1 (4)
Insular	1 (4)
Deep	
Thalamic	1 (4)
Basal Ganglia	1 (4)
Cerebellar	1 (4)
Total	25

There were 24 patients who underwent 25 cases.

large size of the lesions. In 5 (21%) cases, two trajectories were used to ablate tumor. Postoperative MRI was performed on postoperative day 1 for evaluation of the extent of ablation and establishment of a baseline.

Time of surgery was comparable to craniotomy with an average of 219 min (range 105–490). Although not statistically significant, there was a downward trend over time in operative time ($R^2 = 0.21$, data not shown). There was no correlation between surgery time and tumor size or location (data not shown).

Complications

There was one (4%) perioperative complication and 4 (16%) later complications leading to unplanned readmissions within 30 days (**Table 2**). The perioperative complication was a seizure that occurred in a patient with a large tumor (10.09 cm^3). He was given a dose of 2 mg Ativan and 200 mg of Vimpat which abated the seizures and was discharged in stable condition to rehab on POD 6 on Keppra and Vimpat. One of the re-admission cases was also potentially due to seizures with presentation of altered mental status on POD 16. After treatment, this patient and family opted for comfort care. Two of the readmissions were due to edema, one of which was secondary to hyponatremia and responded well to correction of the sodium and the other, transient hemiparesis, which resolved with a course of steroids. Analysis of the patients who suffered a complication/readmission showed that cases with complications were associated with tumors with larger volume (mean volume 12.32 $cm^3 \pm 7.4$) compared to those who had no complications (mean volume 5.93 $cm^3 \pm 4.96$) (unpaired t-test, $p = 0.032$).

Outcome Data

Of the 25 metastatic brain tumor cases treated with LITT, tumor volumetric and blue TDT line coverage data were available on 23 patients. Eight of the cases (32%), either had biopsy performed at the time of LITT to confirm the diagnosis of metastasis or did not have prior SRS or RT. Zero patients were lost to follow-up. At the time of analysis, five (21%) patients were still alive, with a mean follow-up of 32.26 months (range 7.20–46.73). Among the 19 expired patients, we can identify systemic disease burden as the cause of death in four patients and CNS disease as cause of death in six patients whereas specific cause of death cannot be determined in the remaining nine patients. The median overall survival (OS) was 13.27 months [95% confidence interval (CI) = 9.83–23.20] (**Figure 1A**). The median progression-free survival (PFS) was 6.30 months (95% CI = 5.3–17.43) (**Figure 1B**). Stratified by location, frontal (8 of 24), parietal (5 of 24) or other (6 of 24), did not make a significant difference on OS ($p = 0.429$) or PFS ($p = 0.364$).

To determine if pre-operative tumor size plays a role in outcome after LITT, pre-procedural tumor volumes were dichotomized with a cut-off at the median volume of 5.62 cm^3. PFS of patients with tumor volumes greater than 5.62 cm^3 was significantly shorter than that of patients with tumors smaller than or equal to 5.62 cm^3 [$p = 0.024$, HR 2.89 (1.12–7.49)] (**Figure 2B**). However, analysis of OS between the same two groups did not show a significant difference [$p = 0.164$, HR 1.89 (0.76–4.69)] (**Figure 2A**). To determine if treatment coverage area based on the blue TDT line has an effect on outcomes, patients were dichotomized into two groups based on a treatment coverage cut-off at the median of 97%. PFS in cases with treatment coverage greater than 97% was significantly longer than those with less than or equal to 97% blue TDT coverage [$p = 0.029$, HR 0.36 (0.14–0.93)] (**Figure 3B**). OS of cases similarly dichotomized based on a 97% coverage area was not significantly different [$p = 0.052$, HR 0.4 (0.16–1.04)] (**Figure 3A**). Although dataset numbers are limited, an exploratory multivariate logistic regression analysis was performed to identify independent predictors of patient survival outcome. Four variants were included in the model—age, sex (M vs. F), percentage of blue TDT line coverage area (>0.97 vs. ≤ 0.97), and tumor volume (>5.62 vs. ≤ 5.62). Multivariate analysis did not show any significant association between any of the tested parameters and PFS or OS.

DISCUSSION

Our retrospective case series demonstrated that the PFS of patients with metastatic brain tumors treated with LITT is improved when greater than 97% of the tumor is treated to the blue TDT line (**Figure 3**). The OS of this group trended to significance ($p = 0.052$). This is consistent with similar

TABLE 2 | Complication table.

Patient	Pathology	Age, years	Sex	Volume, cm^3	Type	POD	Complication	Management
1	L Frontal Melanoma	60	M	10.09	Perioperative	1	Seizures	Antiepileptic
2	R Frontal Melanoma	56	M	8.91	Readmission	4	Confusion	Negative workup. Sent to rehab on day 2
3	R Parietal Breast	59	F	12.8	Readmission	8	Edema, Left-sided hemiparesis	Edema treated with steroid
4	L Parietal Lung	58	F	5.3	Readmission	10	Aphasia, edema, hyponatremia	Fluid restriction, hypertonic saline, rehab on day 3
5	R Parietal Lung	65	M	24.59	Readmission	16	AMS, seizures	Made comfort care*

*One perioperative complication and four readmissions. *Patient 5 came back on post-operative day 16 with altered mental status believed to be secondary to seizures who opted for comfort care and ultimately expired. POD, post operative day; AMS, altered mental status.*

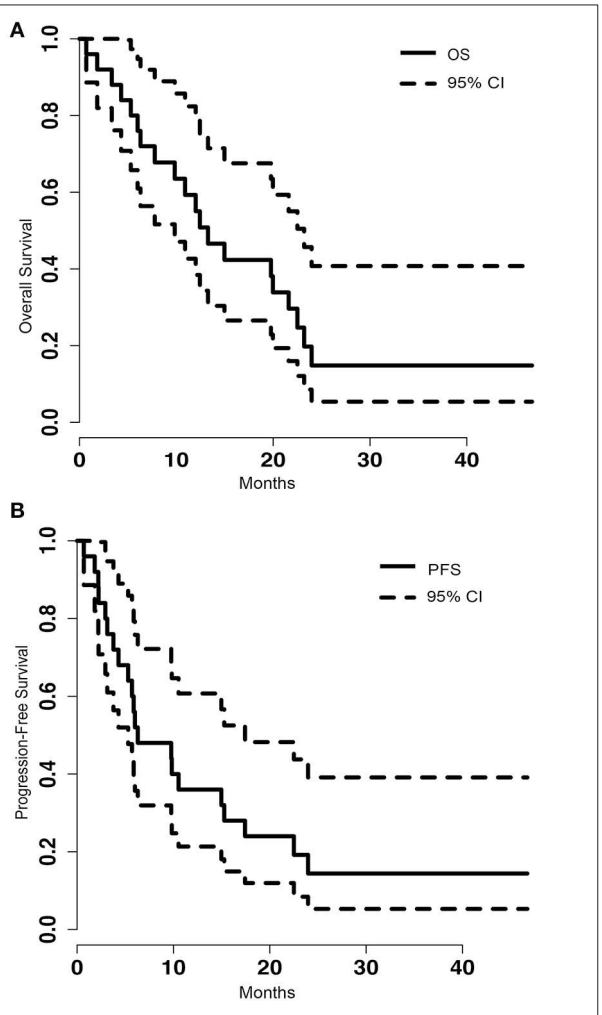


FIGURE 1 | (A) Kaplan-Meier graph of the overall survival (OS) of the population and the 95% confidence interval (CI). The median OS was 13.27 (95% CI = 9.83–23.20). **(B)** Shows the progression free survival (PFS) of the population and the 95% CI. The median PFS was 6.30 (95% CI = 5.3–17.43).

studies describing that extent of surgical resection of metastatic tumors correlates positively with better outcome (16, 17). Lee et al. showed that median survival differs significantly when comparing gross total resection (median survival = 20.4) to subtotal resection (median survival = 15.1) ($p = 0.016$). Our findings suggest that even in cases of irregularly shaped tumors, use of single or multiple trajectories to achieve greater than 97% blue TDT treatment coverage, if safe, may be worth pursuing. A caveat of our study is the possibility that some of the lesions treated may have represented radiation necrosis. In our series, 32% of cases either had biopsy done at the time of LITT to confirm the diagnosis of metastasis or did not have prior SRS or RT, excluding the possibility of radiation necrosis at least in these cases. The lack of biopsy-proven tumor in the remaining cases is noted to be a limitation of our study. Nevertheless, recent studies have shown that LITT is also an effective treatment option for radiation necrosis in medically refractory cases (13, 15). The overall survival of 13.27 months seen in our group was comparable to that seen in other studies with surgery and radiation for recurrent metastatic cases. As another point of comparison, Koiso et al. retrospectively reviewed 859 patients with metastatic disease who underwent a second SRS and reported a median survival of 7.4 months (18).

Furthermore, we showed that larger pre-treatment tumor size is associated with worse outcome, with significantly shorter PFS and an increase in post-operative complications. However, as with our extent of TDT coverage data, we did not observe a clear impact of this factor on OS in patients. This can perhaps be explained by the fact that overall survival may be dominantly associated with systemic disease burden rather than central nervous system disease.

To keep complications at a minimum, patient selection is of great importance. LITT is ideal for lesions that are deeply seated and for which open surgery would be difficult, morbid, or at least transgress some amount of normal brain. However, LITT is also well-suited for more superficial lesions in patients who are too ill for surgery, have a thin scalp due to radiation or multiple prior

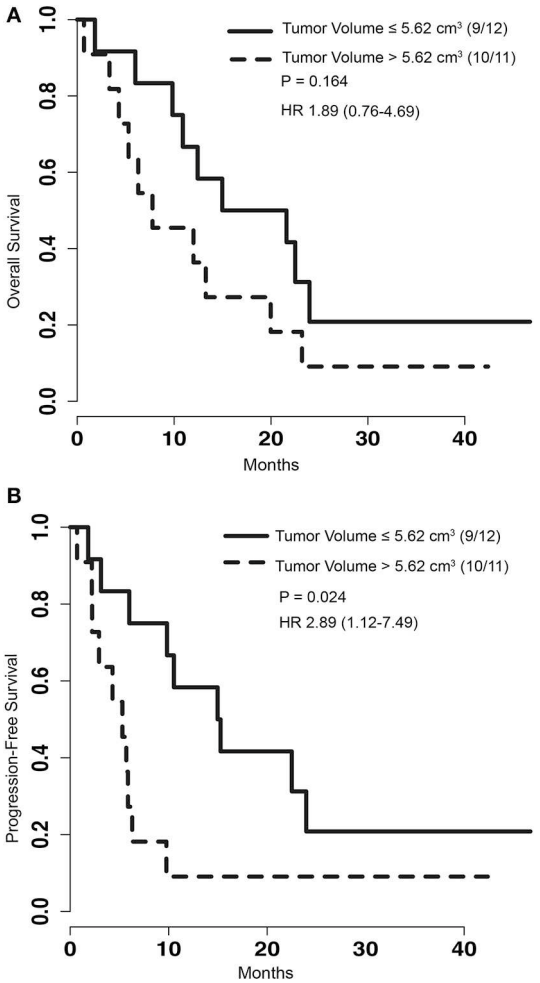


FIGURE 2 | (A) Kaplan-Meier graph depicting the OS of patients with the group dichotomized based on the volume of tumors greater than 5.62 cm^3 or less than and equal to 5.62 cm^3. *P*-value for log rank test and hazard ratio are depicted on the graph. **(B)** Kaplan-Meier graph of PFS for patients with tumor volumes greater than 5.62 cm^3 or less than and equal to 5.62 cm^3. Log rank test comparing this two groups shows significantly improved survival for patients with smaller tumors ($p = 0.024$).

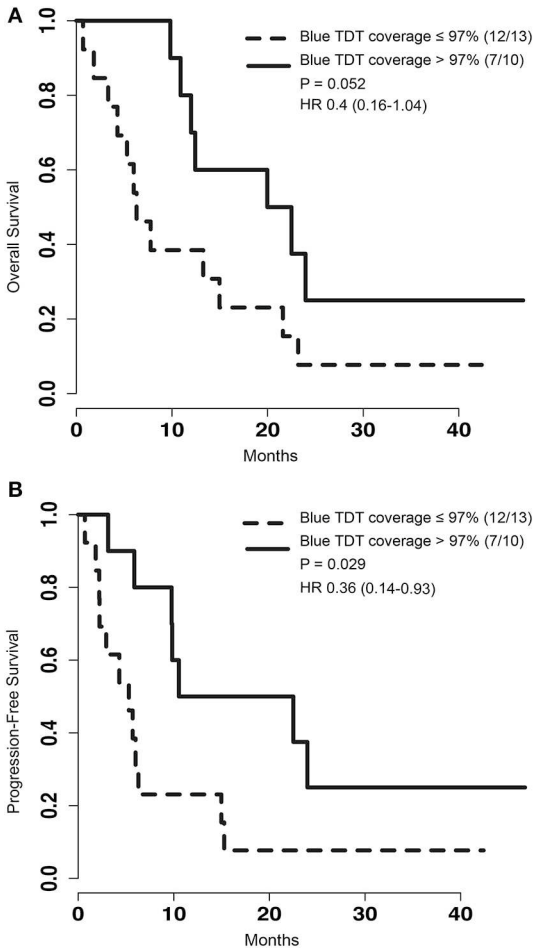


FIGURE 3 | (A) Kaplan-Meier graph depicting the OS of patients with the group dichotomized based on the blue thermal dose threshold (TDT) coverage area of 97%. *P*-value for log rank test and hazard ratio are depicted on the graph. **(B)** Kaplan-Meier graph of PFS for patients with treatment coverage area greater than 97% or less than and equal to 97%. Log rank test comparing these two group shows a significantly improved survival for patients with blue TDT line coverage >97%.

surgeries, or have tenuous baseline functional status. Ideally, the target lesion for LITT would be (1) well-circumscribed such that the lesion could be treated within a 3 cm-diameter cylinder; (2) average to low vascularity; and (3) accessible via a safe linear trajectory that avoids inadvertent heating of eloquent structures. Additionally, the patient and laser apparatus combined must fit into the bore of the MRI scanner, which can be a limitation for obese patients. The efficacy of LITT as frontline therapy, particularly in small tumors, remains to be determined and will likely require a clinical trial testing the clinical benefit of LITT vs. SRS with a larger number of patients. But it is the opinion of the authors that safe supramarginal ablation by LITT might represent an interesting alternative to SRS.

With any surgical procedure, operative morbidity and different treatment options has to be weighed against possible benefits from surgery. In our series we had two cases (8%) of seizures (**Table 2**). As a comparison, Gokhale et al. showed risk of post-operative seizures after craniotomy to be about 7.3% with Keppra treatment (19), which is similar to the current study. Post-operative edema is another factor that must be considered with LITT. In our series, two cases experienced swelling requiring readmission. Post-LITT edema may potentially be more fulminant than post-craniotomy edema due to the lack of any decompression with LITT alone. A prolonged steroid course (2–3 weeks) or a minimally invasive craniotomy and limited resection immediately following LITT of larger tumors may represent strategies to mitigate this phenomenon (20, 21).

The management of incompletely treated tumors by LITT or recurrent tumors following LITT remains an open question. In four patients, LITT was repeated for

recurrent lesions and in three cases the recurring tumors were treated with SRS. For larger lesions that may be incompletely ablated, there may be a role for adjuvant SRS for the residual. There may also be a role for administration of chemotherapeutic drugs in the post-LITT period given our prior finding that the BBB is permeable for 4–6 weeks post-LITT (22).

In summary, LITT is an increasingly attractive treatment modality for various types of intracranial lesions including brain metastasis. It offers a minimally invasive option for tumors that are difficult to access or refractory to prior treatment while at the same time offering comparable survival outcome to other salvage therapies.

AUTHOR CONTRIBUTIONS

AS and AHK contributed to concept and design of the study. AS wrote the first draft of the paper as well as the major revisions. AHK edited drafts. AAK wrote sections of the manuscript. AHK and EL performed the surgeries and maintained the database. All authors contributed to manuscript revision, and have read and approved the submitted version.

REFERENCES

1. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. (2017) 18:1049–60. doi: 10.1016/S1470-2045(17)30441-2
2. Smedby KE, Brandt L, Bäcklund ML, Blomqvist P. Brain metastases admissions in Sweden between 1987 and 2006. *Br J Cancer* (2009) 101:1919–24. doi: 10.1038/sj.bjc.6605373
3. Sharma R, Wagner JL, Hwang RF. Ablative therapies of the breast. *Surg Oncol Clin N Am*. (2011) 20:317–39, viii. doi: 10.1016/j.soc.2010.11.003
4. Nikfarjam M, Christophi C. Interstitial laser thermotherapy for liver tumours. *Br J Surg*. (2003) 90:1033–47. doi: 10.1002/bjs.4326
5. Patel P, Patel NV, Danish SF. Intracranial MR-guided laser-induced thermal therapy: single-center experience with the visualase thermal therapy system. *J Neurosurg*. (2016) 125: 853–60. doi: 10.3171/2015.7.JNS15244
6. Missios S, Bekelis K, Barnett GH. Renaissance of laser interstitial thermal ablation. *Neurosurg Focus* (2015) 38:E13. doi: 10.3171/2014.12.FOCUS14762
7. Kamath AA, Friedman DD, Hacker CD, Smyth MD, Limbrick DD, Kim AH, et al. MRI-guided interstitial laser ablation for intracranial lesions: a large single-institution experience of 133 cases. *Stereotact Funct Neurosurg*. (2017) 95:417–28. doi: 10.1159/000485387
8. Hawasli AH, Kim AH, Dunn GP, Tran DD, Leuthardt EC. Stereotactic laser ablation of high-grade gliomas. *Neurosurg Focus* (2014) 37:E1. doi: 10.3171/2014.9.FOCUS14471
9. Hawasli AH, Bagade S, Shimony JS, Miller-Thomas M, Leuthardt EC. Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: single-institution series. *Neurosurgery* (2013) 73:1007–17. doi: 10.1227/NEU.0000000000000144
10. Mohammadi AM, Hawasli AH, Rodriguez A, Schroeder JL, Laxton AW, Elson P, et al. The role of laser interstitial thermal therapy in enhancing progression-free survival of difficult-to-access high-grade gliomas: a multicenter study. *Cancer Med*. (2014) 3:971–9. doi: 10.1002/cam4.266
11. Voigt JD, Barnett G. The value of using a brain laser interstitial thermal therapy (LITT) system in patients presenting with high grade gliomas where maximal safe resection may not be feasible. *Cost Eff Resour Alloc*. (2016) 14:6. doi: 10.1186/s12962-016-0055-2
12. Schwarzmaier HJ, Eickmeyer F, von Tempelhoff W, Fiedler VU, Niehoff H, Ulrich SD, et al. MR-guided laser-induced interstitial thermotherapy of recurrent glioblastoma multiforme: preliminary results in 16 patients. *Eur J Radiol*. (2006) 59:208–15. doi: 10.1016/j.ejrad.2006.05.010
13. Fabiano AJ, Qiu J. Delayed failure of laser-induced interstitial thermotherapy for postradiosurgery brain metastases. *World Neurosurg*. (2014) 82:e559–63. doi: 10.1016/j.wneu.2014.06.007
14. Carpentier A, McNichols RJ, Stafford RJ, Guichard JP, Reizine D, Delaloge S, et al. Laser thermal therapy: real-time MRI-guided and computer-controlled procedures for metastatic brain tumors. *Lasers Surg Med*. (2011) 43:943–50. doi: 10.1002/lsm.21138
15. Rahmathulla G, Recinos PF, Valerio JE, Chao S, Barnett GH. Laser interstitial thermal therapy for focal cerebral radiation necrosis: a case report and literature review. *Stereotact Funct Neurosurg*. (2012) 90:192–200. doi: 10.1159/000338251
16. Thon N, Kreth FW, Tonn JC. The role of surgery for brain metastases from solid tumors. *Handb Clin Neurol*. (2018) 149:113–21. doi: 10.1016/B978-0-12-811161-1.00008-6
17. Lee CH, Kim DG, Kim JW, Han JH, Kim YH, Park CK, et al. The role of surgical resection in the management of brain metastasis: a 17-year longitudinal study. *Acta Neurochir (Wien)*. (2013) 155:389–97. doi: 10.1007/s00701-013-1619-y
18. Koiso T, Yamamoto M, Kawabe T, Watanabe S, Sato Y, Higuchi Y, et al. Follow-up results of brain metastasis patients undergoing repeat Gamma Knife radiosurgery. *J Neurosurg*. (2016) 125(Suppl. 1):2–10. doi: 10.3171/2016.6.GKS161404
19. Gokhale S, Khan SA, Agrawal A, Friedman AH, McDonagh DL. Levetiracetam seizure prophylaxis in craniotomy patients at high risk for postoperative seizures. *Asian J Neurosurg*. (2013) 8:169–73. doi: 10.4103/1793-5482.125658
20. Wright J, Chugh J, Wright CH, Alonso F, Hdeib A, Gittleman H, et al. Laser interstitial thermal therapy followed by minimal-access transsulcal resection for the treatment of large and difficult to access brain tumors. *Neurosurg Focus* (2016) 41:E14. doi: 10.3171/2016.8.FOCUS16233
21. Pisipati S, Smith KA, Shah K, Ebersole K, Chamoun RB, Camarata PJ. Intracerebral laser interstitial thermal therapy followed by tumor resection to minimize cerebral edema. *Neurosurg Focus* (2016) 41:E13. doi: 10.3171/2016.7.FOCUS16224
22. Leuthardt EC, Duan C, Kim MJ, Campian JL, Kim AH, Miller-Thomas MM, et al. Hyperthermic laser ablation of recurrent glioblastoma leads to temporary disruption of the peritumoral blood brain barrier. *PLoS ONE* (2016) 11:e0148613. doi: 10.1371/journal.pone.0148613

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Salehi, Kamath, Leuthardt and Kim. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

MINI REVIEW
published: 13 November 2018
doi: 10.3389/fneur.2018.00959

Preoperative Stereotactic Radiosurgery for Brain Metastases

*David M. Routman[1], Elizabeth Yan[1], Sujay Vora[2], Jennifer Peterson[3,4], Anita Mahajan[1], Kaisorn L. Chaichana[3], Nadia Laack[1], Paul D. Brown[1], Ian F. Parney[5], Terry C. Burns[5] and Daniel M. Trifiletti[3,4]**

[1] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, United States, [2] Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, United States, [3] Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, United States, [4] Department of Neurological Surgery, Mayo Clinic, Jacksonville, FL, United States, [5] Department of Neurological Surgery, Mayo Clinic, Rochester, MN, United States

Stereotactic radiosurgery (SRS) is increasingly utilized to treat the resection cavity following resection of brain metastases and recent randomized trials have confirmed postoperative SRS as a standard of care. Postoperative SRS for resected brain metastases improves local control compared to observation, while also preserving neurocognitive function in comparison to whole brain radiation therapy (WBRT). However, even with surgery and SRS, rates of local recurrence at 1 year may be as high as 40%, especially for larger cavities, and there is also a known risk of leptomeningeal disease after surgery. Additional treatment strategies are needed to improve control while maintaining or decreasing the toxicity profile associated with treatment. Preoperative SRS is discussed here as one such approach. Preoperative SRS allows for contouring of an intact metastasis, as opposed to an irregularly shaped surgical cavity in the post-op setting. Delivering SRS prior to surgery may also allow for a "sterilizing" effect, with the potential to increase tumor control by decreasing intra-operative seeding of viable tumor cells beyond the treated cavity, and decreasing risk of leptomeningeal disease. Because there is no need to treat brain surrounding tumor in the preoperative setting, and since the majority of the high dose volume can then be resected at surgery, the rate of symptomatic radiation necrosis may also be reduced with preoperative SRS. In this mini review, we explore the potential benefits and risks of preoperative vs. postoperative SRS for brain metastases as well as the existing literature to date, including published outcomes with preoperative SRS.

Keywords: preoperative, neoadjuvant, stereotactic radiosurgery (SRS), postoperative, brain metastases, local recurrence, radionecrosis, leptomeningeal disease

OPEN ACCESS

Edited by:
Arjun Sahgal,
University of Toronto, Canada

Reviewed by:
Zain Husain,
Yale University, United States
Jonathan P. S. Knisely,
Weill Cornell Medicine, United States

***Correspondence:**
Daniel M. Trifiletti
trifiletti.daniel@mayo.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *20 July 2018*
Accepted: *25 October 2018*
Published: *13 November 2018*

Citation:
Routman DM, Yan E, Vora S, Peterson J, Mahajan A, Chaichana KL, Laack N, Brown PD, Parney IF, Burns TC and Trifiletti DM (2018) Preoperative Stereotactic Radiosurgery for Brain Metastases. Front. Neurol. 9:959. doi: 10.3389/fneur.2018.00959

INTRODUCTION

The incidence of brain metastases (BrM) is increasing with approximately 175,000–200,000 patients developing BrM in the United States yearly (1, 2). This increase is likely multifactorial and related to both increased detection and an increase in actual development of BrM in cancer patients. Patients are now more frequently surveilled with dedicated imaging, leading to greater rates of detection. And, improvements in local and systemic options for cancer patients are improving overall survival (OS), allowing more time for BrM to occur, especially in the setting of targeted agents that may not penetrate the central nervous system (CNS). Indeed, up to 20–30% of patients with solid tumors

may ultimately develop BrM (3, 4). The rate of BrM can be even higher in select populations, such as patients with HER2 positive breast cancer receiving directed therapy (5). Additionally, patients with BrM are living longer. For example, ALK-rearranged lung cancer patients may live a median of 49.5 months *after* the development of BrM (6). Thus, optimal management becomes an important consideration, including balancing the effectiveness of treatment with associated toxicity. Here, we present a review of the management of surgically resected BrM with consideration for strategies to improve local tumor control and potentially decrease toxicity in long term survivors, focusing on preoperative stereotactic radiosurgery (SRS) as one such novel strategy.

SURGERY FOR BRAIN METASTASES

Surgery continues to play a significant role in the management of BrM for decompression and relief of symptoms secondary to mass effect, tissue diagnosis including relevant molecular analysis, local control in select cases such as larger lesions, and/or for a combination of these reasons (7). Surgery has been associated with improved overall survival (OS), especially in the setting of a single or solitary BrM (8, 9). In a seminal study by Patchell et al. patients randomized to surgery followed by adjuvant whole brain radiation therapy (WBRT) lived longer as compared to those receiving WBRT alone, with a median overall survival (OS) of 40 weeks as compared to 15 weeks, respectively (8). However, additional work by Patchell et al. revealed that surgery alone, with no adjuvant radiation therapy, results in a local recurrence rate of nearly 50% (10).

While there have been improvements in stereotactic guidance, surgical techniques, as well as cross sectional imaging, the rate of recurrence for surgery alone for BrM is still close to 50% in more modern cohorts (11). To reduce this rate of recurrence, postoperative radiosurgery or radiotherapy is generally recommended, with recent trials informing practice and favoring SRS over WBRT because of the global neurocognitive deficits associated with WBRT (3, 12).

ADJUVANT RADIOSURGERY AND RADIOTHERAPY

WBRT as adjuvant therapy for surgically resected BrM has traditionally been considered the standard of care (8, 12). However, this type of therapy comes with the cost of substantial dose to functioning normal brain parenchyma leading to a decline in neurocognition. A recent cooperative randomized trial by Brown et al., N107c, revealed that postoperative SRS has equivalent OS in comparison to WBRT with median OS of 12.2 months vs. 11.6 months, respectively ($p = 0.70$). However, SRS was associated with statistically significant decreased rates of neurocognitive decline and functional independence (12). At 6 months post treatment, 85% of patients assigned to receive WBRT experienced cognitive deterioration as compared to 52% of patients assigned to receive SRS ($p < 0.001$). Postoperative SRS is thus now considered a standard of care and becoming a more frequently employed modality after surgically resected metastases.

However, WBRT has demonstrated improved local control in comparison to SRS (12). For example, in N107c, the 12 month surgical bed control rate was 61% in the SRS arm as compared to 81% in the WBRT arm ($p < 0.001$). Nevertheless, the rate of local recurrence with the combination of surgery followed by WBRT still approximates 20% at 12 months, including with 36 Gy in 12 fractions of adjuvant WBRT and in more modern series (8, 12). Furthermore, though treatment generally has improved with advancements in cross sectional imaging, surgical advances, targeted systemic therapy, and advanced delivery of radiation, the rate of recurrence after resection followed by SRS, as demonstrated by Mahajan et al. approximates 28% at 1 year and is even higher at 44% for lesions $\geq$3.0 cm (11). While the lower SRS doses utilized for this study may have been a factor in recurrence rates, local control for larger BrM has proven particularly challenging; and the potential local control advantage of WBRT previously described may not hold for larger metastases (12). Therefore, the potential for improvement in the treatment of BrM remains and alternative strategies are needed, with the goal to continue to improve local control while attempting to maintain the low toxicity profile associated with SRS.

ALTERNATIVE APPROACHES, INCLUDING NEOADJUVANT RADIATION (PREOPERATIVE SRS)

While results of recent randomized trials have informed practice, the optimal approach to the management of surgically resected brain metastases has yet to be determined with centers providing multiple approaches to care, including observation after resection, adjuvant SRS, adjuvant WBRT, fractionated SRS, and neoadjuvant SRS, or alternative therapies besides or in addition to radiation therapy, such laser interstitial thermal therapy (LITT).

Fractionated SRS may offer advantages in comparison to a single fraction of radiosurgery including the potential to improve local control. Fractionation takes advantage of radiobiologic principles such as normal tissue repair and reoxygenation to deliver a higher dose of radiation with potentially similar or lower rates of toxicity including radiation necrosis, in comparison to single fraction SRS. The hypothesized improvement in local control with fractionated SRS could be anticipated to be similar to the differences in surgical bed control rates between WBRT and SRS described above. Retrospective series including an analysis by Minniti et al. have demonstrated improved 12 month local control of 91% in consecutive patients receiving fractionated SRS as opposed to a 12 month local control rate of 77% for patients receiving a single fraction (13, 14). Randomized comparisons are needed for further comparison.

A neoadjuvant (preoperative) approach to radiation therapy additionally offers the potential to improve rates of local control while decreasing rates of toxicity. Neoadjuvant radiation therapy is becoming popular across a number of disease sites. It is now a standard of care in sarcoma, rectal, esophageal, and pancreatic

TABLE 1 | Potential advantages and disadvantages of preoperative stereotactic radiosurgery compared to postoperative stereotactic radiosurgery.

Potential advantages	Disadvantages
↑ Local Control • Improved target delineation • Sterilization effect • Improved oxygenation ratio	Lack of Pathologic Confirmation Prior to SRS
↓ Leptomeningeal Disease • Sterilization effect	Not Compatible with Emergent Surgery (uncommon)
↓ Radiation Necrosis • Less normal brain irradiated • Resection of majority of irradiated tissue	↓ Wound Healing
↑ Systemic Control • Improved time to systemic therapy • Immunogenicity	

cancer (15–19). For example, the German rectal cancer study group reported results of a randomized trial which showed improved outcomes including better local control and less grade 3 or 4 toxicity with receipt of preoperative as compared to postoperative radiotherapy (16). It has also been shown that patients with resectable pancreatic tumors, who historically were not offered adjuvant radiation due to lack of proven benefit, do gain a significant benefit from a neoadjuvant approach (17). These findings are related to a number of advantages associated with neoadjuvant radiation therapy in comparison to adjuvant radiation therapy, and specific potential advantages in the preoperative vs. postoperative SRS setting for BrM are listed in **Table 1** and explored in more detail below.

Target Delineation

Preoperative SRS allows for less complex target delineation with less uncertainty when contouring an intact BrM. Postoperative SRS is more complex, attributable to the need to recreate a tumor bed, correctly interpret the altered appearance of manipulated dural surfaces in superficial cases, and decisions whether or not to include portions of the surgical tract for deeper lesions (**Figure 1**). Furthermore, the tumor bed can evolve postoperatively over time, adding the challenge of delineating residual tumor from postoperative changes, and contouring an irregularly shaped target whilst ensuring coverage of all areas of prior contact for previously resected BrM (20, 21). Retrospective analyses have found conflicting results in regards to the likelihood of surgical cavity increase vs. constriction post-operatively (22, 23). However, in either case, dynamic surgical bed changes after simulation but prior to the delivery of SRS represents an additional challenge in delineation unique to postoperative LINAC based SRS.

Radiation Necrosis

Radiation necrosis is a potential morbidity of SRS that can occur in up to 10–20% of patients and require further intervention, such as steroids, bevacizumab, resection, and/or LITT in select cases (24). The rate of radiation necrosis is proportional to radiation dose and the size of the lesion, with up to a 49.4% cumulative risk at 24 months of radiation necrosis (including asymptomatic treatment change) reported in lesions exceeding 1.0 cm treated with definitive SRS. Therefore, increasing prescription target dose to improve local control of BrM is limited by toxicity such as necrosis, particularly for larger lesions (24). Furthermore, newer systemic agents including immunotherapy and targeted biologics are being used more frequently and in combination with SRS. These agents generally have been shown to be efficacious, but in turn may increase the rate of radiation necrosis for patients receiving SRS (24, 25).

Preoperative SRS could reduce rates of necrosis relative to postoperative SRS (**Table 2**). After preoperative SRS, much of the irradiated rim of normal tissue receiving near target dose and surrounding the adjacent tumor will be resected at the time of surgery, potentially attenuating the availability of injured tissue and cytokine concentrations needed to catalyze radiation necrosis (**Figure 1**) (29, 30). In comparison, after surgical resection, postoperative SRS includes the surgical tumor bed and a rim or margin of normal tissue which receives prescription dose, potentially increasing the volume of normal brain irradiated and increasing risk of radiation necrosis (21).

Local Control

As noted above, local recurrence following postoperative SRS remains high, especially for larger lesions, with a rate of 44% reported at 1 year for lesions of 3 cm or larger (11). Local recurrence is associated with worse OS in some series (12, 31). That local recurrence was decreased with postoperative WBRT in comparison to postoperative SRS (12) suggests viable cells can persist outside of the radiation treatment volume when delivery is performed in the postoperative setting, a problem that could be avoided with preoperative SRS. A circa 50% local recurrence rate following surgery alone (11) highlights the fact that tumor cells are frequently "spilled" at the time of surgery. When possible, en bloc resection technique can help mitigate that risk (32, 33). The unfortunate reality of many tumors, however, is that several factors from fragile cystic walls to dural contact, or vascular involvement, preclude effectively or safely performing an en bloc resection. Moreover, tumors approached via a trans-sulcal, trans-sylvian, interhemispheric, or transventricular approach present opportunities for dissemination of viable cells into the far reaches of those surgical access corridors. By operating after prior radiation, any tumor cells spilled are treated or "sterilized" and thus likely no longer replication competent, reducing the risk of recurrence beyond the treatment field.

Appropriate tumors in non-eloquent regions amenable to either en bloc resection, or generous resection of peri-tumor parenchyma, may be candidates for preoperative SRS dose escalation if rates of radiation necrosis risk could indeed be minimized through this approach. This would equate to improved control without increased toxicity.

Finally, the biologic effect of radiation therapy is in part dependent on generation of oxygen free radicals. As noted by Prabhu et al. oxygenation is decreased in the postoperative environment, making preoperative SRS theoretically more

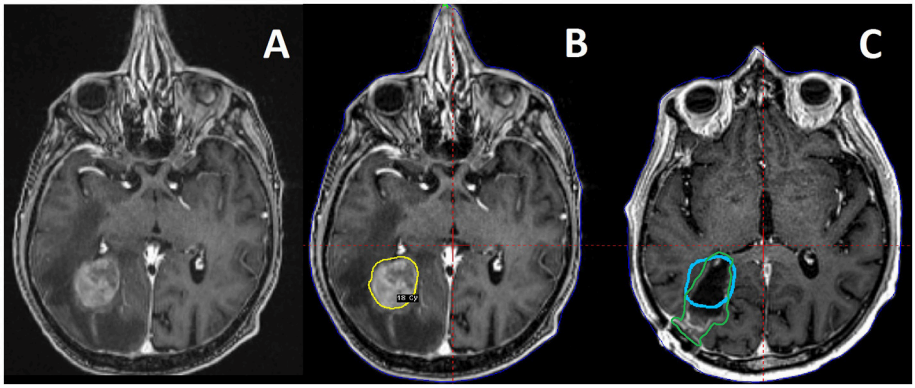


FIGURE 1 | A 73 year old male patient with metastatic soft tissue sarcoma and three brain metastases, one large right occipital metastasis with associated edema **(A)**, as well as smaller tumors in the right motor strip and left temporal lobe (not pictured). He was treated with preoperative SRS **(B)** to 18 Gy to the 50% isodose line (20 Gy to the other, smaller tumors) followed by surgical resection of the occipital tumor the next day. Also pictured is a 3 month follow up MRI with the preoperative target depicted in blue, compared to the postoperative target depicted in green as per consensus guidelines **(C)**, demonstrating the change in the tumor cavity geometry after resection.

TABLE 2 | Studies Investigating Preoperative SRS.

References	Patients		Outcomes					
			Local recurrence		Radiation necrosis		Leptomeningeal disease	
			Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Asher et al. (26)	$N = 47$		71.8%~	N/A	Considered Local Recurrence	N/A	0%	N/A
Patel et al. (27)	$N = 66$	$N = 114$	15.9%	12.6% (SRS)	3.09%	20.0% (SRS)	3.2%	8.3% (SRS)
Patel et al. (28)	$N = 66$	$N = 36$	24.5%*	25.1%* (WBRT)	9.9%*	0%* (WBRT)	3.5%	9.0%* (WBRT)

All timepoints are 1 year unless otherwise noted.
**Denotes 24 month timepoints.*
~Freedom from local recurrence.

effective at comparable or even lower doses (34). The results of initial series of preoperative SRS are described in greater detail below. No local control benefit has been shown to date, however systematic, prospective evaluation is needed to reduce the impact of selection bias.

Leptomeningeal Disease

Leptomeningeal carcinomatosis can occur in the setting of BrM as well as other primary CNS malignancies. In the context of BrM, it is most common in certain malignancies such as breast cancer, particularly after neurosurgical resection, most especially in the posterior fossa (35). Development of diffuse leptomeningeal disease is associated with a particularly poor prognosis (36). WBRT has been associated with decreased rates of leptomeningeal disease in comparison to postoperative SRS. However, as described below, preoperative SRS appears to have similar rates of development of leptomeningeal disease compared to WBRT, without the associated neurocognitive deficit (28). This could be due to the above mentioned "sterilization" effect, which prevents the dissemination of replication-competent tumor cells at the time of surgery, potentially decreasing the rate of development of leptomeningeal disease in comparison to postoperative SRS.

Logistics

The logistics of performing SRS in a recent postoperative patient may be complicated by competing needs to coordinate discharge or rehabilitation (rehab) placement needs with SRS, which is typically performed at the same institution, but on an outpatient basis. Rehab or skilled nursing facilities may be reluctant to accept a patient who has upcoming procedures scheduled. Moreover, patients in the postoperative setting may have pain control needs that put additional strain on both patient and staff. For facilities employing frame based SRS, frame placement may be easier and more comfortable without a tender or swollen incision, or underlying craniotomy, to negotiate. For these reasons, postoperative frame based SRS is rarely performed in the immediate postoperative setting, but usually 2–5 weeks after surgery, prolonging the total episode of care. An additional practical concern is the subset of patients undergoing resection who do not complete intended therapy with adjuvant SRS or WBRT, due to early progression or failure to follow up. Undergoing SRS 1–2 days prior to surgery has proven a logistically favorable and comfortable strategy for patients at our

institution, allowing minimal time from diagnosis to completion of treatment.

Although pending SRS is not necessarily a contra-indication to chemotherapy, a prior series by Chang et al. comparing SRS to WBRT showed that WBRT resulted in an increased time to systemic therapy and may have been associated with worse overall outcomes as a result of this delay (37). As such, the impact of time to completion of management of BrM should be considered for potential impact on systemic management.

Additional Considerations—Timing of Therapy and Immune Activation

Radiation therapy is well-recognized to be both immunosuppressive and immunogenic (38). The precise timing, dose, fractionation, and ideal combination with systemic therapy to promote anti-tumor immune activation remain to be determined (39). The immune system has been shown to be important in controlling BrM, with immunotherapy, including dual checkpoint blockade, having demonstrated activity in the CNS (40). The combination of SRS and immunotherapy in the treatment of BrM is an area of active investigation. Ideally, the timing and dose of SRS in the treatment of BrM would consider optimizing potential benefits of radiation on any anti-tumor immune response. Thus, although preoperative SRS permits expeditious management, with surgery performed even as soon as the same day immediately following SRS, this–like postoperative SRS–may suboptimally exploit opportunities to harness the pro-immunogenic impact of tumor radiation (41).

This concept is well-illustrated in preclinical work by De La Maza et al. exploring radiation therapy prior to surgery and the short-term and long-term effect on the immune system. In a murine model, surgery alone or treatment with hypofractionated radiation therapy followed by surgery 1 day later resulted in zero tumor rejection to tumor re-challenge 90 days after treatment, demonstrating minimal long term immunologic memory response. However, hypofractionated radiation therapy followed by surgery 7 days later resulted in a 33% complete rejection of tumor on re-challenge 90 days after treatment, and this cohort of radiation therapy followed by surgery 7 days later had the lowest growth rate overall, as defined by tumor area, on tumor re-challenge. These findings were confirmed to be immunologic in origin, as they were markedly diminished when the mice were depleted of CD4+ T-cells (42).

How neoadjuvant radiation followed by surgery compares to surgery followed by adjuvant radiation therapy in terms of immune activation and so called *in situ* vaccination remains to be specifically tested. However, postoperative radiation therapy is likely less immunogenic compared to preoperative radiation therapy in the setting of recovery from a resection, including decreased neoantigen stimulation with likely only microscopic residual disease in the adjuvant setting (43). Finally, large ablative doses as prescribed in SRS may result in immune suppression in comparison to more moderate hypofractionation, making a fractionated pre-operative SRS approach with surgery 7 days or even more after radiation potentially the most immunogenic of all paradigms discussed (39, 44, 45).

Ultimately, the role and timing of achieving local control may require patient-specific considerations in the context of primary diagnosis, total intracranial and systemic disease burden, and immune status to optimize care. A patient's symptoms, performance status, treatment timeline, prior course, primary malignancy, type of systemic therapy and more may ultimately guide decision making, and where pre-operative SRS could be the ideal approach for a certain patient with BrM, another may benefit more so from a postoperative approach, including WBRT with memantine and potentially hippocampal avoidance in select circumstances (46, 47).

Disadvantages

Preoperative SRS is not without limitations. One significant disadvantage of treatment of a lesion prior to resection is that the SRS is delivered before pathologic confirmation is available. This leads to the real possibility that a lesion which is radiologically and clinically consistent with a BrM is found not to be a metastasis, but a primary CNS malignancy, lymphoma, or an autoimmune condition, entities where the already delivered SRS would not be the treatment of choice for the diagnosis (and where radiation therapy may not be indicated).

Another disadvantage is that surgery is often indicated for highly symptomatic patients with mass effect, and preoperative SRS potentially delays the time from presentation to operation. This delay may be on the order of 6–48 h at centers with routine availability of SRS and neurosurgery and not significant for most patients. However, a preoperative SRS approach may not work for all patients nor be feasible in all care settings. Finally, preoperative SRS could lead to issues with wound healing compared to patients undergoing surgery prior to any therapy.

LITERATURE EVALUATING PREOPERATIVE SRS AND FUTURE TRIALS

Limited data exist to evaluate the theoretical risks and benefits of preoperative SRS discussed above but generally support the safety, efficacy, as well as potential advantages of preoperative SRS. Asher et al. reported on 47 patients with many treated prospectively on trial, demonstrating the safety and efficacy of preoperative SRS, reporting local control rates of 85.6 and 71.8% at 12 and 24 months, respectively (26). Importantly, no perioperative morbidity or mortality attributable to the preoperative SRS was noted, although theoretical concerns (e.g., wound complications) are not infrequently raised. However, and again drawing on other existing literature from other disease sites, series have reported neoadjuvant radiation therapy was associated with decreased surgical complications and improved margin negative resection rates in certain instances (19, 48).

Preoperative SRS has been compared to postoperative SRS and postoperative WBRT in retrospective series. Patel et al. reviewed outcomes retrospectively of 66 patients treated with preoperative SRS in the largest series to date and in comparison to 114 patients who were treated postoperatively (27). In this analysis, preoperative SRS showed advantages in comparison to postoperative SRS. The preoperative cohort had statistically

significant decreased rates of development of leptomeningeal disease (3.2 vs. 16.2% at 2 years), as well as statistically significant decreased rates of symptomatic radiation necrosis (4.9 vs. 16.4% at 2 years). However, this study showed no differences in local control between these two approaches (27). In a subsequent analysis, Patel et al. compared preoperative SRS to postoperative WBRT, finding no differences in local control or rate of development of leptomeningeal disease (28).

Further studies are necessary to compare preoperative vs. postoperative SRS. Phase II data described above support the safety and efficacy of pre-operative SRS, with mixed retrospective findings in regards to outcomes. When possible, future studies should continue to consider meaningful endpoints such as radiation necrosis, leptomeningeal disease, and local control, while taking into account considerations in timing, and utilizing correlative analysis to drive better understanding of the biologic response. Only with robust prospective and randomized data will we be able to determine if any of these hypothetical advantages to preoperative SRS are real and justify the known risks of preoperative treatment including SRS of a non BrM. If advantageous, eventual comparison will be needed to additional promising strategies such as fractionated SRS.

The NRG is currently developing a trial at the national level and several institutional trials are currently in development or enrolling, including Mayo Clinic MC167C, comparing preoperative SRS to postoperative SRS with a primary composite endpoint encompassing time to event of local recurrence, symptomatic radiation necrosis, or development of leptomeningeal disease.

CONCLUSION

For surgically resected brain metastases, postoperative SRS has been adopted as the current standard of care in comparison to postoperative observation or WBRT. Recurrence rates after postoperative SRS, especially for larger BrM, are unfortunately high. Novel approaches including preoperative SRS may improve local control and decrease rates of leptomeningeal disease while also decreasing toxicity such as radiation necrosis. Further consideration regarding timing of intervention and prospective evaluation of preoperative SRS is warranted in prospective studies, which are currently underway.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Arvold ND, Lee EQ, Mehta MP, Margolin K, Alexander BM, Lin NU. Updates in the management of brain metastases. *Neuro Oncol.* (2016) 18:1043–65. doi: 10.1093/neuonc/now127
2. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. Epidemiology of metastatic brain tumors. *Neurosurg Clin N Am.* (2011) 22:1–6. doi: 10.1016/j.nec.2010.08.007
3. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi: 10.1001/jama.2016.9839
4. Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Gonçalves A. Recent trends in epidemiology of brain metastases: an overview. *Anticancer Res.* (2012) 32:4655–62.
5. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* (2003) 97:2972–7. doi: 10.1002/cncr.11436
6. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND. Extended survival and prognostic factors for patients with ALK-rearranged non–small-cell lung cancer and brain metastasis. *J Clin Oncol.* (2016) 34:123–129. doi: 10.1200/JCO.2015.62.0138
7. Nabors LB, Portnow J, Ammirati M, Baehring J, Brem H, Brown P. Network NCC. *NCCN Clinical Practice Guidelines in Oncology Central Nervous System Cancers Version 1.*(2018) Available online at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf (Accessed July 15, 2018).
8. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* (1990) 322:494–500. doi: 10.1056/NEJM199002223220802
9. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol.* (1993) 33:583–90. doi: 10.1002/ana.410330605
10. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* (1998) 280:1485–9. doi: 10.1001/jama.280.17.1485
11. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1040–8. doi: 10.1016/S1470-2045(17)30414-X
12. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1049–60. doi: 10.1016/S1470-2045(17)30441-2
13. Keller A, Doré M, Cebula H, Thillays F, Proust F, Darié I. Hypofractionated stereotactic radiation therapy to the resection bed for intracranial metastases. *Int J Radiat Oncol Biol Phys.* (2017) 99:1179–89. doi: 10.1016/j.ijrobp.2017.08.014
14. Minniti G, Scaringi C, Paolini S, Lanzetta G, Romano A, Cicone F. Single-fraction versus multifraction (3 x 9 Gy) stereotactic radiosurgery for large (>2 cm) brain metastases: a comparative analysis of local control and risk of radiation-induced brain necrosis. *Int J Radiat Oncol Biol Phys.* (2016) 95:1142–8. doi: 10.1016/j.ijrobp.2016.03.013
15. Lazarev S, McGee H, Moshier E, Ru M, Demicco EG, Gupta V. Preoperative vs postoperative radiation therapy in localized soft tissue sarcoma: nationwide patterns of care and trends in utilization. *Pract Radiat Oncol.* (2017) 7:e507–16. doi: 10.1016/j.prro.2017.04.010
16. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* (2004) 351:1731–40. doi: 10.1056/NEJMoa040694
17. Van Tienhoven G, Versteijne E, Suker M, Groothuis KBC, Busch OR, Bonsing BA, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): a randomized, controlled, multicenter phase III trial. *J Clin Oncol.* (2018) 36(18 Suppl):LBA4002. doi: 10.1200/JCO.2018.36.18_suppl.LBA4002
18. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* (2012) 366:2074–84. doi: 10.1056/NEJMoa1112088
19. Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in

patients with resectable or borderline resectable pancreatic cancer. *Br J Surg.* (2018) 105:946–58. doi: 10.1002/bjs.10870
20. Ahmed S, Hamilton J, Colen R, Schellingerhout D, Vu T, Rao G. Change in postsurgical cavity size within the first 30 days correlates with extent of surrounding edema: consequences for postoperative radiosurgery. *J Comput Assist Tomogr.* (2014) 38:457–60. doi: 10.1097/RCT.0000000000000058
21. Soliman H, Ruschin M, Angelov L, Brown PD, Chiang VLS, Kirkpatrick JP. Consensus contouring guidelines for postoperative completely resected cavity stereotactic radiosurgery for brain metastases. *Int J Rad Oncol Biol Phys.* (2018) 100:436–42. doi: 10.1016/j.ijrobp.2017.09.047
22. Patel RA, Lock D, Helenowski IB, Chandler JP, Sachdev S, Tate MC, et al. Postsurgical cavity evolution after brain metastasis resection: how soon should postoperative radiosurgery follow? *World Neurosurg.* (2018) 110:e310–4. doi: 10.1016/j.wneu.2017.10.159
23. Shah JK, Potts MB, Sneed PK, Aghi MK, McDermott MW. Surgical cavity constriction and local progression between resection and adjuvant radiosurgery for brain metastases. *Cureus* (2016) 8:e575. doi: 10.7759/cureus.575
24. Kohutek ZA, Yamada Y, Chan TA, Brennan CW, Tabar V, Gutin PH. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases. *J NeuroOncol.* (2015) 125:149–56. doi: 10.1007/s11060-015-1881-3
25. Diao K, Bian SX, Routman DM, Yu C, Ye JC, Wagle NA. Stereotactic radiosurgery and ipilimumab for patients with melanoma brain metastases: clinical outcomes and toxicity. *J Neurooncol.* (2018) 139:421–9. doi: 10.1007/s11060-018-2880-y
26. Asher AL, Burri SH, Wiggins WF, Kelly RP, Boltes MO, Mehrlich M. A new treatment paradigm: neoadjuvant radiosurgery before surgical resection of brain metastases with analysis of local tumor recurrence. *Int J Radiat Oncol Biol Phys.* (2014) 88:899–906. doi: 10.1016/j.ijrobp.2013.12.013
27. Patel KR, Burri SH, Asher AL, Crocker IR, Fraser RW, Zhang C. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: a multi-institutional analysis. *Neurosurgery* (2016) 79:279–85. doi: 10.1227/NEU.0000000000001096
28. Patel KR, Burri SH, Boselli D, Symanowski JT, Asher AL, Sumrall A. Comparing pre-operative stereotactic radiosurgery (SRS) to post-operative whole brain radiation therapy (WBRT) for resectable brain metastases: a multi-institutional analysis. *J Neurooncol.* (2017) 131:611–8. doi: 10.1007/s11060-016-2334-3
29. Schaue D, Kachikwu EL, McBride WH. Cytokines in radiobiological responses: a review. *Radiat Res.* (2012) 178:505–23. doi: 10.1667/RR3031.1
30. Yang R, Duan C, Yuan L, Engelbach JA, Tsien CI, Beeman SC. Inhibitors of HIF-1alpha and CXCR4 mitigate the development of radiation necrosis in mouse brain. *Int J Radiat Oncol Biol Phys.* (2018) 100:1016–25. doi: 10.1016/j.ijrobp.2017.12.257
31. Eaton BR, Gebhardt B, Prabhu R, Shu HK, Curran WJ, Crocker I. Hypofractionated radiosurgery for intact or resected brain metastases: defining the optimal dose and fractionation. *Radiat Oncol.* (2013) 8:135. doi: 10.1186/1748-717X-8-135
32. Patel AJ, Suki D, Hatiboglu MA, Abouassi H, Shi W, Wildrick DM. Factors influencing the risk of local recurrence after resection of a single brain metastasis. *J Neurosurg.* (2010) 113:181–9. doi: 10.3171/2009.11.JNS09659
33. Suki D, Hatiboglu MA, Patel AJ, Weinberg JS, Groves MD, Mahajan A. Comparative risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis. *Neurosurgery* (2009) 64:664–74; discussion 674–6. doi: 10.1227/01.NEU.0000341535.53720.3E
34. Prabhu RS, Patel KR, Press RH, Soltys SG, Brown PD, Mehta MP. Preoperative vs postoperative radiosurgery for resected brain metastases: a review. *Neurosurgery* (2018) doi: 10.1093/neuros/nyy146. [Epub ahead of print].
35. Atalar B, Modlin LA, Choi CY, Adler JR, Gibbs IC, Chang SD. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys.* (2013) 87:713–8. doi: 10.1016/j.ijrobp.2013.07.034
36. Lee S, Ahn HK, Park YH, Nam DH, Lee JI, Park W. Leptomeningeal metastases from breast cancer: intrinsic subtypes may affect unique clinical manifestations. *Breast Cancer Res Treat.* (2011) 129:809–17. doi: 10.1007/s10549-011-1682-0
37. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* (2009) 10:1037–44. doi: 10.1016/S1470-2045(09)70263-3
38. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol.* (2016) 13:516–24. doi: 10.1038/nrclinonc.2016.30
39. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. *Nat Commun.* (2017) 8:15618. doi: 10.1038/ncomms15618
40. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med.* (2018) 379:722–30. doi: 10.1056/NEJMoa1805453
41. Schoenfeld JD, Mahadevan A, Floyd SR, Dyer MA, Catalano PJ, Alexander BM. Ipilmumab and cranial radiation in metastatic melanoma patients: a case series and review. *J Immunother Cancer* (2015) 3:50. doi: 10.1186/s40425-015-0095-8
42. De La Maza L, Wu M, Wu L, Yun H, Zhao Y, Cattral M. *In situ* vaccination after accelerated hypofractionated radiation and surgery in a mesothelioma mouse model. *Clin Cancer Res.* (2017) 23:5502–13. doi: 10.1158/1078-0432.CCR-17-0438
43. Spiotto M, Fu YX, Weichselbaum RR. The intersection of radiotherapy and immunotherapy: mechanisms and clinical implications. *Sci Immunol.* (2016) 1:EAAG1266. doi: 10.1126/sciimmunol.aag1266
44. Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys.* (2012) 83:1306–10. doi: 10.1016/j.ijrobp.2011.09.049
45. Werner LR, Kler JS, Gressett MM, Riegert M, Werner LK, Heinze CM. Transcriptional-mediated effects of radiation on the expression of immune susceptibility markers in melanoma. *Radiother Oncol.* (2017) 124:418–26. doi: 10.1016/j.radonc.2017.08.016
46. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.* (2013) 15:1429–37. doi: 10.1093/neuonc/not114
47. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol.* (2014) 32:3810–6. doi: 10.1200/JCO.2014.57.2909
48. Cheng TY, Sheth K, White RR, Ueno T, Hung CF, Clary BM. Effect of neoadjuvant chemoradiation on operative mortality and morbidity for pancreaticoduodenectomy. *Ann Surg Oncol.* (2006) 13:66–74. doi: 10.1245/ASO.2006.02.003

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Routman, Yan, Vora, Peterson, Mahajan, Chaichana, Laack, Brown, Parney, Burns and Trifiletti. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 31 August 2018
doi: 10.3389/fonc.2018.00342

Postoperative Cavity Stereotactic Radiosurgery for Brain Metastases

*Eduardo M. Marchan[1], Jennifer Peterson[1], Terence T. Sio[2], Kaisorn L. Chaichana[3], Anna C. Harrell[1], Henry Ruiz-Garcia[1], Anita Mahajan[4], Paul D. Brown[4] and Daniel M. Trifiletti[1,3]**

[1] Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, United States, [2] Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, United States, [3] Department of Neurological Surgery, Mayo Clinic, Jacksonville, FL, United States, [4] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, United States

During the past decade, tumor bed stereotactic radiosurgery (SRS) after surgical resection has been increasingly utilized in the management of brain metastases. SRS has risen as an alternative to adjuvant whole brain radiation therapy (WBRT), which has been shown in several studies to be associated with increased neurotoxicity. Multiple recent articles have shown favorable local control rates compared to those of WBRT. Specifically, improvements in local control can be achieved by adding a 2 mm margin around the resection cavity. Risk factors that have been established as increasing the risk of local recurrence after resection include: subtotal resection, larger treatment volume, lower margin dose, and a long delay between surgery and SRS (>3 weeks). Moreover, consensus among experts in the field have established the importance of (a) fusion of the pre-operative magnetic resonance imaging scan to aid in volume delineation (b) contouring the entire surgical tract and (c) expanding the target to include possible microscopic disease that may extend to meningeal or venous sinus territory. These strategies can minimize the risks of symptomatic radiation-induced injury and leptomeningeal dissemination after postoperative SRS. Emerging data has arisen suggesting that multifraction postoperative SRS, or alternatively, preoperative SRS could provide decreased rates of radiation necrosis and leptomeningeal disease. Future prospective randomized clinical trials comparing outcomes between these techniques are necessary in order to improve outcomes in these patients.

Keywords: postoperative, radiosurgery, metastasis, resection, radiation

OPEN ACCESS

Edited by:
Sunit Das,
St. Michael's Hospital, Canada

Reviewed by:
Pierpaolo Peruzzi,
Harvard Medical School, United States
Alfredo Conti,
Università degli Studi di Messina, Italy

***Correspondence:**
Daniel M. Trifiletti
trifiletti.daniel@mayo.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *17 June 2018*
Accepted: *06 August 2018*
Published: *31 August 2018*

Citation:
Marchan EM, Peterson J, Sio TT, Chaichana KL, Harrell AC, Ruiz-Garcia H, Mahajan A, Brown PD and Trifiletti DM (2018) Postoperative Cavity Stereotactic Radiosurgery for Brain Metastases. Front. Oncol. 8:342. doi: 10.3389/fonc.2018.00342

INTRODUCTION

While postoperative whole-brain radiation therapy (WBRT) can minimize the likelihood of both local recurrence within the surgical cavity and distant recurrence elsewhere in the brain, it has been associated with increased morbidity (1) [level 1 evidence]. WBRT can cause a clinically significant decrease in neurocognitive function (1, 2) and also quality of life (3).

Because of the increased neurotoxicity associated with WBRT, stereotactic radiosurgery (SRS) to the resected cavity has established itself as an effective alternative in the management of brain metastases after surgery. Favorable local control rates have previously been reported (4–6). Nonetheless, it is imperative to understand the factors that affect local control, patterns of failure, and symptomatic radiation-induced injury when considering SRS to the resected cavity. Among these key parameters include: appropriate target delineation (4, 6), cavity volume, margin dose

and isodose selection (7), SRS timing after surgery (7), and radiologic follow-up (4). Furthermore, alongside with the adoption of postoperative SRS for brain metastases during the last decade, alternative strategies have also been developed that could minimize symptomatic radiation-induced injury and leptomeningeal dissemination. These include: multi-fractional postoperative SRS (8, 9) and preoperative SRS (10).

Given the rapidly changing literature and advances associated with the field of brain metastasis treatment, this brief review will provide a global overview of the current paradigms in the postoperative SRS applications, and outline future directions which may improve the outcome for this particular group of patients.

Historical Role of Postoperative Radiation for Brain Metastases

Patchell et al. was among the first to confirm that surgical resection of a single brain metastasis followed by whole brain radiotherapy (WBRT) improved survival when compared to patients who underwent WBRT alone (median survival 40 weeks with resection + WBRT vs. 15 weeks with WBRT alone, $p < 0.01$) (11) [level 1 evidence]. In a separate prospective randomized trial for patients with single brain metastasis, Patchell et al. subsequently found that adjuvant WBRT after resection improved local tumor control and decreased the likelihood of distant brain failure and neurologic death, compared to surgery alone (12). As a result, WBRT became an important therapeutic option in the postoperative management of patients with cerebral metastases.

Some investigators have combined WBRT and SRS postoperatively with the goal of maximizing the tumoricidal dose to the resected cavity (13, 14). For example, Roberge et al. retrospectively reviewed the outcomes of 27 patients treated with WBRT and postoperative SRS (14). Given that only one patient (4%) required surgical intervention for symptomatic radiation necrosis, the authors concluded that WBRT and SRS can be safely combined (14).

The utilization of WBRT has declined during the last decade due to increasing concerns about radiotherapy-related neurologic toxicities leading to cognitive impairment. For example, N0574 enrolled 213 patients with 1–3 brain metastases which were randomized to SRS with or with WBRT (30 Gy in 12 fractions) (15) [level 1 evidence]. The primary endpoint was cognitive function and patients treated with WBRT were 45% more likely to experience cognitive deterioration at 3 months than those treated with SRS alone. Quality of life was higher at 3 months with SRS alone, including overall quality of life and there was no difference in overall survival between the treatment groups (median overall survival 10.4 months SRS alone and 7.4 months SRS plus WBRT). These results confirmed the cognitive impact of WBRT and suggested for patients with 1–3 brain metastases amenable to radiosurgery, SRS alone was the preferred strategy.

More recently, SRS has been utilized in patients with up to 10 brain metastases. Specifically, Yamamoto et al. reported in their series that SRS without WBRT in patients with five to 10 brain metastases conferred non-inferior survival when compared to those patients found to have two to four brain metastases (16).

Emergence of SRS for Resected Brain Metastases

Given the neurotoxicity concerns associated with WBRT, technological improvement has been made over the last 10–15 years for utilizing SRS to the resected cavity. Multiple studies have found 12-month crude local control rates at 70–100% (4, 6, 8, 17–27), although most have been retrospective in nature. Brennan et al. reported the first prospective study on the efficacy of adjuvant SRS in patients with a limited number of brain metastases following surgery (27). Their median follow-up was 12.0 months (range: 1.0–94.1 months). Following surgical resection, 39 patients with 40 lesions were treated with SRS to the surgical bed to a median dose of 18 Gy (median time to SRS was 31 days). Their findings were consistent with a local control rate approximating 85%. Additionally, they found that non-small cell lung cancer (NSCLC) histology, tumor diameter <3 cm, and deep parenchymal tumors were associated with improved local control. Superficial dural/pial involvement and tumor diameter >3 cm were associated with increased local failure. Infratentorial lesions were at significantly increased risks of developing regional failure as opposed to supratentorial lesions.

The importance of larger target volume size (>3 cm) negatively impacting outcomes, as evidenced by Brennan et al.'s findings, has also been corroborated by other investigators as well (27). Jensen et al. reported a series of 106 patients (112 lesions) with no prior WBRT, who were treated using radiosurgery directed to the resected cavity (18). Overall survival at 12 months was 46.8%, and local control at 12 months was 80.3%. Multivariate analysis revealed that preoperative lesion diameters of >3 cm were predictive of increased local failure. Similarly, Hartford et al. reported the outcomes of 47 patients with 49 brain metastases treated with resection and postoperative SRS (26). After a median follow-up of 9.3 months, they found a 12-month local control rate of 85.5%. On univariate analysis, tumor size ≥3 cm was associated with a shorter period of time to local failure. Finally, Jagannathan et al. studied 47 patients who underwent SRS to the postoperative resection cavity following gross-total resection of the tumor (28). The mean volume of the cavity was 10.5 cm^3. Three patients had recurrences within the resection cavity (6%). Increased surgical cavity size was associated with increased risk of local recurrence. Specifically, the volumes of these three patients' resection cavities were: 15.5, 18.4, and 21.1 cm^3, while the mean volume for the rest of cases was 9.9 cm^3 (28).

Degree of symmetrical expansion of the target volume for treatment has also been shown to play a key role in impacting treatment outcome. For example, Soltys et al. studied 72 patients treated from 1998 to 2006 who had SRS delivered to the resection cavity, with a median marginal dose of 18.6 Gy (6). The actuarial rate of local control at 12 months was 79%. Interestingly, improved local control was found in those treatment plans with less conformality. In fact, the conformity index was the only parameter that was significantly associated with improved local control. With this in mind, Choi et al. retrospectively studied

whether adding a margin would affect treatment outcome (4). The addition of a 2-mm margin was correlated with a statistically significant reduction in local failure at 12 months from 16% to 3%, without statistically increasing clinical toxicity profiles.

Surveillance imaging is also important following SRS. In their series, Choi et al. also illustrated the importance of close follow-up and surveillance if SRS was chosen as adjuvant treatment after surgery (4). This is evident by the high rate of distant brain failure found in this series (54% at 12 months), as well as in other clinical series for surgical cavity-based SRS (recurrence rates at 44–72%) (6, 19–21, 28). Therefore, frequent surveillance imaging (typically initial follow up MRI brain 2–3 months after SRS) is strongly recommended (17).

Dose selection for resected cavity SRS has largely been dependent on the size of the postsurgical cavities on thin-slice MRI and planning CT scan. Many of the published series still utilized the SRS dose-escalation algorithm for intact tumors as outlined by the landmark trial, Radiation Therapy Oncology Group (RTOG) 90–05, and extrapolate that to the postsurgical cavity cases (27, 29). As an example, Brennan et al.'s selection of postoperative SRS doses (27) was related to the maximal surgical cavity diameter (msc) as seen from the fusion of the MRI brain and planning CT, which was: (a) 22 Gy for msc:≤2.0 cm; 18 Gy for 2.1–3.0 cm, and 15 Gy for 3.1–4.0 cm. This strategy, of margin dose reduction for large targets, has been similarly applied to the postoperative setting, including in prospective trials, to reduce the volume of normal brain exposed to high doses.

The timeliness of delivering SRS after surgery has also been highlighted by recent published studies (30, 31). For instance, Iorio-Morin et al. found that, on multivariate analysis, one of the risk factors for local recurrence included a longer surgery-to-SRS delay (more than 3 weeks) (7). Their recommendation was that SRS should take place as promptly as possible, with a target date of 3 weeks after surgical resection. These recommendations are consistent with Patel et al. who recently postulated, based on his findings of an increase in the tumor bed cavity size after surgery (32), that delaying postoperative SRS beyond 3 weeks in hopes of significant tumor bed cavity contraction should not be advised. Performing SRS within 2–3 weeks after surgery may be the ideal balance for allowing the patient to recover surgically, without excessive delay in postoperative treatment that could increase the risk of tumor recurrence.

Expert Consensus on Accurate Contour Delineation in Tumor Bed Radiosurgery

Recently, Soliman et al. published their consensus guidelines on accurate contour delineation in tumor bed radiosurgery (33). This is the first study published which comprehensively provides guidelines on design for the appropriate treatment SRS volumes for resected cavity cases. Here, internationally recognized authorities in the field each contoured ten postoperative completely resected cases of diverse clinical scenarios and cases consisted of tumors located in various regions of the brain. The level of agreement was adequate (mean sensitivity and specificity were 0.75 and 0.98, respectively). There were two cases of metastatic disease in the infratentorial compartment where significant differences were detected among the contours, in regard to how generous the clinical target volume (CTV) should be along the bone flap.

This finding led the researchers to propose the following recommendations in regard to CTV design. First, the CTV should completely cover the contrast-enhancing surgical cavity with the use of the T1-weighted gadolinium-enhanced axial MRI scan, excluding any vasogenic edema; second, the CTV should completely encompass the surgical tract visualized on postoperative imaging; third, if preoperatively there was tumor contacting the dura, the CTV should include a 5–10 mm margin along the bone flap that extends beyond the area where there was existing contact before surgery; fourth, if there is no contact that is identified between the tumor and dura, the CTV should include a margin of 1–5 mm where the bone flap is located; finally, if there is any contact pre-operatively with any of the venous sinuses, there should be a 1–5 mm margin applied to the CTV in the area where the sinus is located (33). Hence, the authors concluded that venous sinus/meningeal coverage should be generous in the CTV to prevent failures in these high risk regions. While this study is helpful, it is important to recognize that these recommendations are based on expert opinion and further study is needed.

Complications and Recurrence Patterns Following Postoperative SRS

Radiation necrosis is a known potential complication after SRS and can be difficult to distinguish clinically and radiographically from tumor progression (34). Advanced techniques for distinguishing radiation necrosis from tumor recurrence now include nMR spectroscopy using Choline/N-Acetyl Aspartate and Choline/Creatine ratios and MR perfusion with the use of relative cerebral blood volume (35, 36). Current treatment options include glucocorticoids, hyperbaric oxygen, and surgery, bevacizumab, and focused interstitial laser thermal therapy, with varying degrees of effectiveness (37).

The literature has shown rates of radiographic radiation necrosis in patients treated with SRS (for intact brain metastases) to be as high as 24% (34). Meanwhile, wider ranges of rates of radiation necrosis have been observed after postoperative SRS. These rates of radionecrosis in tumor bed SRS cases have ranged from 1.5 to 18.5% (9, 27, 38–40). As reported by Keller et al., the infratentorial location was predictive of increased radionecrosis (hazard ratio [HR]: 2.97; 95% confidence interval [95% CI]: 1.47–6.01; $p = 0.0025$) (40). The V14Gy (volume of brain receiving 14 Gy) was also associated with the risk of radionecrosis following resected cavity SRS.

Regarding tumor progression, elsewhere intraparenchymal tumor progression remains the predominate location of intracranial failure after SRS for brain metastases. While these recurrence rates are generally similar to patients receiving SRS alone for intact brain metastases, some have postulated that rate of leptomeningeal carcinomatosis is higher with resection of brain metastases and surgical violation of the tumor capsule (30). The overall rate of leptomeningeal disease (LMD) in solid malignancies is estimated in the range of 5–15%, and varies based on several clinical and pathologic features (17, 30, 31, 41),

and LMD rates followed resected cavity SRS have ranged from 8 to 24% (18, 20, 42). Current research has yet to pinpoint whether LMD in the postoperative SRS setting is a manifestation of the tumor's natural history, or if dissemination is secondary to the surgery itself (tumor spill) and whether postoperative SRS may also be indirectly contributing to it (higher incidences of distant tumor progression leading to LMD, etc.) (9). Several series have reported on this topic; for example, Atalar et al. reported a higher rate of LMD in patients with metastatic breast cancer which may be related to tumor biology (43). It has also been shown that piecemeal resections and brain metastases in the infratentorial compartment may lead to increased LMD (17, 20, 44). While tumor histology has clear implications on systemic therapy options and patient survival, there are very limited data to support a differing postoperative radiosurgical management (dose, timing, etc.) based on tumor histology alone.

Alternative Strategies: Fractionated and Preoperative SRS

Single-fraction SRS may have increased side effects, particularly for lesions >3 cm (27), or those located in eloquent regions (45, 46). As a result, hypofractionated SRS is a reasonable alternative to single-fraction SRS in both preserving tumor control and also reducing radionecrosis (**Figure 1**). Steinmann et al. studied 33 patients with single brain metastasis (median volume, 25.6 cc) who underwent surgery followed by hypofractionated SRS (8). A high local control rate of 71% at 1 year was achieved. Similarly, Wang reported a local control of 80% at 6 months with hypofractionated treatments. Meanwhile, Keller et al. published a series of 181 patients treated with a 3-fractionation schedule of 33 Gy to the resected cavity. The 1-year local control rate was 88% (9). Interestingly, on multivariate analysis, tumor contact with the meninges was predictive of increased local failure, which validated the importance of adding generous margin to the CTV in that region as suggested by the consensus guidelines as discussed above (33).

Preoperative SRS is another potential strategy (**Figures 2**, **3**). Recently, Patel et al. published findings from a multi-institutional study retrospectively comparing outcomes in the pre-operative vs. postoperative SRS settings (66 and 114 patients, respectively) (10). With a median follow-up of 24.6 months, no difference was found between groups for overall survival, local recurrence, or distant brain failure. However, surprisingly, postoperative SRS had significantly increased rates of LMD and symptomatic radionecrosis. A follow-up study was subsequently performed comparing outcomes between preoperative SRS and postoperative WBRT (47). A total of 102 patients were analyzed (66 in the pre-SRS group, vs. 36 in the post-op WBRT group), and the authors reported the 12-month overall survival rates were similar between groups, as were 24-month outcomes for local control, distant control, and the presence of LMD. Crude rates of radiation necrosis were 5.6 and 0% for the preoperative SRS and the postoperative WBRT groups, respectively. Future prospective studies should direct their effort to address whether preoperative SRS may be superior to postoperative SRS, and to evaluate the optimal radiation doses, timing between surgery and SRS treatments, and also salvage options for these patients requiring locoregional control for their limited brain metastases (9).

Recent Prospective Studies

In the past year, two randomized prospective trials have been published highlighting the effectiveness of postoperative SRS. Mahajan et al. compared 2 groups: those who underwent SRS (64 patients) vs. those who were observed after gross total tumor resection (68 patients) (48) [level 1 evidence]. Findings revealed that the 12 month freedom from local recurrence was significantly higher in the SRS group (72% in the SRS group vs. 43% in the observation group). In both

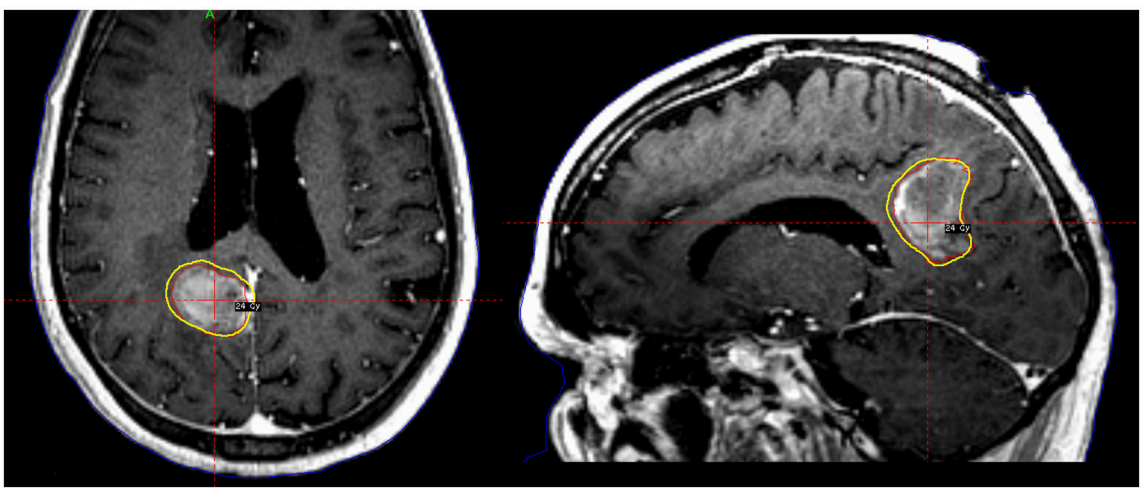


FIGURE 1 | A patient with a large tumor cavity following resection for brain metastasis received postoperative fractionated stereotactic radiosurgery to 24 Gy in 3 fractions.

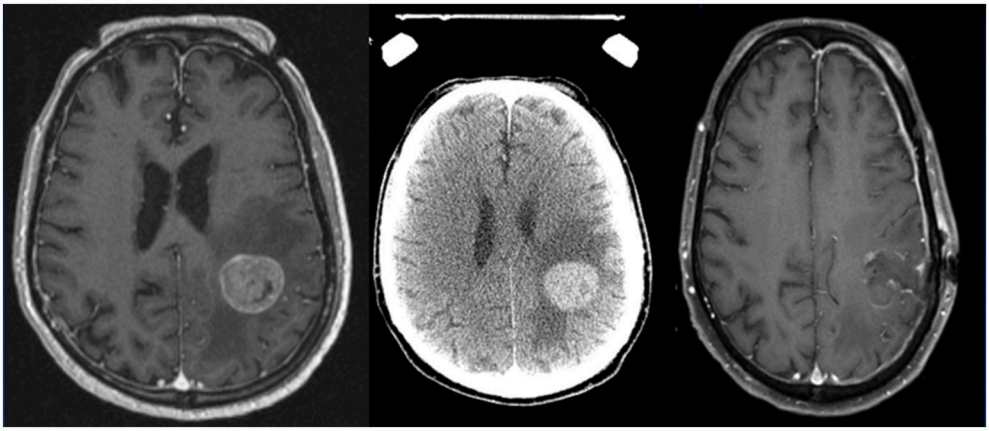


FIGURE 2 | Axial MRI and CT images of a patient with a brain metastases treated with preoperative stereotactic radiosurgery followed by resection days later.

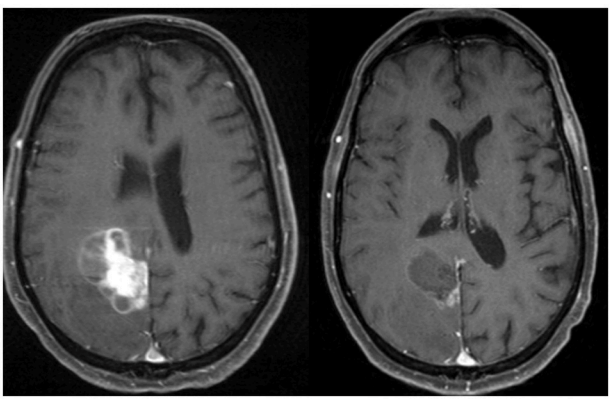


FIGURE 3 | Axial MRI and CT images of a patient with a brain metastases treated with preoperative stereotactic radiosurgery followed by resection days later.

groups, there were no adverse events or deaths attributed to either treatment. This study validated the recommendation for adjuvant radiosurgery even after gross total neurosurgical resection.

In a parallel cooperative group study, Brown et al. enrolled 194 patients randomized between postoperative SRS (98 patients) or WBRT (96 patients) (49). The results showed a greater decline in cognitive function, worse quality of life, and worse functional independence with the use of WBRT as compared to SRS. Although surgical bed control and intracranial control were improved with WBRT, there was no difference in overall survival was observed between the two groups.

The Future of Postoperative Radiosurgery

Postoperative SRS is associated with an acceptable rate of local control by multiple studies, and causes less neurotoxicity when compared to WBRT. As a result, postoperative SRS should be regarded as a standard of care in lieu of WBRT after surgery. Nonetheless, while most patients will still develop distant failure after SRS treatment, the ability of postoperative SRS to spare or delay WBRT is an important advantage and of significant appreciation clinically by the patients who may otherwise require upfront WBRT.

Recent collaborative efforts such as Soliman et al. have been essential in establishing a standard on how to safely and successfully execute radiation contouring treatment design in tumor bed SRS cases (33). However, it is not yet known how to best utilize preoperative tumor extent in postoperative SRS target delineation. Moreover, margin dose selection and contouring techniques should be employed for unusual cases such as those with hemorrhage in the surgical cavity and those with piecemeal resections (33).

It remains to be seen whether prospective studies can show (a) a benefit in local control and/or improved toxicity for hypofractionated tumor bed SRS vs. single fraction tumor bed SRS and (b) whether pre-operative SRS can lead to decreased risks of radiation necrosis and/or LMD vs. postoperative SRS, and studies are underway to analyze these strategies.

In parallel, advancements in systemic therapy's intracranial effectiveness could be leveraged in combination with SRS. For example, we have witnessed the rapid rise in the use of immunotherapy as the first line therapy for many metastatic cancers (lung, melanoma, and renal). Recently, prospective data has emerged which supports the use of immunotherapy alone (without local therapy) for small, asymptomatic brain metastases. Specifically, a phase II study of the PD-1 (anti-programmed cell death protein 1) antibody pembrolizumab in patients with brain metastases from non-small cell lung cancer and melanoma (NCT02085070) was published showing that a durable brain metastasis response was achieved in 22% of patients with melanoma and 33% of patients with NSCLC (50). Toxic effects were consistent with those reported in previous trials of pembrolizumab in these diseases and neurological adverse events associated with drug or disease were infrequent and non-life threatening (50). The results of many prospective studies that combine immunotherapy and SRS are pending, which could inform synergy between these

modalities to improve local, as well as distant, tumor control (51). Intraoperative radiation therapy (IORT) has also been postulated as an alternative technique to improve the results of postoperative SRS, and likewise it may also prove to be a highly efficacious technique when combined with immunotherapy (52).

There are several active areas of research that may serve to redefine the role of radiosurgery in patients with metastatic cancer, not the least of which is immuno-radiosurgery. Recently, there has been a flurry of reports of possible synergy between radiosurgery and various immunomodulatory systemic agents (51, 53). Radiosurgery will, without doubt, play a key role in the management of patients with metastatic disease in the future. As advances in surgical techniques, radiosurgical delivery, and systemic therapies develop, the relative role of these strategies will need to be continually refined.

AUTHOR CONTRIBUTIONS

EM and DT contributed conception and design of the mini-review. EM wrote the first draft of the manuscript. DT contributed the figures enclosed in the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

REFERENCES

1. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* (2009) 10:1037–44. doi: 10.1016/S1470-2045(09)70263-3
2. Trifiletti DM, Lee CC, Schlesinger D, Larner JM, Xu Z, Sheehan JP. Leukoencephalopathy after stereotactic radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* (2015) 93:870–8. doi: 10.1016/j.ijrobp.2015.07.2280
3. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A european organisation for research and treatment of cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol.* (2013) 31:65–72. doi: 10.1200/JCO.2011.41.0639
4. Choi CY, Chang SD, Gibbs IC, Adler JR, Harsh GRt, Lieberson RE, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases: prospective evaluation of target margin on tumor control. *Int J Radiat Oncol Biol Phys.* (2012) 84:336–42. doi: 10.1016/j.ijrobp.2011.12.009
5. Roberge D, Parney I, Brown PD. Radiosurgery to the postoperative surgical cavity: who needs evidence? *Int J Radiat Oncol Biol Phys.* (2012) 83:486–93. doi: 10.1016/j.ijrobp.2011.09.032
6. Soltys SG, Adler JR, Lipani JD, Jackson PS, Choi CY, Puataweepong P, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys.* (2008) 70:187–93. doi: 10.1016/j.ijrobp.2007.06.068
7. Iorio-Morin C, Masson-Cote L, Ezahr Y, Blanchard J, Ebacher A, Mathieu D. Early Gamma Knife stereotactic radiosurgery to the tumor bed of resected brain metastasis for improved local control. *J Neurosurg.* (2014) 121 Suppl:69–74. doi: 10.3171/2014.7.GKS141488
8. Steinmann D, Maertens B, Janssen S, Werner M, Fruhauf J, Nakamura M, et al. Hypofractionated stereotactic radiotherapy (hfSRT) after tumour resection of a single brain metastasis: report of a single-centre individualized treatment approach. *J Cancer Res Clin Oncol.* (2012) 138:1523–9. doi: 10.1007/s00432-012-1227-x
9. Keller A, Dore M, Cebula H, Thillays F, Proust F, Darie I, et al. Hypofractionated stereotactic radiation therapy to the resection bed for intracranial metastases. *Int J Radiat Oncol Biol Phys.* (2017) 99:1179–89. doi: 10.1016/j.ijrobp.2017.08.014
10. Patel KR, Burri SH, Asher AL, Crocker IR, Fraser RW, Zhang C, et al. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: a multi-institutional analysis. *Neurosurgery* (2016) 79:279–85. doi: 10.1227/NEU.0000000000001096
11. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* (1990) 322:494–500. doi: 10.1056/NEJM199002223220802
12. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* (1998) 280:1485–9. doi: 10.1001/jama.280.17.1485
13. Luther N, Kondziolka D, Kano H, Mousavi SH, Engh JA, Niranjan A, et al. Predicting tumor control after resection bed radiosurgery of brain metastases. *Neurosurgery* (2013) 73:1001–6. discussion: 6. doi: 10.1227/NEU.0000000000000148
14. Roberge D, Petrecca K, El Refae M, Souhami L. Whole-brain radiotherapy and tumor bed radiosurgery following resection of solitary brain metastases. *J Neuro-Oncol.* (2009) 95:95–9. doi: 10.1007/s11060-009-9899-z
15. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs. radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi: 10.1001/jama.2016.9839
16. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol.* (2014) 15:387–95. doi: 10.1016/S1470-2045(14)70061-0
17. Ojerholm E, Lee JY, Thawani JP, Miller D, O'Rourke DM, Dorsey JF, et al. Stereotactic radiosurgery to the resection bed for intracranial metastases and risk of leptomeningeal carcinomatosis. *J. Neurosurg.* (2014) 121(Suppl.):75–83. doi: 10.3171/2014.6.GKS14708
18. Jensen CA, Chan MD, McCoy TP, Bourland JD, deGuzman AF, Ellis TL, et al. Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis. *J. Neurosurg.* (2011) 114:1585–91. doi: 10.3171/2010.11.JNS10939
19. Karlovits BJ, Quigley MR, Karlovits SM, Miller L, Johnson M, Gayou O, et al. Stereotactic radiosurgery boost to the resection bed for oligometastatic brain disease: challenging the tradition of adjuvant whole-brain radiotherapy. *Neurosurg Focus.* (2009) 27:E7. doi: 10.3171/2009.9.FOCUS09191
20. Iwai Y, Yamanaka K, Yasui T. Boost radiosurgery for treatment of brain metastases after surgical resections. *Surg Neurol.* (2008) 69:181–6. discussion: 186. doi: 10.1016/j.surneu.2007.07.008
21. Do L, Pezner R, Radany E, Liu A, Staud C, Badie B. Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastases. *Int J Radiat Oncol Biol Phys.* (2009) 73:486–91. doi: 10.1016/j.ijrobp.2008.04.070
22. Quigley MR, Fuhrer R, Karlovits S, Karlovits B, Johnson M. Single session stereotactic radiosurgery boost to the post-operative site in lieu of whole brain radiation in metastatic brain disease. *J Neuro-Oncol.* (2008) 87:327–32. doi: 10.1007/s11060-007-9515-z
23. Prabhu R, Shu HK, Hadjipanayis C, Dhabaan A, Hall W, Raore B, et al. Current dosing paradigm for stereotactic radiosurgery alone after surgical resection of brain metastases needs to be optimized for improved local control. *Int J Radiat Oncol Biol Phys.* (2012) 83:e61–6. doi: 10.1016/j.ijrobp.2011.12.017
24. Ogiwara H, Kalakota K, Rakhra SS, Helenowski IB, Marymont MH, Kalapurakal JA, et al. Intracranial relapse rates and patterns, and survival trends following post-resection cavity radiosurgery for patients with single intracranial metastases. *J Neuro-Oncol.* (2012) 108:141–6. doi: 10.1007/s11060-012-0808-5
25. Minniti G, Esposito V, Clarke E, Scaringi C, Lanzetta G, Salvati M, et al. Multidose stereotactic radiosurgery (9 Gy x 3) of the postoperative resection

cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys.* (2013) 86:623–9. doi: 10.1016/j.ijrobp.2013.03.037
26. Hartford AC, Paravati AJ, Spire WJ, Li Z, Jarvis LA, Fadul CE, et al. Postoperative stereotactic radiosurgery without whole-brain radiation therapy for brain metastases: potential role of preoperative tumor size. *Int J Radiat Oncol Biol Phys.* (2013) 85:650–5. doi: 10.1016/j.ijrobp.2012.05.027
27. Brennan C, Yang TJ, Hilden P, Zhang Z, Chan K, Yamada Y, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. *Int J Radiat Oncol Biol Phys.* (2014) 88:130–6. doi: 10.1016/j.ijrobp.2013.09.051
28. Jagannathan J, Yen CP, Ray DK, Schlesinger D, Oskouian RJ, Pouratian N, et al. Gamma Knife radiosurgery to the surgical cavity following resection of brain metastases. *J Neurosurg.* (2009) 111:431–8. doi: 10.3171/2008.11.JNS08818
29. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys.* (2000) 47:291–8. doi: 10.1016/S0360-3016(99)00507-6
30. Mahajan A, Borden J, Tsai JS. Carcinomatous meningitis: are surgeryand gamma knife radiosurgery treatment risk factors? *J Neurosurg.* (2002) 97(5 Suppl):441–4. doi: 10.3171/jns.2002.97.supplement
31. Trifiletti DM, Romano KD, Xu Z, Reardon KA, Sheehan J. Leptomeningeal disease following stereotactic radiosurgery for brain metastases from breast cancer. *J Neuro-Oncol.* (2015) 124:421–7. doi: 10.1007/s11060-015-1854-6
32. Patel RA, Lock D, Helenowski IB, Chandler JP, Sachdev S, Tate MC, et al. Postsurgical cavity evolution after brain metastasis resection: how soon should postoperative radiosurgery follow? *World Neurosurg.* (2018) 110:e310–4. doi: 10.1016/j.wneu.2017.10.159
33. Soliman H, Ruschin M, Angelov L, Brown PD, Chiang VLS, Kirkpatrick JP, et al. Consensus contouring guidelines for postoperative completely resected cavity stereotactic radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* (2018) 100:436–42. doi: 10.1016/j.ijrobp.2017.09.047
34. Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol* (2011) 6:48. doi: 10.1186/1748-717X-6-48
35. Chuang MT, Liu YS, Tsai YS, Chen YC, Wang CK. Differentiating radiation-induced necrosis from recurrent brain tumor using MR perfusion and spectroscopy: a meta-analysis. *PLoS ONE* (2016) 11:e0141438. doi: 10.1371/journal.pone.0141438
36. Barajas RF, Chang JS, Sneed PK, Segal MR, McDermott MW, Cha S. Distinguishing recurrent intra-axial metastatic tumor from radiation necrosis following gamma knife radiosurgery using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *Am J Neuroradiol.* (2009) 30:367–72. doi: 10.3174/ajnr.A1362
37. Chao ST, Ahluwalia MS, Barnett GH, Stevens GH, Murphy ES, Stockham AL, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys.* (2013) 87:449–57. doi: 10.1016/j.ijrobp.2013.05.015
38. Ahmed KA, Freilich JM, Abuodeh Y, Figura N, Patel N, Sarangkasiri S, et al. Fractionated stereotactic radiotherapy to the post-operative cavity for radioresistant and radiosensitive brain metastases. *J Neuro-Oncol.* (2014) 118:179–86. doi: 10.1007/s11060-014-1417-2
39. Dore M, Martin S, Delpon G, Clement K, Campion L, Thillays F. Stereotactic radiotherapy following surgery for brain metastasis: predictive factors for local control and radionecrosis. *Cancer Radiother.* (2017) 21:4–9. doi: 10.1016/j.canrad.2016.06.010
40. Keller A, Dore M, Antoni D, Menoux I, Thillays F, Clavier JB, et al. [Risk of radionecrosis after hypofractionated stereotactic radiotherapy targeting the postoperative resection cavity of brain metastases]. *Cancer Radiother.* (2017) 21:377–88. doi: 10.1016/j.canrad.2017.01.017
41. Taillibert S, Laigle-Donadey F, Chodkiewicz C, Sanson M, Hoang-Xuan K, Delattre JY. Leptomeningeal metastases from solid malignancy: a review. *J Neuro-Oncol.* (2005) 75:85–99. doi: 10.1007/s11060-004-8101-x
42. Robbins JR, Ryu S, Kalkanis S, Cogan C, Rock J, Movsas B, et al. Radiosurgery to the surgical cavity as adjuvant therapy for resected brain metastasis. *Neurosurgery* (2012) 71:937–43. doi: 10.1227/NEU.0b013e31826909f2
43. Atalar B, Modlin LA, Choi CY, Adler JR, Gibbs IC, Chang SD, et al. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys.* (2013) 87:713–8. doi: 10.1016/j.ijrobp.2013.07.034
44. Suki D, Abouassi H, Patel AJ, Sawaya R, Weinberg JS, Groves MD. Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. *J Neurosurg.* (2008) 108:248–57. doi: 10.3171/JNS/2008/108/2/0248
45. Trifiletti DM, Lee CC, Kano H, Cohen J, Janopaul-Naylor J, Alonso-Basanta M, et al. Stereotactic radiosurgery for brainstem metastases: an international cooperative study to define response and toxicity. *Int J Radiat Oncol Biol Phys.* (2016) 96:280–8. doi: 10.1016/j.ijrobp.2016.06.009
46. Trifiletti DM, Lee CC, Shah N, Patel NV, Chen SC, Sheehan JP. How does brainstem involvement affect prognosis in patients with limited brain metastases? results of a matched-cohort analysis. *World Neurosurg.* (2015) 88:563–8. doi: 10.1016/j.wneu.2015.10.089
47. Patel KR, Burri SH, Boselli D, Symanowski JT, Asher AL, Sumrall A, et al. Comparing pre-operative stereotactic radiosurgery (SRS) to post-operative whole brain radiation therapy (WBRT) for resectable brain metastases: a multi-institutional analysis. *J Neuro-Oncol.* (2017) 131:611–8. doi: 10.1007/s11060-016-2334-3
48. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1040–8. doi: 10.1016/S1470-2045(17)30414-X
49. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1049–60. doi: 10.1016/S1470-2045(17)30441-2
50. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol.* (2016) 17:976–83. doi: 10.1016/S1470-2045(16)30053-5
51. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol.* (2016) 13:516–24. doi: 10.1038/nrclinonc.2016.30
52. Herskind C, Wenz F, Giordano FA. Immunotherapy combined with large fractions of radiotherapy: stereotactic radiosurgery for brain metastases-implications for intraoperative radiotherapy after resection. *Front Oncol.* (2017) 7:147. doi: 10.3389/fonc.2017.00147
53. Kiess AP, Wolchok JD, Barker CA, Postow MA, Tabar V, Huse JT, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. *Int J Radiat Oncol Biol Phys.* (2015). 2:368–75. doi: 10.1016/j.ijrobp.2015.01.004

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Marchan, Peterson, Sio, Chaichana, Harrell, Ruiz-Garcia, Mahajan, Brown and Trifiletti. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 02 October 2018
doi: 10.3389/fonc.2018.00379

Hypofractionated Radiation Therapy for Large Brain Metastases

*Giuseppina Laura Masucci**

Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada

Single fraction radiosurgery (SRS) treatment is an effective and recognized alternative to whole brain radiation for brain metastasis. However, SRS is not always possible, especially in tumors of a larger diameter where the administration of high dose in a single fraction is limited by the possibility of acute and late side effects and the dose to the surrounding organs at risk. Hypofractionated radiation therapy allows the delivery of high doses of radiation per fraction while minimizing adverse events, all the while maintaining good local control of lesions. The optimal dose fractionation has however not been established. This overwiew presents available evidence and rationale supporting usage of hypofractionated radiation therapy in the treatment of large brain metastases.

Keywords: large brain metastasis, hypofractionation, stereotactic radiotherapy, radiosurgery, brain metastasis

OPEN ACCESS

Edited by:
Arjun Sahgal,
University of Toronto, Canada

Reviewed by:
Riccardo Soffietti,
Università degli Studi di Torino, Italy
David M. Peereboom,
Cleveland Clinic Lerner College of Medicine, United States

***Correspondence:**
Giuseppina Laura Masucci
g.laura.masucci.chum@ssss.gouv.qc.ca

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *02 June 2018*
Accepted: *23 August 2018*
Published: *02 October 2018*

Citation:
Masucci GL (2018) Hypofractionated Radiation Therapy for Large Brain Metastases. Front. Oncol. 8:379. doi: 10.3389/fonc.2018.00379

Brain metastases (BM) are a common occurrence in oncologic patients (1). Large BM can be defined according to their diameter or volume, with lesions measuring either ≥2 or ≥3 cm in diameter or ≥ 4 cm^3 (2–8) being considered in this category. The optimal treatment for these tumors has not yet been established. The combination of surgery with post operative radiation either to the cavity or to the whole brain (WBRT), SRS alone or hypofractionated radiation therapy (HFRT) have been proposed to address these tumors (3–16) However, local control (LC) rates of large brain metastasis are known to be inferior to those of smaller dimension (4, 5, 14–20). When possible, surgery, with post operative radiation, should be considered (21) to decrease mass effect, alleviate neurological symptoms and facilitate management. For patients with large brain metastasis unable to undergo surgical resection, WBRT has been considered to be the standard of care. However, WBRT is associated with a poor local control for lesions of larger diameter (22). Nieder et al. (22) analyzed the efficacy of WBRT in controlling 336 brain metastasis in 108 patients. Local failure was estimated to be 48% in tumors measuring <0.5 cm^3; however, all lesions measuring >10 cm^3 recurred. Complete response was observed only in tumors measuring <6.4 cm^3 although partial response was seen in large or necrotic metastases.

Radiosurgery (SRS) is increasingly becoming the preferred treatment for BM, not only for its efficacy in providing good local control, but also for its limited long term toxicity profile, especially regarding neurocognitive function when compared to whole brain radiation therapy (WBRT) (10, 23, 24). Moreover, the usage of SRS alone has not been linked to a decrease in OS (25). SRS alone is an effective treatment for smaller metastases. However, as tumor size increases, the dose that can be administered safely, without any neurological toxicity, decreases (26). In the dose escalation study RTOG 90-05 (27), lesions measuring ≤2, 2.1–3, and 3.1–4 cm were treated by radiosurgery with doses of 24, 18, and 15 Gy, respectively. By using this fractionation scheme, Vogelbaum et al. (20) reported that, while treatment with radiosurgery achieved only a LC of 49 and 45% in lesions measuring 2.1–3 cm in diameter and 3.1–4 cm, lesions measuring ≤2 cm achieved a LC of more than 85% when treated with a dose of 24 Gy. The same conclusions were made by Elliott et al. (28) and Schoeggl et al. (29) where the treatment of lesions measuring >10 and >17 mm, respectively

by radiosurgery had more local failure. Petrovich et al. (30) concluded that 1 year LC of lesions <3 cc was greater (90%) when compared to that of lesions >3 cc (78%). Ebner et al. (15) concluded that lesions measuring ≥3 cm had a worse LC at 1 year (68%) then lesions <3 cm (86%). It has been speculated that better LC could possibly be achieved with a higher prescribed dose (18, 20, 24, 31). However, the administration of greater doses of radiation in one single fraction to a large volume is limited by the possibility of acute and late side effects and the dose to surrounding organs (OAR), for example the brainstem or optic nerves (32–34).

OUTCOMES WITH HYPOFRACTIONATION FOR LARGE METASTASIS

In an attempt to increase the biologically equivalent dose (BED) administered to BM and possibly LC while minimizing the risk of radiation induced toxicity, the administration of large doses of radiation in a few fractions (typically 2–6) has been studied (7, 12, 13, 16). Although this alternative to radiosurgery requires the patient to undergo multiple days of treatment, it has been associated with a median OS of 7–17 months and a 1 year LC of 64 to 100%. (3, 6, 7, 12, 13, 16, 35–42). In a review of 448 patients treated in eight series, it was concluded that HFRT can safely be administered in patients with lesions measuring >1 cm; furthermore, for tumors with a diameter >2 cm, HFRT seemed preferable to SRS, with LC of 68.2–93% and a low rate of radionecrosis of 3.1% (43).

Multiple studies have looked at the outcomes of patients treated with HFRT (**Table 1**). A prospective phase II study (36) evaluated the efficacy of HFRT in patients not amenable to SRS. Patients with lesions with a volume of >3 cc or located in eloquent area were considered. Median diameter of lesions treated was 2.27 cm. Seventy-two patients received 5 treatments of 6 Gy if WBRT was given or 5X 7 Gy in patients treated singlehandedly with HFRT. Complete response was seen in 66% of patients, possibly because of the median gross tumor volume (GTV volume) measured at 6 cc (0.29–65.57). Local control was deemed to be over 70% 1 year after treatment. Size of the treated volume was associated with a 7 months disease specific survival (DDSS) of 81% for tumors < 6 cc vs. 53% for lesions ≥ 6 cc). Inoue et al. (40) looked at 88 patients treated with large BM measuring ≥10 cm^3 (10–74.6 cm^3). Tumors measuring 10–19.9 cm^3 received 27–30 gy in three fractions (fx); the majority received 31–35 Gy in 5 fx for lesions 20–29.9 cm^3 and 35–42 Gy in 8–10 fx was administered to those measuring ≥ 30 cm^3. Median single dose equivalent of the maximum dose was 46–48 Gy. LC was seen in 90.2% of patients with no difference in LC, regardless of the volume treated. A study by Rajakesari et al. (41). retrospectively reviewed the outcomes of 112 patients treated with HFRT (87% received a dose of 25 Gy in 5 fx), 70 of which had brain metastasis measuring >3 cm. With a median follow up of 13.5 months, 1 year LC was 56%. Navarria et al. (7) treated 102 patients with HFRT. In this study, 27 Gy in 3 daily fx was administered to 51 brain metastasis measuring 2.1–3 cm; lesions of 3.1–5 c in diameter received 32 Gy in 4 daily fx. The fractionation was chosen to provide a biologically equivalent dose ($BEDGY_{10}$) > 50 Gy. With these fractionation schemes, lesions, irrespective of the dose administered, had a 1 year LC of 96%.

Srs vs. Hypofx

Feuvret et al. (16) published the outcomes of 36 patients treated for solitary BM larger than 3 cm in diameter (median diameter 3.7 cm), with either radiosurgery or HFRT. Patients in this case series received either 14 Gy in one fraction or 3 fractions of 7.7 Gy. One year LC rates differed between the two cohorts, with 100% of lesions treated with HFRT being controlled vs. 58% in patients treated with SRS. Moreover, no cases of radionecrosis were reported. Minniti et al. (12) confirmed these results in a retrospective study of patients treated with BM measuring >2 cm. A HFRT treatment of 27 Gy in 3 fx was compared to a SRS in which tumors measuring 2–3 cm received 18 Gy and lesions measuring ≥3 cm 15–16 Gy. One year LC rates were statistically different between the two groups, with 90% of patients treated with HFRT vs. 77% of patients treated with SRS attaining LC at 1 year (12).

FACTORS INFLUENCING LOCAL CONTROL AND OVERALL SURVIVAL AFTER HFRT FOR LARGE METASTASES

Multiples prognostic factors have been analyzed to assess OS and LC of brain metastases treated with HFRT (**Table 2**). However, none of the studied factors were predictive of OS or LC by all authors. Patient overall well-being, identified with the Karnofsky Performance Score (KPS) as well as the patient's recursive partitioning analysis (RPA) score seem to be predictive of overall survival in a number of studies (3, 7, 12, 13, 36–38). Local control seems to be influenced by the dose administered and the size of the treated tumor, albeit not by all.

MULTIPLE STAGES STEREOTACTIC RADIOSURGERY

A possible alternative to single fraction SRS and hypofractionation for large brain metastasis is a planned multiple treatment radiosurgery over two or more sessions separated by weeks or months (3, 35, 39, 42). Higuchi et al. (39) published in 2009, a study involving 43 patients treated for BM measuring ≥10 cm^3 with 30 Gy delivered in 3 fx every 2 weeks. After delivery of 10 and 20 Gy, a reduction in volume of 18.8% and almost 40%, respectively, was noted in more than 90% of tumors. A 12 months LC of 75.9% was reported. Yomo and Hayashi (42) used a two stage treatment with radiation administered every 3–4 weeks. Fifty-eight BM with a volume of >10 cc were treated with a total of 20–30 Gy. One year LC of 64% was observed. Angelov et al. (3) reported results from 54 patients treated for 63 BM ≥2 cm in diameter with a total dose of 24–33 Gy (median 30 Gy) ($BEDGy_{10}$: 44–73; median 62.5 Gy) in 2–3 fx to the target. Time between the first and second treatment was 1 month. Tumors were usually replanned before each treatment and volumes redefined. Analogous to the results

TABLE 1 | Selected series of patients treated with HFRT.

	No of Pts/BM	Volume (cm^3) diameter (cm) (median)	Median dose [prescribed isodose (%)]	$BEDGy_{10}$	Median 1 year overall survival (OS) (months) (%)	1 year local control (LC) (%)	Radionecrosis (%)
Feuvret et al. (16)	12 pts	29.4 c cm^3 4.4 cm	3X7.7Gy to PTV	39.4	504 days	100%	None
Fokas et al. (38)	102 pts	Gr 1: 2.04 cm^3 Gr 2: 5.93 cm^3	Gr.1($n = 61$): 7X5gy Gr 2 ($n = 61$): 10X4Gy	Gr 1: 52.5 Gr 2: 56	Gr 1: 7 mo Gr 2: 10 mo	Gr 1: 75% Gr 2: 71%	1 patient in Gr 1
Inoue et al. (40)	88 pts/ 92 BM	16.2 c cm^3	Gr 1: 10–19.9 cm^3: 27–30 Gy in 3 fx Gr 2: 20–29.0 cm^3: 31–35 Gy in 5 fx Gr 3: >30 cm^3: 35–42 Gy in 8–10 fx (55–57%)	Gr 1: 51.3–60 Gr 2: 50.2–59.5 Gr 3: 50.7–59.6	9 mo	Marginal recurrences: GR 1: 7% Gr 2: 11% Gr 3: 0%	
Jiang et al. (13)	40 pts	17.5 cm^3 4.1 cm	40 gy (20–53) in 10 fx (4–15) isodose: 90% + boost 20 gy (10–35) in 4 fx (2–10) in 23 patients 1–3 months after tx	56 + 30	15 mo 55.3%	94%	None
Minniti et al. (12)	138 pts	12.5 cm^3	27 Gy in 3 fx (80–90%)	51.3	13.4 months 56%	90% (for lesions ≥3 cm 73%)	9% for HFRT 14% for lesions >3 cm
Navarria et al. (7)	102 pts 51 Gr 1 51 Gr 2	16.3 cm^3 2.9 cm	Gr 1: diameter 2.1–3 cm: 27 Gy in 3 fx Gr 2: diameter 3.1–5 cm: 32 Gy in 4 fx (80%)	Gr 1: 51.3 Gr 2: 57.6	14 mo 69% Gr 1: 14 mo 60% Gr 2:14 mo 80%	96% Gr 1: 100% Gr 2:91%	5.8%
Murai et al. (6)	54 pts/ 61 BM	≥2.5 cm	diameter 2.5–3 cm: 3 fx diameter ≥4 cm: 5 fx Gr 1: 18–22 Gy in 3 fx 21–25 Gy in 5 fx Gr 2: 22–27 Gy in 3 fx 25–31 Gy in 5 fx Gr 3: 27–30 Gy in 3 fx 31–35 Gy in 5 fx	Gr 1: 28.8–39.4 29.8–37.5 Gr 2: 39–51.3 37.5–50.2 Gr 3: 51.3–60 50.2–59.5	31%	69% Gr1: 66% Gr 2: 65% Gr 3: 68%	None
Rajakesari et al. (41)	70 pts	1.7 cm	25 Gy in 5 fx (90–95%)	37.5	10.7 mo	56%	4.3%
Fahrig et al. (37)	150 pts/ 228 BM Gr 1: 72 Gr 2: 59 GR 3: 97	6.1 cm^3	Gr 1: 5X 6–7Gy Gr 2: 10 X 4 Gy Gr 3: 7X 5Gy (90%)	Gr 1: 48–59.5 Gy Gr 2: 56 Gy GR 3: 52.5 Gy	16 mo 83% Gr 2 and Gr 3: 17 mo Gr 1: 11 mo	Gr 1: 87% Gr 2: 95% GR 3: 96%	1.3%
Aoyama et al. (44)	87 pts/ 159 BM		35 Gy in 4 fx	62.9	8.7 mo	81%	
Ernst-Stecken et al. (36)	51 pts/ 72 BM	2.27 cm 6 cm^3	Gr 1: If WBRT prior: 5X 6Gy Gr 2: no WBRT: 5X 7Gy (90%)	Gr 1: 58 Gr2: 59.5	11 mo	76%	2%

(Continued)

TABLE 1 | Continued

	No of Pts/BM	Volume (cm^3) diameter (cm) (median)	Median dose [prescribed isodose (%)]	$BEDGy_{10}$	Median 1 year overall survival (OS) (months) (%)	1 year local control (LC) (%)	Radionecrosis (%)
MULTIPLE STAGE RADIOSURGERY SERIES							
Higuchi et al. (39)	43 pts	17.8 cm^3	10 Gy in 3 fx, 2 weeks apart	60	8.8 mo 76.2%	75.9%	None
Yomo and Hayashi (42)	58 pts	16.4 cm^3	20–30 Gy in 2 fx; 3–4 weeks apart (45%)	40–75	11.8 mo 47%	64%	None
Angelov et al. (3)	54 pts/ 63 BM	10.54 cm^3 3.3 cm	30 Gy in 2 fx 1 months apart (54%)	75	10.8 49%	88% (@ 6 mo)	3.17%
Dohm et al. (35)	33 pts/ 39 BM	11.68 cm^3	15 Gy in 1 fx followed a month later by 14 Gy in 1 fx (50%)	37.5–33.6	60%	87%	10.2%

published by Higuchi, they noted a median decrease in tumor volume of 17%; 90% of the lesions showed no progression with 67% of lesions showing a decrease in volume of ≥30 and 24% remaining stable. At 6 months follow up, LC was 88%. Dohm et al. (35) reported the results of 33 patients treated for 39 lesions in 2 treatments separated by 4 weeks. A median dose of 15 Gy (10–21 Gy) and 14 Gy (10–18 Gy) were administered on first and second treatment, respectively. One year local failure was 13%. Median volume reduction after first treatment was 32.6% and was observed in 33 tumors.

DOSE TO TARGET VOLUMES AND ORGANS AT RISK (OAR)

In the treatment of BM with a single radiosurgery treatment, most radiation oncologists will prescribe doses in keeping with RTOG 90-05 (26); larger brain metastases, with a diameter of 3–4 cm, would therefore receive a single dose of 15 Gy. However, for these tumors, LC rates at 12 months are suboptimal, ranging from 37 to 62% (18, 26, 27). Vogelbaum et al. (20) published results from more than 200 patients that received radiosurgery in a single fraction. Although the results were similar to the ones previously stated, LC was deemed to be 45–49% when lesions received 15–18 Gy, but increased to 85% when 24 Gy was administered. However, doses of 24 Gy have been associated with a higher risk of CNS toxicity, of which the most feared is radionecrosis (26).

One of the advantages of hypofractionation is the delivery of a higher BED while minimizing the risk of side effects to the surrounding OAR. Nevertheless, the optimal dose to administer is not known. In the literature, multiple fractionation schemes have been studied (**Table 1**). Most use a minimum of 4 Gy and a maximum of 10 Gy per fraction. A total $BEDGy_{10}$ of at least 50 Gy seems to provide better local control (38). Marcrom et al. (45) compared a dose of 25 Gy in 5 fx to 30 Gy in 5 fx in 72 patients treated for 182 BM measuring up to 5.5 cm (39 cc); 36 lesions being ≥3 cm in diameter. A total dose of 30 Gy was associated with a better LC 1 year after treatment (72 vs. 40% for lesions receiving 25 Gy). Fahrig et al. (37) assessed three different doses to BM with a maximal diameter >3 cm. Patients received either 5 fx of 6–7 Gy (total: 30–35 Gy) in group 1, 10 fx of 4 Gy (total 40 Gy) in group 2 or 7 fx of 5 Gy (total 35 Gy) in group 3. Of these three regiments, the last two seemed to provide better 1 year LC and median OS when compared to group 1. This difference in OS between the three groups could possibly be explained by the fact that there were significantly less patients with RPA class I in group 1. CNS toxicity was deemed to be lesser for patients in group 2. On the other hand, a dose escalation study administering doses ranging from 18–22 Gy in 3 fx to 31–35 Gy in 5 fx did not demonstrate any difference in local control or overall survival in patients (6).

Dose to OAR

Although the optimal doses to be administered to the brain metastasis are not known, dose constraints to be applied to nearby critical organs (OAR) are less controversial. Maximum doses have been limited to 21–25 Gy in 5 fx or 15–18 Gy in 3 fx (40, 45, 46) for the optical apparatus and to 31 Gy in 5 fx or 23 Gy in 3 fx for the brainstem (45, 46). Other possible dose limits that have been described for the brainstem are D1% (dose administered to 1% of the volume) ≤20 Gy or V26Gy (volume of the brainstem receiving 26 Gy) <1 cc, D1% ≤15 Gy or V20Gy (volume receiving 20 Gy) <0.2 cc for the optical nerves and D1% <1 Gy for the lenses (7, 45). Maintaining a V14Gy < 3 cm^3 for the brain parenchyma and <1 cm^3 for critical areas such as motor cortex, basal ganglia or thalamus has been described (40).

POST OPERATIVE TREATMENT OF LARGE CAVITIES

Cyst Aspiration

Tumor size can influence the local control of brain metastases and overall survival of patients as stated above. It can therefore be of interest to reduce their volume prior to radiation treatment,

TABLE 2 | Selected series with factors influencing OS and local control in patient treated with HFRT.

	Overall survival		Local control	
	SS	**NS**	**SS**	**NS**
Ebner et al. (15)	**UVA:** • Age (<65 years) • Controlled primary **MVA:** • Age <65 years	**Size:** • <3.0 cm vs. ≥3 cm		**UVA:** • Gender • Age ≥65 • Histology • Surgical resection status • Dose (≤16 vs. >16 Gy) • Tumor size: 3–4 cm vs. ≥4 cm
Inoue et al. (40)	Lower survival for lesions ≥ 30 cm^3			**On UVA and MVA:** • Age • Gender • Tumor location within brain • Tumor volume • Number of fraction of RT • V14 • Tumor size: 10–19.9 cm^3 vs. 20–29.9 cm^3 vs. ≥ 30 cm^3
Fokas et al. (38)	**UVA:** • Chemotherapy status (yes vs. no) • RPA class: I vs. II-III • Single BM (vs. multiple BM) • Presence of extracerebral disease **MVA**: RPA class I	• Surgical resection status • Age • Gender	Dose administered (srs vs. 7X 5gy vs. 10X 4gy)	
Jiang et al. (13)	• Controlled primary tumor • KPS≥ 80	• Gender • Age • Number of brain mets • presence of extracranial disease • RPA class		• Gender • Age • number of brain mets • presence of extracranial metastasis • KPS • RPA class
Minniti et al. (12)	**MVA:** • Extracranial disease (stable) • Histology: breast cancer (better) • KPS >70		Histology: melanoma worse local control	• No other actors were predictive of local failure; • Tumor size > 3 cm was of borderline significance
Navarria et al. (7)	**UVA and MVA:** • KPS • Extracranial disease (stable)		**UVA and MVA:** • Gender • Age • KPS • Histology • Presence of extracranial disease • RPA-GPA class • Tumor size	
Yomo and Hayashi (42)	• Extracranial disease (stable) • Interval from cancer diagnosis to RT treatment (< 12 vs. > 12 months) • Single vs. multiple BM	• Age (≤65 vs. >65) • KPS ≥90		
Fahrig et al. (37)	**MVA:** • RPA class	**MVA:** • RT dose (5 X 7Gy vs. 10X 4Gy vs. 7 X5gy)	Trend for better LC for lesions treated with 5X6-7Gy and 7X5Gy vs. 10X4Gy	

(Continued)

TABLE 2 | Continued

	Overall survival		Local control	
	SS	**NS**	**SS**	**NS**
Ernst-Stecken et al. (36)	• Tumor size • KPS • Number of metastases (1 vs. >1)	• Extracranial disease • Age (≤65 vs. >65) • Gender		
Angelov et al. (3)	**UVA:** • Interval from cancer diagnosis to RT treatment (< 12 vs. > 12 months) • KPS (<70) • Number of lesions <2 cm • Greater volume of tumor present at second hypofx treatment (≤3.5 vs. >3.5 cm^3) **MVA**: • KPS • Number of lesions <2 cm • greater volume of tumor present at second hypofx treatment (≤3.5 vs. >3.5 cm^3)		**UVA:** • Volume change between first and second hypofx treatment • KPS **MVA:** • Volume change between first and second hypofx treatment	

SS, statistically significant; NS, non-statistically significant; RPA, recursive partitioning analysis; KPS, Karnofsky Performance Score; GPA, graded prognostic assessment; UVA, univariate analysis; MVA, multivariate analysis; BM, brain metastasis.

permitting the administration of a higher radiation dose. An option for size reduction of cystic lesions is cyst aspiration, where a substantial decrease in tumor volume has been reported (47–50) (50.8–77.9%). This could potentially allow for treatment with a higher radiation dose (48). By combining this method to adjuvant radiation, better local control can be obtained, ranging from 45.8 to 63% (47–50). The latter also allows for the relief of acute symptoms related to mass effect (51, 52).

Surgical Resection

As previously mentioned, surgery should be considered for the treatment of large brain metastases. Post operatively, cavities can easily have a diameter > 3–4 cm, rendering a radiosurgery treatment difficult. Larger cavities are thus usually treated with a hypofractionated treatment with doses ranging from 24 Gy in 3 fractions to 36 Gy in 6 fractions (53–56). Most studies published have used a planning tumor volume (PTV) of 2–3 mm (57–59). With most failures occurring within the surgical cavities (60), a PTV margin of 2–3 mm seems to be sufficient.

The treatment of surgical cavities with fractionated radiation confers good local control, ranging from 77 to 93% (2, 12, 54, 61, 62) in the literature. Moreover, local control of larger cavities does not appear to be associated with the number of fractions or dose used (63). Histology of the primary, does not seem to influence recurrence, with similar local control for radiosensitive (i.e., breast and lung up to 94%) and radioresistant tumors [up to 90% i.e., melanoma, renal cell carcinoma (2, 12)] reported. Median survival after surgery and hypofractionated radiation treatment to cavities of large metastasis is 5.5–17 months (2, 11, 12, 60, 61, 64). A possible advantage of WBRT over HFRT in the post operative setting is the risk of leptomeningeal disease. The rate of leptomeningeal spread to meninges and cerebrospinal fluid in patients treated with WBRT is 5–12% (65, 66) vs. 14–28% (66, 67).

ADVERSE EFFECTS

In the setting of hypofractionation, the rate of radiation necrosis has been estimated to be up to 10–15% (3, 6, 7, 11, 12, 16, 35–42). Authors have tried to determine dosimetric parameters and tumor characteristics that could possibly predict the risk of radionecrosis and severe CNS toxicity. In series comparing the usage of SRS vs. HFRT for the treatment of metastases, the rate of radionecrosis seems to be higher when patients are treated with a single fraction. Data (12) has showed that large tumors treated with 9 Gy in 3 fx had a 14% risk of radionecrosis vs. 33% for lesions treated in a single fraction. The risk of RN when treated with 3 fractions seems to be related to the volume receiving 18 Gy (12). Rates of radionecrosis are estimated to be 5% for V18 $\leq$ 30.2 cm^3 and up to 14% for V18 > 30 cm^3 (12). When analyzed according to quartile distribution, the risk was estimated to be: 0, 6, 13, and 24% for V18 < 22.8, 22.8–30.2, 30.3–41.2, and >41.2 cm^3, respectively (12). Others, Inoue et al. (40) have found that the surrounding brain volume treated to the equivalent of a single dose of 14 Gy (V14Gy) can be predictive of the risk of radionecrosis, with V14 $\geq$ 7.0 cm^3 being a risk factor for developing extensive brain oedema and RN. It has been concluded that the risk of RN can be maintained under 2–15% when a BED of 90–127 Gy3 ($\alpha/\beta = 3$) is used (dose of 24–35 Gy in 3–5 fx) (12, 36). Size has also been reported as a possible culprit, however inconsistently, with lesions of >3 cm at a higher risk (45).

Neurological symptoms related to HFRT has been reported in patients necessitating long term steroid treatment (13, 35, 36). Deaths secondary to surrounding oedema and the presence of radionecrosis, although rare, have also been described (13). Toxicity of lesser severity (grade 1–3) (according to the *National Cancer Institute Common Terminology Criteria for Adverse Events v.3 and v.4*) has been reported in 2–52% (12, 16, 36, 38) of patients treated with HFRT. Age (>60), treatment with less than five fractions, and a greater treated volume (possibly of >20 cm^3) (36, 40) have been suggested to be predictive of brain oedema necessitating steroids. Lesions located deep within the white matter are perhaps more likely to cause oedema necessitating corticosteroids, and it has been suggested for these to keep V14Gy to $\leq$3 cm^3 (40).

PLANNING FOR RADIATION THERAPY

Planning of a hypofractionated radiation treatment for large brain metastases is very similar to that of a radiosurgery treatment. Patients usually undergo a planning CT and a high-field 3D distortion corrected T1 contrast MRI with isotropic voxels $\leq$ 1 m MRI with gadolinium to help delineate tumor volumes. Gross target volume (GTV) is delineated on CT scan and MRI and is defined as the area of contrast enhancement. Clinical target volume (CTV) is usually not defined in the treatment of brain metastasis treated with upfront radiation. However, in post operative treatment, it is defined as any contrast enhancing post operative changes on planning MRI and does usually not include the surgical tract (65, 68). In both situations, surrounding oedema is usually not included in treatment volumes. Planning tumor volume (PTV) is defined by adding a geometric margin of 1–3 mm (6, 7, 16, 24, 36). Treatment can be administered using different delivery systems and is usually linear-accelerator based to avoid head frame fixation as patients are usually treated with multiple fractions. However, treatments with dedicated intracranial radiosurgery unit such as the *Gamma Knife* have been published, especially in the setting for multi-staged treatment administered weeks apart (3, 42).Treatments can be delivered using multiple conformal arcs, static field IMRT or a dedicated radiosurgery unit such as *CyberKnife*®. As with any high dose per fraction treatment, image guidance is a must and has to be performed daily for patient set up and positioning verification.

CONCLUSIONS

Hypofractionated radiation therapy treatment is a viable alternative to WBRT for the upfront treatment of brain metastasis that are not amenable to radiosurgery or surgery, or in the postoperative setting. It is associated with an accepted toxicity profile and good local control of lesions. The optimal dose fractionation is however still unknown and necessitates further investigation.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Soffietti R, Ruda R, Trevisan E. Brain metastases: current management and new developments. *Curr Opin Oncol*. (2008) 20:676–84. doi: 10.1097/CCO.0b013e32831186fe
2. Choi CY, Chang SD, Gibbs IC, Adler JR, Harsh GR IV, Atalar B. What is the optimal treatment of large brain metastases? An argument for a multidisciplinary approach. *Int J Radiat Oncol Biol Phys*. (2012) 84:688–93. doi: 10.1016/j.ijrobp.2012.01.028
3. Angelov L, Mohammadi AM, Bennett EE, Abbassy M, Elson P, Chao ST, et al. Impact of 2-staged stereotactic radiosurgery for treatment of brain metastases ≥2 cm. *J Neurosurg*. (2017) 129:366–82. doi: 10.3171/2017.3.JNS162532
4. Han JH, Kim DG, Chung HT, Paek SH, Park CK, Jung HW. Radiosurgery for large brain metastases. *Int J Radiat Oncol Biol Phys*. (2012) 83:113–20. doi: 10.1016/j.ijrobp.2011.06.1965
5. Lee CC, Yen CP, Xu Z, Schlesinger D, Sheehan J. Large intracranial metastatic tumors treated by Gamma Knife surgery: outcomes and prognostic factors. *J Neurosurg*. (2014) 120:52–9. doi: 10.3171/2013.9.JNS131163
6. Murai T, Ogino H, Manabe Y, Iwabuchi M, Okumura T, Matsushita Y, et al. Fractionated stereotactic radiotherapy using CyberKnife for the treatment of large brain metastases: a dose escalation study. *Clin Oncol*. (2014) 26:151–8. doi: 10.1016/j.clon.2013.11.027
7. Navarria P, Pessina F, Cozzi L, Ascolese AM, De Rose F, Fogliata A, et al. Hypo-fractionated stereotactic radiotherapy alone using volumetric modulated arc therapy for patients with single, large brain metastases unsuitable for surgical resection. *Radiat Oncol*. (2016) 11:76. doi: 10.1186/s13014-016-0653-3
8. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chappell R, Buatti JM, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys*. (2002) 53:519–26. doi: 10.1016/S0360-3016(02)02770-0
9. Mehta MP, Tsao MN, Whelan TJ, Morris DE, Hayman JA, Flickinger JC, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. (2005) 63:37–46. doi: 10.1016/j.ijrobp.2005.05.023
10. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi: 10.1001/jama.2016.9839
11. Jeong WJ, Park JH, Lee EJ, Kim JH, Kim CJ, Cho YH. Efficacy and safety of fractionated stereotactic radiosurgery for large brain metastases. *J Korean Neurosurg Soc*. (2015) 58:217–24. doi: 10.3340/jkns.2015.58.3.217
12. Minniti G, D'Angelillo RM, Scaringi C, Trodella LE, Clarke E, Matteucci P, et al. Fractionated stereotactic radiosurgery for patients with brain metastases. *J Neurooncol*. (2014) 117:295–301. doi: 10.1007/s11060-014-1388-3
13. Jiang XS, Xiao JP, Zhang Y, Xu YJ, Li XP, Chen XJ, et al. Hypofractionated stereotactic radiotherapy for brain metastases larger than three centimeters. *Radiat Oncol*. (2012) 7:36. doi: 10.1186/1748-717X-7-36
14. Ogura K, Mizowaki T, Ogura M, Sakanaka K, Arakawa Y, Miyamoto S, et al. Outcomes of hypofractionated stereotactic radiotherapy for metastatic brain tumors with high risk factors. *J Neurooncol*. (2012) 109:425–32. doi: 10.1007/s11060-012-0912-6
15. Ebner D, Rava P, Gorovets D, Cielo D, Hepel JT. Stereotactic radiosurgery for large brain metastases. *J Clin Neurosci*. (2015) 22:1650–4. doi: 10.1016/j.jocn.2015.05.019
16. Feuvret L, Vinchon S, Martin V, Lamproglou I, Halley A, Calugaru V, et al. Stereotactic radiotherapy for large solitary brain metastases. *Cancer Radiother*. (2014) 18:97–106. doi: 10.1016/j.canrad.2013.12.003
17. Baschnagel AM, Meyer KD, Chen PY, Krauss DJ, Olson RE, Pieper DR, et al. Tumor volume as a predictor of survival and local control in patients with

brain metastases treated with Gamma Knife surgery. *J Neurosurg*. (2013) 119:1139–44. doi: 10.3171/2013.7.JNS13431
18. Molenaar R, Wiggenraad R, Verbeek-de Kanter A, Walchenbach R, Vecht C. Relationship between volume, dose and local control in stereotactic radiosurgery of brain metastasis. *Br J Neurosurg*. (2009) 23:170–8. doi: 10.1080/02688690902755613
19. Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for non-small cell lung carcinoma metastatic to the brain: long-term outcomes and prognostic factors influencing patient survival time and local tumor control. *J Neurosurg*. (2002) 97:1276–81. doi: 10.3171/jns.2002.97.6.1276
20. Vogelbaum MA, Angelov L, Lee SY, Li L, Barnett GH, Suh JH. Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin. *J Neurosurg*. (2006) 104:907–12. doi: 10.3171/jns.2006.104.6.907
21. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* (1998) 280:1485–9. doi: 10.1001/jama.280.17.1485
22. Nieder C, Berberich W, Schnabel K. Tumor-related prognostic factors for remission of brain metastases after radiotherapy. *Int J Radiat Oncol Biol Phys*. (1997) 39:25–30. doi: 10.1016/S0360-3016(97)00154-5
23. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. (2009) 10:1037–44. doi: 10.1016/S1470-2045(09)70263-3
24. Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys*. (2007) 68:1388–95. doi: 10.1016/j.ijrobp.2007.03.048
25. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* (2006) 295:2483–91. doi: 10.1001/jama.295.21.2483
26. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys*. (2000) 47:291–8. doi: 10.1016/S0360-3016(99)00507-6
27. Shaw E, Scott C, Souhami L, Dinapoli R, Bahary JP, Kline R, et al. Radiosurgery for the treatment of previously irradiated recurrent primary brain tumors and brain metastases: initial report of radiation therapy oncology group protocol (90-05). *Int J Radiat Oncol Biol Phys*. (1996) 34:647–54. doi: 10.1016/0360-3016(95)02106-X
28. Elliott RE, Rush SC, Morsi A, Mehta N, Spriet J, Narayana A, et al. Local control of newly diagnosed and distally recurrent, low-volume brain metastases with fixed-dose (20 gy) gamma knife radiosurgery. *Neurosurgery* (2011) 68:921–31; discussion 31. doi: 10.1227/NEU.0b013e318208f58e
29. Schoeggl A, Kitz K, Ertl A, Reddy M, Bavinzski G, Schneider B. Prognostic factor analysis for multiple brain metastases after gamma knife radiosurgery: results in 97 patients. *J Neurooncol*. (1999) 42:169–75. doi: 10.1023/A:1006110631704
30. Petrovich Z, Yu C, Giannotta SL, O'Day S, Apuzzo ML. Survival and pattern of failure in brain metastasis treated with stereotactic Gamma knife radiosurgery. *J Neurosurg*. (2002) 97:499–506. doi: 10.3171/jns.2002.97.supplement
31. Mohammadi AM, Schroeder JL, Angelov L, Chao ST, Murphy ES, Yu JS, et al. Impact of the radiosurgery prescription dose on the local control of small (2 cm or smaller) brain metastases. *J Neurosurg*. (2017) 126:735–43. doi: 10.3171/2016.3.JNS153014
32. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. *Int J Radiat Oncol Biol Phys*. (2010) 76:S28–35. doi: 10.1016/j.ijrobp.2009.07.1753
33. Mayo C, Yorke E, Merchant TE. Radiation associated brainstem injury. *Int J Radiat Oncol Biol Phys*. (2010) 76:S36–41. doi: 10.1016/j.ijrobp.2009.08.078
34. Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander E III, Kooy HM, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *Int J Radiat Oncol Biol Phys*. (1993) 27:215–21. doi: 10.1016/0360-3016(93)90230-S
35. Dohm A, McTyre ER, Okoukoni C, Henson A, Cramer CK, LeCompte MC, et al. Staged stereotactic radiosurgery for large brain metastases: local control and clinical outcomes of a one-two punch technique. *Neurosurgery* (2017) 83:114–21. doi: 10.1093/neuros/nyx355
36. Ernst-Stecken A, Ganslandt O, Lambrecht U, Sauer R, Grabenbauer G. Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: results and toxicity. *Radiother Oncol*. (2006) 81:18–24. doi: 10.1016/j.radonc.2006.08.024
37. Fahrig A, Ganslandt O, Lambrecht U, Grabenbauer G, Kleinert G, Sauer R, et al. Hypofractionated stereotactic radiotherapy for brain metastases–results from three different dose concepts. *Strahlenther Onkol*. (2007) 183:625–30. doi: 10.1007/s00066-007-1714-1
38. Fokas E, Henzel M, Surber G, Kleinert G, Hamm K, Engenhart-Cabillic R. Stereotactic radiosurgery and fractionated stereotactic radiotherapy: comparison of efficacy and toxicity in 260 patients with brain metastases. *J Neurooncol*. (2012) 109:91–8. doi: 10.1007/s11060-012-0868-6
39. Higuchi Y, Serizawa T, Nagano O, Matsuda S, Ono J, Sato M, et al. Three-staged stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors. *Int J Radiat Oncol Biol Phys*. (2009) 74:1543–8. doi: 10.1016/j.ijrobp.2008.10.035
40. Inoue HK, Sato H, Suzuki Y, Saitoh J, Noda SE, Seto K, et al. Optimal hypofractionated conformal radiotherapy for large brain metastases in patients with high risk factors: a single-institutional prospective study. *Radiat Oncol*. (2014) 9:231. doi: 10.1186/s13014-014-0231-5
41. Rajakesari S, Arvold ND, Jimenez RB, Christianson LW, Horvath MC, Claus EB, et al. Local control after fractionated stereotactic radiation therapy for brain metastases. *J Neurooncol*. (2014) 120:339–46. doi: 10.1007/s11060-014-1556-5
42. Yomo S, Hayashi M. A minimally invasive treatment option for large metastatic brain tumors: long-term results of two-session Gamma Knife stereotactic radiosurgery. *Radiat Oncol*. (2014) 9:132. doi: 10.1186/1748-717X-9-132
43. Schlienger M, Nataf F, Huguet F, Pene F, Foulquier JN, Orthuon A, et al. [Hypofractionated stereotactic radiotherapy for brain metastases]. *Cancer Radiother*. (2010) 14:119–27. doi: 10.1016/j.canrad.2009.10.004
44. Aoyama H, Shirato H, Onimaru R, Brown PD, Chiang VLS, Kirkpatrick JP, et al. Hypofractionated stereotactic radiotherapy alone without whole-brain irradiation for patients with solitary and oligo brain metastasis using noninvasive fixation of the skull. *Int J Radiat Oncol Biol Phys*. (2003) 56:793–800. doi: 10.1016/S0360-3016(03)00014-2
45. Marcrom SR, McDonald AM, Thompson JW, Popple RA, Riley KO, Markert JM, et al. Fractionated stereotactic radiation therapy for intact brain metastases. *Adv Radiat Oncol*. (2017) 2:564–71. doi: 10.1016/j.adro.2017.07.006
46. Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol*. (2008) 18:215–22. doi: 10.1016/j.semradonc.2008.04.001
47. Ebinu JO, Lwu S, Monsalves E, Arayee M, Chung C, Laperriere NJ, et al. Gamma knife radiosurgery for the treatment of cystic cerebral metastases. *Int J Radiat Oncol Biol Phys*. (2013) 85:667–71. doi: 10.1016/j.ijrobp.2012.06.043
48. Franzin A, Vimercati A, Picozzi P, Serra C, Snider S, Gioia L, et al. Stereotactic drainage and Gamma Knife radiosurgery of cystic brain metastasis. *J Neurosurg*. (2008) 109:259–67. doi: 10.3171/JNS/2008/109/8/0259
49. Higuchi F, Kawamoto S, Abe Y, Kim P, Ueki K. Effectiveness of a 1-day aspiration plus Gamma Knife surgery procedure for metastatic brain tumor with a cystic component. *J Neurosurg*. (2012) 117(Suppl.):17–22. doi: 10.3171/2012.7.GKS121001
50. Park WH, Jang IS, Kim CJ, Kwon DH. Gamma knife radiosurgery after stereotactic aspiration for large cystic brain metastases. J Korean Neurosurg Soc (2009) 46:360–4. doi: 10.3340/jkns.2009.46.4.360
51. Li Y, Xu D, Zhang Z, Zhang Y, Liu D, Liu X, et al. Gamma Knife surgery for brainstem metastases. J Neurosurg 2012;117 Suppl:13-6.
52. Liu X, Yu Q, Zhang Z, Zhang Y, Li Y, Liu D, et al. Same-day stereotactic aspiration and Gamma Knife surgery for cystic intracranial tumors. *J Neurosurg*. (2012) 117(Suppl.):45–8. doi: 10.3171/2012.7.GKS121019
53. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol*. (2004) 22:2865–72. doi: 10.1200/JCO.2004.12.149

54. Connolly EP, Mathew M, Tam M, King JV, Kunnakkat SD, Parker EC, et al. Involved field radiation therapy after surgical resection of solitary brain metastases–mature results. *Neuro Oncol*. (2013) 15:589–94. doi: 10.1093/neuonc/nos328
55. Hartford AC, Paravati AJ, Spire WJ, Li Z, Jarvis LA, Fadul CE, et al. Postoperative stereotactic radiosurgery without whole-brain radiation therapy for brain metastases: potential role of preoperative tumor size. *Int J Radiat Oncol Biol Phys*. (2013) 85:650–5. doi: 10.1016/j.ijrobp.2012.05.027
56. Hwang SW, Abozed MM, Hale A, Eisenberg RL, Dvorak T, Yao K, et al. Adjuvant Gamma Knife radiosurgery following surgical resection of brain metastases: a 9-year retrospective cohort study. *J Neurooncol*. (2010) 98:77–82. doi: 10.1007/s11060-009-0051-x
57. Luther N, Kondziolka D, Kano H, Mousavi SH, Engh JA, Niranjan A, et al. Predicting tumor control after resection bed radiosurgery of brain metastases. *Neurosurgery* (2013) 73:1001–6; discussion: 6. doi: 10.1227/NEU.0000000000000148
58. Atalar B, Choi CY, Harsh GR IV, Chang SD, Gibbs IC, Adler JR, et al. Cavity volume dynamics after resection of brain metastases and timing of postresection cavity stereotactic radiosurgery. *Neurosurgery* (2013) 72:180–5; discussion: 5. doi: 10.1227/NEU.0b013e31827b99f3
59. Asher AL, Burri SH, Wiggins WF, Kelly RP, Boltes MO, Mehrlich M, et al. A new treatment paradigm: neoadjuvant radiosurgery before surgical resection of brain metastases with analysis of local tumor recurrence. *Int J Radiat Oncol Biol Phys*. (2014) 88:899–906. doi: 10.1016/j.ijrobp.2013.12.013
60. Vogel J, Ojerholm E, Hollander A, Briola C, Mooij R, Bieda M, et al. Intracranial control after Cyberknife radiosurgery to the resection bed for large brain metastases. *Radiat Oncol*. (2015) 10:221. doi: 10.1186/s13014-015-0523-4
61. Wang CC, Floyd SR, Chang CH, Warnke PC, Chio CC, Kasper EM, et al. Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: efficacy and safety of an 800 cGy x 3 daily fractions regimen. *J Neurooncol*. (2012) 106:601–10. doi: 10.1007/s11060-011-0697-z
62. Al-Omair A, Soliman H, Xu W, Karotki A, Mainprize T, Phan N, et al. Hypofractionated stereotactic radiotherapy in five daily fractions for post-operative surgical cavities in brain metastases patients with and without prior whole brain radiation. *Technol Cancer Res Treat*. (2013) 12:493–9. doi: 10.7785/tcrt.2012.500336
63. Kim PK, Ellis TL, Stieber VW, McMullen KP, Shaw EG, McCoy TP, et al. Gamma Knife surgery targeting the resection cavity of brain metastasis that has progressed after whole-brain radiotherapy. *J Neurosurg*. (2006) 105(Suppl.):75–8. doi: 10.3171/sup.2006.105.7.75
64. Eaton BR, LaRiviere MJ, Kim S, Prabhu RS, Patel K, Kandula S, et al. Hypofractionated radiosurgery has a better safety profile than single fraction radiosurgery for large resected brain metastases. *J Neurooncol*. (2015) 123:103–11. doi: 10.1007/s11060-015-1767-4
65. Suki D, Hatiboglu MA, Patel AJ, Weinberg JS, Groves MD, Mahajan A, et al. Comparative risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis. *Neurosurgery* (2009) 64:664–74; discussion: 74–6. doi: 10.1227/01.NEU.0000341535.53720.3E
66. Johnson MD, Avkshtol V, Baschnagel AM, Meyer K, Ye H, Grills IS, et al. Surgical resection of brain metastases and the risk of leptomeningeal recurrence in patients treated with stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. (2016) 94:537–43. doi: 10.1016/j.ijrobp.2015.11.022
67. Atalar B, Modlin LA, Choi CY, Adler JR, Gibbs IC, Chang SD, et al. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys*. (2013) 87:713–8. doi: 10.1016/j.ijrobp.2013.07.034
68. Soliman H, Ruschin M, Angelov L, et al. Consensus contouring guidelines for postoperative completely resected cavity stereotactic radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. (2018) 100:436–42. doi: 10.1016/j.ijrobp.2017.09.047

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Masucci. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 24 September 2018
doi: 10.3389/fonc.2018.00385

Contemporary Management of 1–4 Brain Metastases

*Sarah M. C. Sittenfeld, John H. Suh, Erin S. Murphy, Jennifer S. Yu and Samuel T. Chao**

Department of Radiation Oncology, Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, United States

Brain metastases remain the most common neurologic complication of cancer. With improvement in surveillance and systemic therapy, patients with limited CNS disease are living longer after diagnosis, thus influencing the importance of optimal radiation treatment in order to maximize local control and minimize morbidity. In patients with a limited number of brain metastases, stereotactic radiosurgery is more recently seen as an appropriate sole modality for management with excellent local control. As newer systemic therapies emerge and with the advent of immunotherapies and targeted therapies for metastatic CNS disease, further research is needed in the optimal timing and sequencing of these modalities.

Keywords: brain metastases (BM), stereotactic radiosurgery (SRS), radiation therapy (XRT), systemic therapy, review (article)

OPEN ACCESS

Edited by:
Sunit Das,
St. Michael's Hospital, Canada

Reviewed by:
Arjun Sahgal,
University of Toronto, Canada
Brigitta G. Baumert,
Maastricht University Medical Centre, Netherlands
Grant Hunter,
Intermountain Healthcare, United States

****Correspondence:***
Samuel T. Chao
chaos@ccf.org

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *27 June 2018*
Accepted: *28 August 2018*
Published: *24 September 2018*

Citation:
Sittenfeld SMC, Suh JH, Murphy ES, Yu JS and Chao ST (2018) Contemporary Management of 1–4 Brain Metastases. Front. Oncol. 8:385. doi: 10.3389/fonc.2018.00385

INTRODUCTION

Up to 30% of cancer patients develop brain metastases during their lifetime making it the most common neurological complication of cancer (1, 2). The most common primary cancers that metastasize to the brain include lung cancer, breast cancer, kidney cancer and melanoma (3, 4). Incidence has increased due to more routine surveillance, detection of smaller lesions with MRI, as well as improved systemic therapies and thus improved length of survival. Given the available treatment options and strong proponents of various treatment options, optimal treatment has been controversial given the historically poor outcomes (5). While overall prognosis after development of brain metastases remains poor, a subset of patients can live several years after diagnosis, especially those with limited CNS disease (6). Given potential for long term survival, stereotactic radiosurgery (SRS), with or without whole-brain radiation (WBRT), has become an increasingly recognized standard of care in order to minimize morbidity. More recently, SRS alone has been supported as a sole modality for the management of1 to 4 brain metastases.

HISTORICAL STANDARDS

The early randomized trials by Patchell et al. (7) answered initial questions about the best management strategy for single brain metastasis. In his initial study, patients with a single brain metastasis were randomized to surgery plus WBRT or biopsy plus WBRT which showed an overall survival (OS) benefit to surgical resection (40 vs. 15 weeks, $p < 0.01$) and local control improvement. Therefore, a subsequent study by Patchell et al. (8) was designed in which patients with a single brain metastasis had complete surgical resection and then randomized to WBRT or observation. Post-operative WBRT reduced intracranial failure from 70 to 18% ($p < 0.001$) and local recurrence (LR) from 46 to 10% ($p < 0.001$). Consequently, the optimal treatment of single brain metastasis was resection followed by WBRT. With the advent of SRS, future investigations focused on the addition of SRS to WBRT in order to improve local control (LC).

WBRT + SRS

One of the earliest uses of SRS for brain metastases was as an adjunct to WBRT. At that time, the maximum number of brain metastases able to be treated was up to 3 or 4 due to technical limitations of the treatment machines. An initial study by Kondziolka et al. (9) randomized 27 patients with 2 to 4 brain metastases, all <2.5 cm, to WBRT vs. WBRT plus SRS boost. WBRT dose was 30 Gy in 12 fractions with an SRS boost of 16 Gy in a single fraction. Patients who received WBRT alone, had local failure rates of 100% vs. only 8% in patients who received SRS boost. Survival was 11 months in patients receiving SRS and 7.5 months in patients receiving WBRT alone ($p = 0.22$), which was expected given the small sample size that was underpowered to detect a survival difference. This data suggested that given poor LC rates with WBRT, SRS boost should be considered in patients with an otherwise reasonable survival expectation.

A subsequent larger randomized study (RTOG 95-08) (1) sought to further investigate the role of SRS boost. Three hundred, 33 patients with 1–3 brain metastases were randomized to WBRT vs. WBRT plus SRS boost. LC at 1 year improved from 71 to 82% with the addition of SRS ($p = 0.01$), though <50% of patients had adequate follow up imaging at 3 months. Overall, there was no difference in survival between the arms. In the subset of patients with single brain metastasis or recursive partition analysis (RPA) Class I, there was improved survival with SRS boost from 4.9 to 6.5 months ($p = 0.39$) and 9.6 to 11.6 months ($p = 0.045$), respectively. On secondary analysis (10), patients were classified by Graded Prognostic Assessment (GPA) score, a more modern prognostic scoring system compared to the RPA initially used. Patients with a high GPA (3.5–4) had improved survival regardless of number of brain metastases. This study further supported the observation that SRS boost improves LC and OS, particularly in patients with good performance status.

A Cochrane Database review updated in 2017 (11) synthesized available data regarding the benefit of SRS boost after WBRT. This review included three randomized trials which included a total of 358 patients. There was decreased local failure in the WBRT plus SRS group (HR 0.27 95% CI 0.14–0.52) as well as an improvement in performance status scores and decreased steroid use (RR 0.64 CI 0.42–0.97). There was no difference in OS in either group, though in participants with single brain metastasis had significantly longer median survival in the WBRT plus SRS group ($p = 0.04$).

SRS ALONE

Subsequent data indicated there may be an association between WBRT and neurocognitive decline as well as an increased risk of dementia, though data was conflicting and some argued that progressive CNS disease caused more deleterious side effects than those related to WBRT (12–14). Thus, future studies focused on maximizing control, while further investigating effects of progressive brain metastases and treatment on neurocognition and quality of life. The debate surrounding the need for upfront WBRT in patients with a limited number of brain metastases was the subject of multiple future investigations. There have been four randomized trials investigating SRS alone vs. SRS plus WBRT (**Table 1**), which overall, have indicated that SRS alone allows for reduced effects on neurocognition, while still effectively managing brain metastases.

Aoyama et al. (15) published the first prospective study exploring this topic. In this phase III randomized control trial (RCT), 132 patients with 4 or less brain metastases <3 cm in size were randomized to SRS plus WBRT vs. SRS alone. The study was underpowered to detect an OS difference, and the primary endpoint was brain tumor recurrence. At 1 year, brain tumor recurrence decreased from 76 to 47% with the addition of WBRT ($p < 0.001$). WBRT also improved 1-year freedom from new brain metastases from 41.5% in SRS group to 64% ($p = 0.003$), and subsequently, there was more salvage treatment in the SRS alone group. There were no noted differences in toxicities between the groups. A subset of 28 patients had neurocognitive testing with Mini-Mental Status Examination (MMSE) at baseline and at least once at follow up. This group showed there was no difference after treatment between the two arms. Conflicting conclusions were drawn by various groups from this data, with the authors concluding that WBRT could be omitted safely, while others felt that WBRT improved LC and brain tumor recurrence and should be delivered routinely. In a secondary analysis of the data, published 9 years later, in the subset of patients with non-small cell lung cancer (NSCLC) with GPA score of 2.5–4, there was an improvement in OS from 10.6 to 16.7 months ($p = 0.04$) in patients receiving SRS plus WBRT (21). As expected, this group of patients had a lower rate of brain metastases recurrence ($p < 0.01$) which may contribute to improved OS. There was no improvement in survival for patients with lower GPA scores. This small sub-study of 47 patients is suggestive of benefit, though with small number of patients with 12 months follow up ($n = 24$), it may be considered hypothesis generating that maximal intracranial control is ideal for patients with potential for long survival.

More modern data have been acquired to further determine the neurocognitive impact of WBRT. Another phase III RCT compared SRS plus WBRT to SRS alone in patients with 1–3 brain metastasis and followed neurocognitive outcomes with the Hopkins Verbal Learning Test Revised (HVLT-R) (16). Fifty-eight patients were enrolled, and at interim analysis, there was a 96% probability that the SRS plus WBRT arm would show a decline in neurocognition, and the trial was ended early. As previously seen, there was a higher rate of CNS recurrence in SRS-only group compared to SRS plus WBRT, 73 vs. 27%, respectively ($p = 0.0003$). Median OS was surprisingly improved in SRS alone group at 15.2 vs. 5.7 months in the SRS plus WBRT group ($p = 0.003$). It was speculated that there was perhaps more surgical salvage and/or earlier start to systemic therapy in SRS alone group, or higher burden of systemic disease in those assigned to SRS plus WBRT. Given improved neurocognitive scores as well as potential for OS benefit, the authors concluded the SRS alone was preferred over SRS plus WBRT provided patients undergo close and careful follow up.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase III trial in patients with 1–3 brain metastases who underwent SRS or surgery, then

TABLE 1 | Summary of SRS alone vs. SRS + WBRT.

	Arm	1 year LC (%)	OS (months)	Clinical outcomes
Aoyama et al. (15)	SRS SRS + WBRT	72.5 ($p = 0.002$) 88.7	8.0 ($p = 0.42$) 7.5	No difference in MMSE scores between groups
Chang et al. (16)	SRS SRS + WBRT	67 ($p = 0.012$) 100	15.2 ($p = 0.003$) 5.7	Decline in HVLT-R scores in SRS + WBRT arm
Kocher et al. (17)	SRS SRS + WBRT	69 (2y, $p = 0.04$) 81 (2y)	10.7 ($p = 0.89$) 10.9	Higher HRQOL scores in SRS alone arm (18)
Sahgal et al. (19)	SRS (≤50 y) SRS + WBRT (≤50 y) SRS (>50 y) SRS + WBRT (>50 y)	68 (crude rates) 89 74 88	13.6 8.2 10.1 8.6	Not reported
Brown et al. (20)	SRS SRS + WBRT	72.8 90.1	10.4 ($p = 0.92$) 7.4	Decline in immediate and delayed recall, verbal fluency, and executive functioning in WBRT arm

randomized patients to WBRT or observation (17). As expected, WBRT decreased the risk of intracranial relapse, however, there was no difference in OS between the groups. Interestingly, there was no difference in functional improvement between the two groups, indicating that while WBRT reduced the risk of recurrence, there was no clinical improvement in functional independence. Follow up publication by Soffietti et al. (18) focused on health-related quality of life (HRQOL) parameters in these patients. Patients in the observation arm had higher HRQOL scores in global health at 9 months ($p = 0.148$), as well as improved physical function and fatigue at 8 weeks, and cognitive functioning at 12 months compared to those in WBRT arm.

An individual patient-level meta-analysis of the above three studies was done to further characterize these findings. This showed that patients younger than 50 years old had improved survival with SRS alone when compared to SRS plus WBRT (10 vs. 8.2 months, $p = 0.04$). This patient group also had no difference in distant brain metastasis rate. It was concluded from this data set that the side effect profile of WBRT coupled with no improvement in distant brain metastasis rate may lead to the survival advantage seen in younger patients receiving SRS alone (19).

The most recent study investigating SRS vs. SRS plus WBRT was the results of the North Central Cancer Treatment Group (NCCTG) N0574 phase III study randomizing patients with 1–3 brain metastases to SRS vs. SRS plus WBRT (20). Two hundred eight patients were enrolled and the primary endpoint was neurocognitive function as defined as decline of >1 standard deviation from baseline in any of 7 cognitive domains at 3 months follow up. 91.7% of patients in the SRS plus WBRT arm had cognitive decline vs. 63.5% in SRS alone group ($p < 0.001$). Particular cognitive domains that were most affected by the addition of WBRT included immediate recall, delayed recall, and verbal fluency. In patients living 12 months or more, there was more frequent cognitive decline with the addition of WBRT, most notably in executive functioning ($p = 0.05$). However, there was improvement in 12 months intracranial control with addition of WBRT (84.6%) vs. SRS alone (50.5%). There was a numerical, though not statistically significant, improvement in median OS for SRS alone of 10.4 vs. 7.4 months ($p = 0.92$), though the study was not powered to detect OS differences. This larger study confirmed previous results (16), with a larger patient population, that in patients with 1–3 brain metastases, SRS alone may be preferred treatment modality.

From these four trials, we are able to glean several important points regarding the preferred treatment of patients with 1–4 brain metastases which were outlined by Arvold et al. (22). First, there is no negative impact on OS by eliminating WBRT in this patient population. Next, there is additive benefit in terms of LC with SRS plus WBRT, though SRS alone has similarly high rates of LC. Determining LC can be complicated by radiographic findings of pseudoprogression and radiation necrosis. Thirdly, when WBRT is withheld, there is increased rate of new distant brain metastases which leads to more frequent salvage treatment, and about a quarter of patients will ultimately require WBRT. Finally, the risk of neurocognitive decline is lower with SRS alone. Additionally, a Cochrane Database analysis of RCTs comparing of SRS or surgery alone vs. SRS or surgery plus whole brain further highlight the important data points (23). At 1 year, adding WBRT to SRS decreased relative risk of intracranial disease progression by 53%. However, there is no clear evidence of OS differences and subgroup analyses show similar OS regardless of therapy used, number of brain metastases as well as dose and sequence of WBRT.

With growing data as outlined above, ASTRO consensus guidelines were updated recommending against the routine use of WBRT in addition to SRS in patients with limited brain metastases. In addition, multiple other groups through editorials as well as groups such as The National Comprehensive Cancer Network (24), Deutsche Gesellschaft fur Radioonkologie (25), and International Stereotactic Radiosurgery Society (ISRS) (26) have voiced that SRS alone is favored in patients with limited brain metastasis burden and WBRT to be reserved for salvage options (27). Further studies have begun investigating the utility of SRS alone in >4 brain metastases. Yamamoto et al. reported their prospective observational study of SRS alone for treatment of 5–10 brain metastases compared to treated of two to four brain metastases (28). They found that overall survival was similar between patients with 2–4 metastases as compared to 5–10

metastases with no difference in acute toxicities. Future study is necessary to optimize appropriate settings for SRS alone.

OPTIMAL TIMING OF SRS AND SYSTEMIC THERAPY

The typical approach for management of systemic disease with brain metastases is treatment of CNS disease first, followed by initiation of systemic therapy. A recent randomized trial out of Korea, specifically evaluated timing of SRS relative to the start of chemotherapy in patients with limited number of asymptomatic brain metastases (29). Patients with NSCLC were randomized to upfront SRS prior to chemotherapy initiation vs. initiation of chemotherapy without treatment of CNS disease. Median OS was equivalent between the groups, though there was a trend toward longer CNS progression free survival, lower symptomatic brain progression rate and lower CNS salvage rates in the upfront SRS group. It appears from this data, that upfront SRS may be preferable, though in cases that urgent chemotherapy is needed, delaying CNS treatment is likely safe.

New emerging data suggests that systemic therapy may be safely given concurrently with SRS. In retrospective studies, there does not appear to be an association between timing of systemic therapy and increased rates of myelosuppression. A retrospective review from Johns Hopkins showed that in patients receiving concurrent systemic therapy with SRS, only 4% of patients developed grade 3 or 4 neurotoxicity (30). There was an association between higher grade of neurotoxicity with concurrent use of immune therapy as well as lower use of steroids with concurrent targeted therapy. There was no difference in rates of radiation necrosis, grade of neurotoxicity, or steroid use based on timing of systemic therapies. Interestingly, in newly diagnosed cancer patients found to have brain metastases, treatment with concurrent systemic therapy and SRS had improved survival compared to SRS alone (41.6 vs. 21.5 months, $p < 0.05$). In a larger retrospective review of 1,650 patients with 27% of patients receiving concurrent systemic therapy, similar results were found. In patients who received SRS plus WBRT, there was a higher rate of radiation necrosis, compared to SRS alone when patients received concurrent vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs; 14.3 vs. 6.6%, $p = 0.04$) or epidermal growth factor receptor TKIs (15.6 vs. 6% $p = 0.04$). There was no association between other systemic therapies, including hormonal therapy, cytotoxic chemotherapy or other targeted agents, and risk of radiation necrosis when given concurrently with SRS (31). Similar results were seen in secondary analysis of patients enrolled on RTOG 0320 and concurrent use of temozolomide or erlotinib with concurrent SRS or SRS plus WBRT. This analysis showed that patients had more toxicity and worse survival when receiving either systemic agent in combination with WBRT plus SRS vs. WBRT or SRS alone (32).

In the era of new targeted therapies, the indications and timing of SRS is not always clear, and in some cases radiation may be deferred for immediate targeted therapy start. A recent multi-institutional retrospective review evaluated 351 patients with EGFR-mutant NSCLC with new brain metastases who were TKI naïve (33). Patients were treated with SRS or WBRT followed by TKI therapy or TKI therapy alone with radiation reserved at time of progression. Outcomes showed that delaying radiation, WBRT or SRS alone, is associated with significantly worse OS in this patient population. Patients treated with SRS followed by TKI had the longest median OS at 46 months, compared to 30 months with WBRT + TKI and 25 months with TKI alone ($P < 0.001$ for each group). Further randomized data is needed to better define the optimal timing and sequencing of radiation and systemic therapy, particularly in the setting of new targeted therapies.

CONCLUSION

Historically, WBRT was used in conjunction with SRS in order to improve intracranial control, with major disadvantage being neurocognitive decline with the addition of WBRT. In the era of improved surveillance with MRI imaging, better systemic therapy, and improved patient survival, goals have transformed to limit late toxicity, particularly in favorable patient populations with limited CNS disease. Multiple studies have shown that SRS alone for 1–4 brain metastases has acceptable local control with reduced neurocognitive decline as compared to WBRT, and thus, is the favored treatment modality in this patient population (15–17, 20, 27). SRS alone may be appropriate for patients with >4 brain metastases, though further study is necessary to clarify optimal patient selection.

AUTHOR CONTRIBUTIONS

SS and SC: development, writing, and editing; JS, EM, and JY: writing and editing.

REFERENCES

1. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* (2004) 363:1665–72. doi: 10.1016/S0140-6736(04)16250-8
2. Wen PY, Loeffler JS. Management of brain metastases. *Oncology* (1999) 13:941–54, 957–61; discussion: 961–2.
3. Le Chevalier T, Smith FP, Caille P, Constans JP, Rouesse JG. Sites of primary malignancies in patients presenting with cerebral metastases. a review of 120 cases. *Cancer* (1985) 56:880–82. doi: 10.1002/1097-0142(19850815)56:4<880::AID-CNCR2820560430>3.0.CO;2-I
4. Suh JHCS, Peereboom DP, Barnett GH. Metastatic cancer to brain. In: DeVita VT, Lawrence TS, Rosenberg S, editiors. *Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Wolters Kluwer (2015). p. 1832-1844.
5. Suh JH. Stereotactic radiosurgery for the management of brain metastases. *N Engl J Med.* (2010) 362:1119–27. doi: 10.1056/NEJMct0806951

6. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND, et al. Extended survival and prognostic factors for patients with ALK-rearranged non-small-cell lung cancer and brain metastasis. *J Clin Oncol.* (2016) 34:123–9. doi: 10.1200/JCO.2015.62.0138
7. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* (1990) 322:494–500. doi: 10.1056/NEJM199002223220802
8. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* (1998) 280:1485–9. doi: 10.1001/jama.280.17.1485
9. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys.* (1999) 45:427–34. doi: 10.1016/S0360-3016(99)00198-4
10. Sperduto PW, Shanley R, Luo X, Andrews D, Werner-Wasik M, Valicenti R, et al. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). *Int J Radiat Oncol Biol Phys.* (2014) 90:526–31. doi: 10.1016/j.ijrobp.2014.07.002
11. Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. *Cochr Database System Rev.* (2017) 9:Cd006121. doi: 10.1002/14651858.CD006121.pub4
12. Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol.* (2004) 22:157–65. doi: 10.1200/JCO.2004.05.128
13. DeAngelis LM, Mandell LR, Thaler HT, Kimmel DW, Galicich JH, Fuks Z, et al. The role of postoperative radiotherapy after resection of single brain metastases. *Neurosurgery* (1989) 24:798–805. doi: 10.1227/00006123-198906000-00002
14. Regine WF, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs. accelerated-hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91-04. *Int J Radiat Oncol Biol Phys.* (2001) 51:711–7. doi: 10.1016/S0360-3016(01)01676-5
15. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs. stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* (2006) 295:2483–91. doi: 10.1001/jama.295.21.2483
16. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* (2009) 10:1037–44. doi: 10.1016/S1470-2045(09)70263-3
17. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol.* (2011) 29:134–41. doi: 10.1200/JCO.2010.30.1655
18. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol.* (2013) 31:65–72. doi: 10.1200/JCO.2011.41.0639
19. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys.* (2015) 91:710–7. doi: 10.1016/j.ijrobp.2014.10.024
20. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs. radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi: 10.1001/jama.2016.9839
21. Aoyama H, Tago M, Shirato H. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases: secondary analysis of the JROSG 99-1 randomized clinical trial. *JAMA Oncol.* (2015) 1:457–64. doi: 10.1001/jamaoncol.2015.1145
22. Arvold ND, Lee EQ, Mehta MP, Margolin K, Alexander BM, Lin NU, et al. Updates in the management of brain metastases. *Neuro Oncol.* (2016) 18:1043–65. doi: 10.1093/neuonc/now127
23. Soon YY, Tham IW, Lim KH, Koh WY, Lu JJ. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochr Database System Rev.* (2014) CD009454. doi: 10.1002/14651858.CD009454.pub2
24. *National Comprehensive Cancer Network: Central Nervous System Cancers*. Available online at: https://www.nccn.org/professionals/physician_gls/default.aspx (Accessed May 10, 2018).
25. Kocher M, Wittig A, Piroth MD, Treuer H, Seegenschmiedt H, Ruge M, et al. Stereotactic radiosurgery for treatment of brain metastases. A report of the DEGRO working group on stereotactic radiotherapy. *Strahlenther Onkol.* (2014) 190:521–32. doi: 10.1007/s00066-014-0648-7
26. Chao ST, De Salles A, Hayashi M, Levivier M, Ma L, Martinez R, et al. Stereotactic radiosurgery in the management of limited (1-4) brain metasteses: systematic review and international stereotactic radiosurgery society practice guideline. *Neurosurgery* (2017) 83:345–53. doi: 10.1093/neuros/nyx522
27. Sahgal A, Larson D, Knisely J. Stereotactic radiosurgery alone for brain metastases. *Lancet Oncol.* (2015) 16:249–50. doi: 10.1016/S1470-2045(14)71106-4
28. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol.* (2014) 15:387–95. doi: 10.1016/S1470-2045(14)70061-0
29. Lim SH, Lee JY, Lee MY, Kim HS, Lee J, Sun JM, et al. A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-cell lung cancer. *Ann Oncol.* (2015) 26:762–8. doi: 10.1093/annonc/mdu584
30. Shen CJ, Kummerlowe MN, Redmond KJ, Rigamonti D, Lim MK, Kleinberg LR. Stereotactic radiosurgery: treatment of brain metastasis without interruption of systemic therapy. *Int J Radiat Oncol Biol Phys.* (2016) 95:735–42. doi: 10.1016/j.ijrobp.2016.01.054
31. Kim JM, Miller JA, Kotecha R, Xiao R, Juloori A, Ward MC, et al. The risk of radiation necrosis following stereotactic radiosurgery with concurrent systemic therapies. *J Neuro Oncol.* (2017) 133:357–68. doi: 10.1007/s11060-017-2442-8
32. Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys.* (2013) 85:1312–8. doi: 10.1016/j.ijrobp.2012.11.042
33. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, et al. Management of brain metastases in tyrosine kinase inhibitor-naive epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol.* (2017) 35:1070–77. doi: 10.1200/JCO.2016.69.7144

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor and reviewer AS declared their involvement as co-editors in the Research Topic, and confirm the absence of any other collaboration.

Copyright © 2018 Sittenfeld, Suh, Murphy, Yu and Chao. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

PERSPECTIVE
published: 13 September 2018
doi: 10.3389/fonc.2018.00380

The Future Is Now—Prospective Study of Radiosurgery for More Than 4 Brain Metastases to Start in 2018!

David Roberge[1], Paul D. Brown[2], Anthony Whitton[3], Chris O'Callaghan[4], Anne Leis[5], Jeffrey Greenspoon[3], Grace Li Smith[6], Jennifer J. Hu[7], Alan Nichol[8], Chad Winch[4] and Michael D. Chan[9]*

[1] Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, [2] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, United States, [3] Division of Radiation Oncology, Juravinski Cancer Centre, Hamilton, ON, Canada, [4] Canadian Cancer Trials Group, Kingston, ON, Canada, [5] Community Health and Epidemiology, College of Medicine, University of Saskatchewan, Saskatoon, SK, Canada, [6] Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, United States, [7] Department of Public Health Sciences, University of Miami School of Medicine, Miami, FL, United States, [8] BC Cancer Agency, Vancouver Centre, Vancouver, BC, Canada, [9] Department of Radiation Oncology, Wake Forest Baptist Medical Center, Winston-Salem, NC, United States

Stereotactic radiosurgery (SRS) has replaced whole brain radiotherapy (WBRT) as standard therapy for most patients with four or fewer brain metastases due to improved cognitive outcomes and more favorable health related quality of life (QoL). Whether SRS or WBRT is the optimal radiation modality for patients with five to fifteen brain metastases remains an open question. Efforts are underway to develop prospective evidence to answer this question. One of the planned trials is a Canadian Cancer Trials Group (CCTG)-lead North American intergroup trial. In general cancer treatments must have two basic aims: prolonging and improving QoL. In this vein, the selection of overall survival and QoL metrics as outcomes appear obvious. Potential secondary outcomes are numerous: patient/disease related, treatment related, economic, translational, imaging, and dosimetric. In designing a trial, one must also ponder what is standard WBRT—specifically, whether it should be associated with memantine. With the rapid accrual of an intergroup trial of hippocampal-sparing WBRT, we may find that the standard WBRT regimen changes in the course of planned trials. As up-front radiosurgery is increasingly used for more than 4 brain metastases without high level evidence, we have a window of opportunity to develop high quality evidence which will help guide our future clinical and policy decisions.

Keywords: brain metastasis, clinical trials, Phase III as topic, whole brain radiation therapy, radiosurgery, neurocognition

OPEN ACCESS

Edited by:
Sunit Das,
St. Michael's Hospital, Canada

Reviewed by:
Riccardo Soffietti,
Università degli Studi di Torino, Italy
Alfredo Conti,
Università degli Studi di Messina, Italy

****Correspondence:***
David Roberge
david.roberge.chum@ssss.gouv.qc.ca

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *21 June 2018*
Accepted: *23 August 2018*
Published: *13 September 2018*

Citation:
Roberge D, Brown PD, Whitton A, O'Callaghan C, Leis A, Greenspoon J, Smith GL, Hu JJ, Nichol A, Winch C and Chan MD (2018) The Future Is Now—Prospective Study of Radiosurgery for More Than 4 Brain Metastases to Start in 2018!. Front. Oncol. 8:380. doi: 10.3389/fonc.2018.00380

BACKGROUND

The development of brain metastases is an unfortunate and common complication in oncology and can occur in 10–30% of cancer patients and up to half of patients with metastatic disease (1). The traditional treatment for many patients with brain metastases has been whole brain radiotherapy (WBRT), although stereotactic radiosurgery (SRS) has replaced WBRT as the standard therapy for most patients with four or fewer brain metastases due to more favorable cognitive and quality of life (QoL) outcomes (**Table 1**) (4, 7).

Although radiosurgery has historically been technically complex for patients with numerous metastases, each of the treatment delivery devices (Gamma Knife, Cyberknife and the isocentric linac) now permits more rapid treatment of multiple metastases. Although patients with more than 4 metastases are at greater risk of rapid distant brain failure we now know that number of brain metastases is not a reliable predictor of future intracranial progression. A multi-institutional nomogram was developed to predict the development of new brain metastases after primary SRS (8). A major finding from this study was that the nomogram was superior in predicting the development of new metastases in comparison to simply using the number of metastases (8).

Barriers to the adoption of radiosurgery for multiple metastases have been decreasing and we know from retrospective and prospective research that SRS alone is feasible in patients with up to 10 brain metastases (9). Additionally, radiosurgery for as many as 15 brain metastases has been found to be safe, notably in a series of more than 300 patients (10).

The question of whether SRS or WBRT is the optimal modality in patients with five to fifteen brain metastases is significant from a societal and medical resources standpoint. In the United States, the charges related to SRS can be considerably higher than those of WBRT (1, 11). An analysis of 2008 non-Medicare charges in different geographic regions of the United States found WBRT charges ranged from $9,201 to $17,003 while SRS charges ranged from $40,715 to $65,000. Methodologies for financing radiotherapy vary across Canada but the marginal cost to the state insurer of a single SRS or WBRT course, including physician billing and memantine, can be similar and as low as $3500–4000 (USD). Quantifying therapy-associated costs can be particularly complex in patients with multiple brain metastases, as such patients are likely to undergo salvage procedures for new brain metastases. Therefore, the costs of salvage treatment need to be incorporated into economic comparisons.

TABLE 1 | Published studies of radiosurgery for < 4 brain metastases.

Study	Treatment	Local control (1 yr) (%)	Distant failure (1 yr) (%)	Overall survival (1 yr) (%)
RTOG 95-08 (2)	WBRT	71	33	23
	WBRT + SRS	82	27	29
EORTC 22952 (3)	SRS	70	44	47
	SRS + WBRT	87	28	46
MDACC (4)	SRS	67	55	60
	SRS + WBRT	100	27	21
JROSG-99-1 (5)	SRS	76	63	28
	SRS + WBRT	90	42	39
Alliance N0574 (6)	SRS	73	30	39
	SRS + WBRT	90	8	36

It is important to develop high quality prospective evidence as adoption of SRS increases for patients with more than 4 metastases. Currently clinicians face ongoing uncertainties about the true cost burden of SRS vs. WBRT from payer and provider perspectives, as well as uncertainties about the comparative risk/benefit of these strategies for survival, CNS control, QoL, and neurocognitive function in patients with more than four metastases. Published reports have already suggested value of SRS in improving cost utility in the population of 1–4 brain metastases. Lal et al. reported a cost-effectiveness analysis of a randomized trial of SRS vs. SRS + WBRT for 1–3 brain metastases and found that SRS alone had a higher average cost but was associated with an improvement in QALYs with an incremental cost-effectiveness ratio of $41,783 per QALY (12). Savitz et al. performed a cost-effectiveness analysis using a Markov model and found that SRS was a cost-effective treatment option, even in patients who had prognoses of six months or less (13). Accordingly, it is important that SRS for five to fifteen brain metastases is studied in a prospective multi-institutional cooperative group trial to evaluate cost, as well as cost-effectiveness and cost utility.

Having made a strong contribution to an intergroup trial, N107C/CEC.3, comparing SRS to WBRT following surgical resection of brain metastases, the Canadian Cancer Trials Group (CCTG) was keen to lead a trial for brain metastases. The concept of a trial of WBRT vs. radiosurgery for brain metastases was first presented to the CCTG's CNS group in April 2016. Over the following year, the members were surveyed and the trial concept was refined. Dr Chan, as part of the Alliance cooperative group, was recruited as co-principal investigator and the trial was submitted to NCI Cancer Therapy Evaluation Program (CTEP). After minor revisions, the trial was approved by CTEP in January 2018. The central IRB approval followed in March 2018 (**Figure 1**). The trial is thus on track to open to accrual across North America in the summer of 2018.

This chapter aims to review the background of the trial and the choices that had to be made in its design. We hope to garner enthusiasm for this important trial. We also hope to illustrate the important role of intergroup trials as we review the landscape of Phase III research within which our trial will fit. The difficulty in completing such trials is exemplified by the recent decision of Dr Zindler and his Dutch co-investigators to end a trial planned to recruit 230 patients with 4–10 metastases (NCT02353000). The primary endpoint of the trial had been QoL—specifically variation in EQ-5D-5L. Accrual ended after 2 years with 30 patients randomized to hypofractionated WBRT (without memantine) or SRS (14).

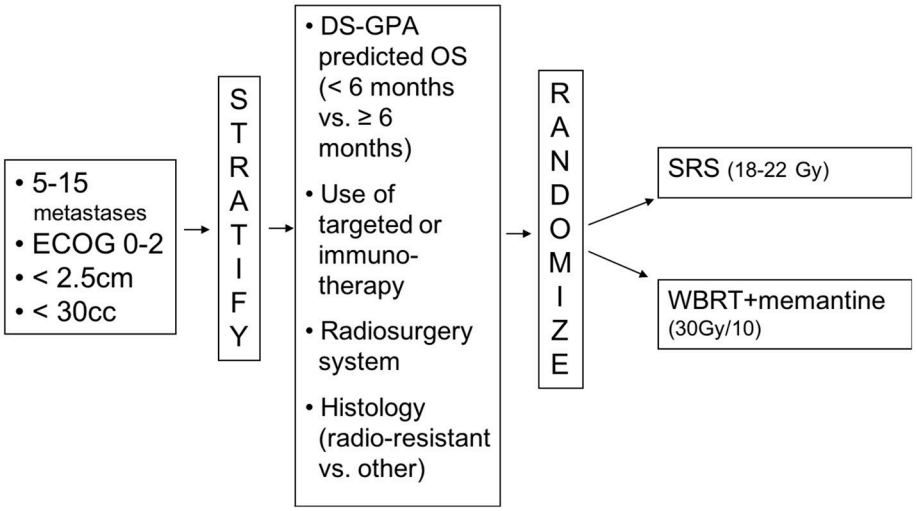


FIGURE 1 | CCTG CE.7 Study Schema.

Selecting Outcomes

Cancer treatments should have two basic aims: prolonging and improving QoL. In this vein, the selection of overall survival and QoL metrics (neurocognitive) as co-primary outcomes for an intergroup trial were obvious.

As one would expect that intracranial control will be better with WBRT than SRS, how could SRS improve overall survival? In addition to its direct toxic effects, WBRT likely delays initiation or re-initiation of increasingly active systemic therapy. Patients initially treated with WBRT will have inferior local control of their metastases and may have less aggressive subsequent management of their intracranial disease. Radiosurgery may thus provide a small survival benefit over WBRT.

The rationale for improvements in QoL is more straightforward. Although quality of life can be defined as a state of general wellbeing reflecting physical, psychological, and social wellbeing, the aspects of QoL that are most likely to be affected in this study are treatment related symptoms and overall QoL. To evaluate QoL the EORTC core questionnaire QLQ-C30, in conjunction with the brain module QLQ-BN20, were selected. Patient performance status, and the EQ-5D questionnaire will also be used.

The EORTC QOL questionnaire core-30 (QLQ-C30, version 3); and the EORTC QOL questionnaire—brain module (QLQ-BN20) have robust psychometric properties and are highly consistent across different language-cultural groups. The EORTC QLQ-C30 consists of 30 questions which comprise five function scales: physical, role (interference of disease with family life or social activities), emotional, cognitive, and social; six single-item scales including dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial effect of tumor and treatment; and overall QOL. EORTC QLQ-BN20 is designed for use with patients with brain tumors and has 20 items that assesses visual disorders, motor dysfunction, communication deficit, various disease symptoms (e.g., headaches and seizures), toxic effects of treatment, and future uncertainty. Since mood disturbances may influence cognitive function, it will be important to interpret QOL data in light of neurocognitive test results.

The neurocognitive evaluations to be used in this study were chosen on the basis of accepted standardization and psychometric principles, published normative data, relevance to general neurocognitive status, and brevity of battery. The tasks selected have either low practice effect or include multiple equivalent formats. Similar variations of this battery have been utilized in multiple multi-institutional trials including N107C/CEC.3, N0574, N0577, E3F05 and RTOG 0614 (15, 16). The tests include:

- Memory (5 min): Hopkins Verbal Learning Test (HVLT) (17).
- Fluency (5 min): Controlled Oral Word Association Test (COWAT) (18).
- Visuomotor speed and attention: Trail Making Test A (3 min) (19).
- Executive function: Trail Making Test B (5 min) (19).
- Delayed Memory (5 min): Recall and Recognition of Word List encoded from the HVLT (20).

What Is Standard of Care?

In designing a Phase III trial of radiosurgery for patients with more than 4 brain metastases, one has to determine the standard treatment for these patients. Reflexively, one would presume that WBRT would be considered the standard. Although WBRT is commonly used, what is the evidence that it improves either overall survival or QoL? A report from Horton and colleagues from the Eastern Cooperative Oncology Group described a study of 48 patients randomized in a three-arm trial to a combination of steroids and whole-brain radiotherapy (21). There was no report of QoL and the overall survival was 14 weeks in the arms containing radiotherapy and 10 weeks

with prednisone alone—no test of statistical significance was performed. Recognizing the weakness of this evidence, a larger trial was designed to randomize patients with NSCLC to WBRT vs. supportive care. In this QUARTZ trial overall survival was nearly identical in both arms (9.2 weeks with WBRT and 8.5 weeks without) and there was no significant difference in patient reported QoL (22). In melanoma, patients have been randomized to chemotherapy (the relatively ineffective drug fotemustine) with or without WBRT (23). Although there was an improvement in progression free survival, the overall survival curves were indiscernible.

Thus, for many patients with less favorable prognoses, no radiation treatment has been clearly demonstrated to be better than supportive care. At the other end of the brain metastasis spectrum, patients with targetable mutations are increasingly being offered systemic therapy. As a recent example, the FLAURA trial for first line treatment of patients with advanced EGFR-mutated NSCLC included patients with previously untreated brain metastases (24). One hundred and sixteen patients with brain metastases were randomized to osimertinib or a choice of gefitinib or erlotinib. Survival data is immature but osimertinib offers a better disease response with less toxicity. One could argue that current evidence supports the use of a TKI alone for patients with asymptomatic brain metastases and an exon 19 deletion or L858R mutation.

It becomes rapidly clear that an evidence-based standard of care is elusive and complex. The question to be answered may then better be expressed as: "in those patients treated with radiation for more than 4 metastases, what is an accepted standard of care against which to compare radiosurgery." The answer to this question is thus WBRT. What is left is to choose details of the WBRT regimen. Although no WBRT fractionation has shown advantage in survival or cognitive function, it was sensible to select 30Gy in 10 fractions as a regimen acceptable in North America.

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist studied in a placebo-controlled, double-blind, randomized trial in patients with brain metastases receiving WBRT (RTOG 0614) (15). Patients received WBRT and were randomized to receive placebo or memantine during and after WBRT for a total of 24 weeks (10 mg twice a day). Between 2008 and 2010, 554 patients were accrued. Grade 3 or 4 toxicities and study compliance were similar between arms. Although the difference in the primary endpoint (decline in HVLT-R at 24 weeks) did not quite reach statistical significance ($p = 0.059$), this may be attributable to the fact that there were fewer analyzable patients than expected significantly impacting study power. Patients in the memantine arm did however have a significantly longer time to cognitive decline (HR 0.78; 95% CI, 0.62–0.99; $p = 0.02$). Following publication of this data, controversy remains but memantine has been integrated into the standard care of patients treated with WBRT in selected practices in the United States and Canada.

Buoyed by favorable Phase II results of hippocampal sparing, Drs Brown, Gondi and co-investigators at the NRG initiated a Phase III trial of hippocampal avoidance in the management of brain metastases (25). After having accrued briskly, the protocol closed in March 2018 and preliminary results are expected later in 2018. Should the results suggest a cognitive benefit to hippocampal sparing, this will replace WBRT for those patients in whom the location of the metastases permits hippocampal sparing (to be eligible for the trial, patients could not have metastases within 5 mm of either hippocampus). Although not tested in CC001, unilateral sparing (especially in the dominant hemisphere) could also be used in those patients with unilateral encroachment on the hippocampal avoidance region—especially when the dominant hemisphere can be spared.

Statistics

As the CCTG trial has co-primary endpoints (overall and neurocognitive progression-free survival), these endpoints are planned to be analyzed jointly. The interpretation is pre-specified:

- If SRS is found to be superior for neurocognitive progression-free survival and non-inferior for overall survival, the study would establish SRS as the standard of care for patients with 5–15 metastases.
- If SRS is found to be superior in terms of neurocognitive progression-free survival but slightly worse in terms of overall survival, then SRS may still have clinical use. In this situation, secondary endpoints, including QoL and economic endpoints may be of particular interest in making policy and treatment decisions.
- If SRS is neither superior in terms of cognition or overall survival, WBRT would be clarified as the standard of care for patients with more than 4 metastases.

In calculating sample size, it was assumed that neurocognitive progression would occur in 50% for patients undergoing WBRT by 6 months post-treatment. The estimated median overall survival in the WBRT was estimated to be 7.5 months. Based on these assumptions, the trial was designed to have a 90% power to detect a 40% risk reduction in the risk of the neurocognitive progression using a 5% 2-sided test. With the sample size of 206 patients, the power to detect a 15% reduction in the hazard of death in the SRS arm would thus be 80%. Based on prior experience with brain metastases in the Cancer Trials Support Unit (CTSU) network, this sample size appears to be reasonable for a trial accruing over 3 years.

Landscape

The question of the best radiotherapeutic management of multiple brain metastases is one which solicits much interest. The CCTG/Intergroup initiative should be the trial which rallies the most institutions but there are other ongoing initiatives of interest:

- Building on prior success in brain metastases trials, the group at MD Anderson are currently performing a trial of radiosurgery vs. WBRT for patients with 4–15 metastases (NCT01592968). The primary outcomes are cognitive decline at 4 months (as measured by change in HVLT-R) and local control. The control arm is WBRT 30Gy in 10 without memantine. The estimated trial accrual is 100 patients.

- In Boston, the groups at Brigham and Women's Hospital and the Dana Farber Cancer Institute plan to accrue 196 patients to a Phase III trial of radiosurgery (which can be fractionated) vs. WBRT for 5–20 metastases (NCT03075072). In this trial the comparator arm is WBRT with possible hippocampal sparing. The primary endpoint is QoL as measured by the MD Anderson Symptom Inventory—Brain Tumor (MDASI-BT).

Recognizing that there is a need to prevent the occurrence of new brain metastases while minimizing toxicity, alternatives to WBRT are of interest as adjuncts to radiosurgery. The most prominent endeavor is "METIS," a trial which aims to improve intracranial control in patients with non-small cell lung cancer and up to 10 metastases (NCT02831959). Patients are randomized to radiosurgery with or without electrical fields—so called "tumor treating fields." In 8 countries, 270 patients are to be randomized with time to intracranial progression as the primary endpoint.

Completing trials where one arm has WBRT can be a challenge, this is exemplified by the failure of the North American Gamma Knife Consortium to accrue in their trial of radiosurgery vs. WBRT for patients with 5 or more brain metastases (NCT01731704).

CONCLUSION

Uncertainty remains as to the best approach to patients with more than 4 brain metastases which are amenable to radiosurgery. Current efforts, including an intergroup trial lead by the CCTG, should generate high quality evidence to inform clinical practice. Despite this new upcoming trial, clinical ambiguity may persist because of the high heterogeneous patient population and further translational research will be needed to better combine available treatments, identify biomarkers, and develop innovative approaches to metastases within the CNS.

AUTHOR CONTRIBUTIONS

DR, PB, AW, CO, AL, JG, GS, JH, AN, CW, and MC participated in the design of the work and review of the manuscript. DR, CW, and MC performed much of the writing of the manuscript.

FUNDING

This work was supported by the NCI Cancer Therapy Evaluation Program (CTEP) and funding support for this trial has been provided by the Canadian Cancer Society (grant #704970), and the US National Institutes of Health (grant #CA180863).

REFERENCES

1. Brown PD, Asher AL, Farace E. Adjuvant whole brain radiotherapy: strong emotions decide but rational studies are needed. *Int J Radiat Oncol Biol Phys.* (2008) 70:1305–9. doi: 10.1016/j.ijrobp.2007.11.047
2. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* (2004) 363:1665–72. doi: 10.1016/S0140-6736(04)16250-8
3. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol.* (2011) 29:134–41. doi: 10.1200/JCO.2010.30.1655
4. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* (2009) 10:1037–44. doi: 10.1016/S1470-2045(09)70263-3
5. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* (2006) 295:2483–91. doi: 10.1001/jama.295.21.2483
6. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi: 10.1001/jama.2016.9839
7. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol.* (2013) 31:65–72. doi: 10.1200/JCO.2011.41.0639
8. Ayala-Peacock DN, Attia A, Hepel J, Lucas JT, Onyeuku N, Stavas MJ, et al. A multi-institutional predictive nomogram for distant brain failure in patients treated with upfront stereotactic radiosurgery without whole brain radiation therapy. *Int J Radiat Oncol Biol Phys.* (2014) 90:S126. doi: 10.1016/j.ijrobp.2014.05.568
9. Yamamoto M, Serizawa T, Higuchi Y, Sato Y, Kawagishi J, Yamanaka K, et al. A Multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 Study Update): irradiation-related complications and long-term maintenance of mini-mental state examination scores. *Int J Radiat Oncol Biol Phys.* (2017) 99:31–40. doi: 10.1016/j.ijrobp.2017.04.037
10. Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Barfod BE, et al. A case-matched study of stereotactic radiosurgery for patients with multiple brain metastases: comparing treatment results for 1-4 vs >/= 5 tumors: clinical article. *J Neurosurg.* (2013) 118:1258–68. doi: 10.3171/2013.3.JNS121900
11. Brown PD, Kee AY, Eshleman JS, Fiveash JB. Adjuvant whole brain radiotherapy: strong emotions decide but rationale studies are needed: in regard to Brown et al. (Int J Radiat Oncol Biol Phys 2008;70:1305-1309). In reply to Drs. Larson and Sahgal. *Int J Radiat Oncol Biol Phys.* (2009) 75:316–17. doi: 10.1016/j.ijrobp.2009.04.079
12. Lal LS, Byfield SD, Chang EL, Franzini L, Miller LA, Arbuckle R, et al. Cost-effectiveness analysis of a randomized study comparing radiosurgery with radiosurgery and whole brain radiation therapy in patients with 1 to 3 brain metastases. *Am J Clin Oncol.* (2012) 35:45–50. doi: 10.1097/COC.0b013e3182005a8f
13. Savitz ST, Chen RC, Sher DJ. Cost-effectiveness analysis of neurocognitive-sparing treatments for brain metastases. *Cancer* (2015) 121:4231–9. doi: 10.1002/cncr.29642
14. Zindler JD, Bruynzeel AME, Eekers DBP, Hurkmans CW, Swinnen A, Lambin P. Whole brain radiotherapy versus stereotactic radiosurgery for 4-10 brain metastases: a phase III randomised multicentre trial. *BMC Cancer* (2017) 17:500. doi: 10.1186/s12885-017-3494-z
15. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving

whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.* (2013) 15:1429–37. doi: 10.1093/neuonc/not114
16. Brown PD, Ballman KV, CerhanJH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1049–60. doi: 10.1016/S1470-2045(17)30441-2
17. Brandt J. The hopkins verbal learning test: Development of a new memory test with six equivalent forms. *Clin Neuropsychol.* (1991) 5:125–42. doi: 10.1080/13854049108403297
18. Benton AL, Hamsher KD, Sivan AB. *Multilingual Aphasia Examination, 3rd ed*. Iowa City, IA: Psychological Assessment Resources Inc (1978).
19. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Motor Skills* (2016) 8:271–6. doi: 10.2466/pms.1958.8.3.271
20. Rasmusson DX, Bylsma FW, Brandt J. Stability of performance on the Hopkins Verbal Learning Test. *Arch Clin Neuropsychol.* (1995) 10:21–6. doi: 10.1093/arclin/10.1.21
21. Horton J, Baxter DH, Olson KB. The management of metastases to the brain by irradiation and corticosteroids. *Am J Roentgenol Radium Ther Nucl Med.* (1971) 111:334–6. doi: 10.2214/ajr.111.2.334
22. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, Mccoll E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* (2016) 388:2004–14. doi: 10.1016/S0140-6736(16)30825-X
23. Mornex F, Thomas L, Mohr P, Hauschild A, Delaunay MM, Lesimple T, et al. [Randomised phase III trial of fotemustine versus fotemustine plus whole brain irradiation in cerebral metastases of melanoma]. *Cancer Radiother.* (2003) 7:1–8. doi: 10.1016/S1278-3218(02)00284-6
24. Vansteenkiste J, Reungwetwattana T, Nakagawa K, Cho BC, Dols MAC, Ramalingam S, et al. CNS response to osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFR-TKI sensitising mutation (EGFRm)-positive advanced non-small cell lung cancer (NSCLC): data from the FLAURA study. *Ann Oncol.* (2017) 28:mdx782. doi: 10.1093/annonc/mdx782
25. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol.* (2014) 32:3810–6. doi: 10.1200/JCO.2014.57.2909

Conflict of Interest Statement: DR: Elekta (research support), VMS, Accuray, Siemens (honoraria and research support), Brainlab, Pfizer, EMD Serono (honoraria). PB: Novella Clinical (DSMB), UpToDate (Contributor). AN: VMS (research support).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Roberge, Brown, Whitton, O'Callaghan, Leis, Greenspoon, Smith, Hu, Nichol, Winch and Chan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

ORIGINAL RESEARCH
published: 02 October 2018
doi: 10.3389/fonc.2018.00424

The Role of Navigated Transcranial Magnetic Stimulation Motor Mapping in Adjuvant Radiotherapy Planning in Patients With Supratentorial Brain Metastases

Maximilian J. Schwendner[1,2], Nico Sollmann[2,3,4], Christian D. Diehl[1], Markus Oechsner[1], Bernhard Meyer[2], Sandro M. Krieg[2,4†] and Stephanie E. Combs[1,5*†]*

[1] Department of Radiation Oncology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, [2] Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, [3] Department of Diagnostic and Interventional Neuroradiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, [4] TUM-Neuroimaging Center, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, [5] Department of Radiation Sciences, Institute of Innovative Radiotherapy (iRT), Helmholtz Zentrum München, Munich, Germany

OPEN ACCESS

Edited by:
Sunit Das,
St. Michael's Hospital, Canada

Reviewed by:
Alfredo Conti,
Università degli Studi di Messina, Italy
Brad E. Zacharia,
Penn State Milton S. Hershey Medical Center, United States
Nir Lipsman,
University of Toronto—University Health Network, Canada

***Correspondence:**
Sandro M. Krieg
sandro.krieg@tum.de
Stephanie E. Combs
stephanie.combs@tum.de

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 16 July 2018
Accepted: 11 September 2018
Published: 02 October 2018

Citation:
Schwendner MJ, Sollmann N, Diehl CD, Oechsner M, Meyer B, Krieg SM and Combs SE (2018) The Role of Navigated Transcranial Magnetic Stimulation Motor Mapping in Adjuvant Radiotherapy Planning in Patients With Supratentorial Brain Metastases. Front. Oncol. 8:424. doi: 10.3389/fonc.2018.00424

Purpose: In radiotherapy (RT) of brain tumors, the primary motor cortex is not regularly considered in target volume delineation, although decline in motor function is possible due to radiation. Non-invasive identification of motor-eloquent brain areas is currently mostly restricted to functional magnetic resonance imaging (fMRI), which has shown to lack precision for this purpose. Navigated transcranial magnetic stimulation (nTMS) is a novel tool to identify motor-eloquent brain areas. This study aims to integrate nTMS motor maps in RT planning and evaluates the influence on dosage modulations in patients harboring brain metastases.

Materials and Methods: Preoperative nTMS motor maps of 30 patients diagnosed with motor-eloquent brain metastases were fused with conventional planning imaging and transferred to the RT planning software. RT plans of eleven patients were optimized by contouring nTMS motor maps as organs at risk (OARs). Dose modulation analyses were performed using dose-volume histogram (DVH) parameters.

Results: By constraining the dose applied to the nTMS motor maps outside the planning target volume (PTV) to 15 Gy, the mean dose (Dmean) to the nTMS motor maps was significantly reduced by 18.1% from 23.0 Gy (16.9–30.4 Gy) to 18.9 Gy (13.5–28.8 Gy, $p < 0.05$). The Dmean of the PTV increased by 0.6 ± 0.3 Gy (1.7%).

Conclusion: Implementing nTMS motor maps in standard RT planning is feasible in patients suffering from intracranial metastases. A significant reduction of the dose applied to the nTMS motor maps can be achieved without impairing treatment doses to the PTV. Thus, nTMS might provide a valuable tool for safer application of RT in patients harboring motor-eloquent brain metastases.

Keywords: brain mapping, brain metastases, eloquent tumor, navigated transcranial magnetic stimulation, radiotherapy

INTRODUCTION

The most frequent brain tumors in adults are brain metastases. In two of three cases, the primary tumors are lung carcinoma, breast carcinoma, or malignant melanoma (1, 2). For the complex treatment of supratentorial metastases, a multimodal approach including therapeutic options like surgery, radiotherapy (RT), and chemotherapy is recommended (3). For patients with single, large brain metastases, surgery followed by external-beam RT is considered an effective treatment strategy (4, 5).

Regarding surgical therapy, especially tumors in close vicinity of eloquent brain areas like the motor cortex are challenging since preserving neurological function is essential and residual tumor after surgery correlates with local tumor progression (6). Therefore, preoperative functional magnetic resonance imaging (fMRI) and intraoperative neurophysiological monitoring and mapping by direct electrical stimulation (DES) are established tools in neurosurgery to delineate eloquent structures (7–10). Furthermore, navigated transcranial magnetic stimulation (nTMS) is a novel method increasingly applied to non-invasively identify eloquent brain areas prior to surgery. In this context, preoperative motor mapping by nTMS for the resection of motor-eloquent brain metastases improved the outcome of such patients and resulted in a lower rate of residual tumor and less surgery-related paresis when compared to patients without preoperative nTMS motor mappings (11).

Concerning RT planning, target volume delineation including the definition of organs at risk (OARs) is an essential element to provide a safe application of the radiation dose in order to prevent side effects. Structures like the brainstem, optical nerves and optic chiasm, eye lenses, and pituitary gland are routinely considered and spared from radiation (12, 13). A functionally critical structure like the motor cortex is commonly not considered in RT and therefore not spared. However, decline in motor function shortly after treatment has been reported, and it can occur mainly due to radiation necrosis and can eventually even require further surgical treatment (14, 15). Progressive deterioration in motor function has also been reported decades after RT in literature (16).

Against this background, nTMS as a non-invasive method to delineate motor-eloquent areas might also be used in RT; however, it has not yet been integrated in RT of brain metastases. Applying nTMS in radiosurgery, for instance, resulted in improved risk-benefit balancing and dose plan modifications for a small number of patients suffering predominantly from brain metastases (17). The aim of this study was to assess the influence of nTMS motor mapping on RT planning of patients suffering from supratentorial brain metastases from a dosimetric point of view.

Abbreviations: 3D, Three-dimensional; BMRC, British Medical Research Council; CT, Computed tomography; DES, Direct electrical stimulation; Dmean, Mean dose; DVH, Dose-volume histogram; FLAIR, Fluid attenuated inversion recovery; fMRI, Functional magnetic resonance imaging; HFSRT, Hypofractioned stereotactic RT; LE, Lower extremity; MEG, Magnetoencephalography; MEP, Motor-evoked potential; MRI, Magnetic resonance imaging; nTMS, Navigated transcranial magnetic stimulation; OAR, Organ at risk; PTV, Planning target volume; rMT, Resting motor threshold; RT, Radiotherapy; UE, Upper extremity; VMAT, Volumetric modulated arc therapy; WBRT, Whole brain radiotherapy.

MATERIALS AND METHODS

Ethics

The experimental setup was approved by the local ethics committee of our university (registration number: 5883/13) and was conducted in accordance with the Declaration of Helsinki. Prior to nTMS motor mapping, written informed consent was obtained from all enrolled patients.

Patients

Thirty patients were enrolled prospectively. However, only eleven patients were considered eligible for recalculation of the RT plans. Decision criteria for inclusion of patients for recalculations of RT plans were (1) the mean dose (Dmean) of the nTMS motor map, (2) the spatial relationship of the nTMS motor map with high isodose levels, and (3) the distance between the edge of the tumor volume and the nTMS motor map (**Supplementary Table 1**).

All patients received preoperative nTMS motor mapping and underwent surgery for tumor removal at our hospital. As part of the clinical routine, they also underwent detailed clinical examinations pre- and postoperatively and at later time points during follow-up visits. RT to the resection cavity was performed within 7 weeks after surgical treatment (median: 21 days after surgery). Only patients with motor-positive spots in nTMS motor mapping and no previous RT to the irradiation field were considered for this study. Exclusion criteria were general contraindications for nTMS mapping (e.g., metal implants such as cardiac pacemakers), age below 18 years, and pregnancy.

Anatomical Imaging

Amongst other sequences, a fluid attenuated inversion recovery (FLAIR) sequence and a three-dimensional (3D) T1-weighted gradient echo sequence without and with application of a contrast agent (T1Gd+; gadopentetate dimeglumine; Magnograf, Marotrast GmbH, Jena, Germany) were acquired preoperatively on a 3T magnetic resonance imaging (MRI) scanner (Achieva; Philips Medical Systems, Best, The Netherlands). Postoperative MRI was carried out within the first 48 h subsequent to surgery using the same sequences as well as diffusion-weighted and T2*-weighted imaging. Further follow-up imaging at later time points was scheduled according to clinical needs.

For the purpose of precise RT planning, eight of eleven patients received additional MRI during the postoperative course to acquire FLAIR and T1-weighted sequences shortly before RT. Furthermore, cranial computed tomography (CT) imaging was added for RT planning purposes (Somatom Emotion 16; Siemens Healthineers, Erlangen, Germany).

Navigated Transcranial Magnetic Stimulation

The 3D contrast-enhanced, T1-weighted gradient echo sequence was uploaded to a Nexstim eXimia NBS system (version 4.3; Nexstim Plc., Helsinki, Finland) for preoperative nTMS motor mapping. An infrared tracking device (Polaris Spectra;

Polaris, Waterloo, Ontario, Canada) combined with a head tracker with reflective sphere markers attached to the patient's forehead was used to align the patient's head with the MRI-based 3D head model using anatomical landmarks, enabling neuronavigation during mapping (18–22). Continuous electromyography with pregelled surface electrodes (Neuroline 720; Ambu, Bad Nauheim, Germany) was derived to record motor-evoked potentials (MEPs) of the M. abductor pollicis brevis, M. abductor digiti minimi, M. flexor carpi radialis, and M. biceps brachii for the upper extremity (UE) and of the M. tibialis anterior and M. gastrocnemius for the lower extremity (LE) (18, 20, 21, 23). Mapping of UE muscle representations was performed with an intensity of 110% of the individual resting motor threshold (rMT), whereas for the mapping of LE muscle representations at least 130% rMT was used during stimulation.

For the identification of motor-positive mapping points, all stimulation spots were analyzed subsequent to the mapping sessions (18, 20, 21). Only stimulation points with an MEP amplitude larger or equal to 50 μV and an MEP onset latency within the common ranges for UE and LE muscles were defined motor-positive and therefore considered during surgery and recalculations of RT plans.

For further analyses, the nTMS motor maps were fused with the contrast-enhanced, T1-weighted gradient echo sequences, which was achieved on an external server using the application's automatic fusion algorithm (Elements; Brainlab AG, Munich, Germany; **Supplementary Figure 1**). The fused datasets were then used for linear measurements of the maximum tumor diameter and the distance between the edge of the tumor volume and the respective nTMS motor map in axial slices. In case of infiltrations of the nTMS motor maps by the tumor volume or direct contact of the edge of the tumor and the respective nTMS motor map, a distance of 0 mm was registered. Furthermore, these datasets were used for measurements of the tumor volume using the built-in volumetric assessment tools.

Radiotherapy Planning and Dose Statistics

The nTMS motor maps, fused with the contrast-enhanced, T1-weighted gradient echo sequences, were imported into the RT planning software (Eclipse, version 13.0; Varian Medical Systems,

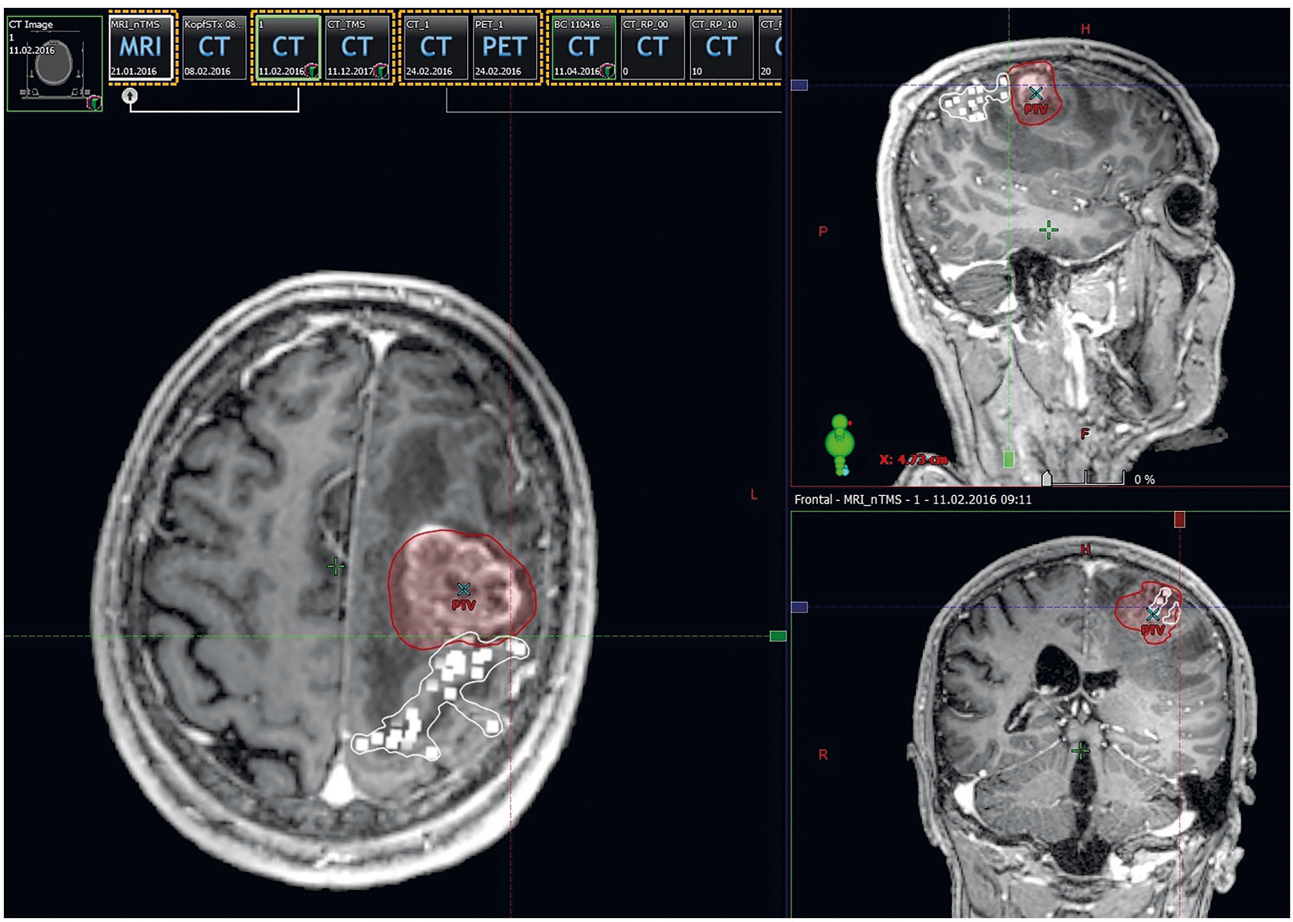


FIGURE 1 | Integration of motor maps in target volume delineation. This figure shows contrast-enhanced, T1-weighted magnetic resonance imaging (MRI) fused with navigated transcranial magnetic stimulation (nTMS) motor-positive points (white squares) in an exemplary patient case. For radiotherapy (RT) planning, nTMS motor maps were contoured as coherent organs at risk (OARs) in terms of target volume delineation. The planning target volume (PTV) is depicted as a red area.

Palo Alto, CA, USA). In the next step, the nTMS motor maps were fused with the respective planning CT scan using automatic registration combined with additional manual registration in case of any inaccuracy according to visual inspection. This fusion was done directly within the RT planning software. The motor map of each patient, consisting of motor-positive points appearing as 3D objects, was contoured as one single OAR (**Figure 1**). Fusion of postoperative MRI scans with planning CT scans was performed accordingly.

All patients were treated with hypofractioned stereotactic RT (HFSRT) of seven fractions of 5 Gy prescribed to the 95% isodose level of the planning target volume (PTV) (24). The PTV as the therapeutically crucial radiation volume covers the resection cavity plus contrast-enhancing lesions including a 2 mm safety margin for potential microscopic spread. All RT plans were reevaluated considering the spatial relation of motor maps to isodose levels and the PTV and Dmean of the motor maps (>15 Gy).

As outlined before, eleven patients were considered eligible for recalculations of RT plans (**Supplementary Table 1**). They obtained two concepts of volumetric modulated arc therapy (VMAT). Regarding the conventional RT plans, plans were optimized without taking into account the nTMS motor maps. Considering nTMS motor maps as an OAR, the RT plans were recalculated by reducing the dose applied to the nTMS motor maps as low as reasonably possible by constraining the dose prescription in this area to 15 Gy (**Figure 2**). To not compromise the dose applied to the PTV, areas of the nTMS motor maps inside the PTV were not spared.

In these eleven patients, dose statistics regarding the Dmean for the PTV, nTMS motor maps, and OARs (optic chiasm, right optical nerve, left optical nerve, eye lenses, and brainstem) were calculated. For better comparison, calculations of the proportional overlap of nTMS motor maps with the PTV and isodose levels (90, 80, 70, 50, and 20%) were performed, and the volumes of the nTMS motor maps receiving a specific dose were plotted in dose-volume histograms (DVHs).

Statistical Analyses

All statistical analyses and generation of graphs were done using SSPS (version 24.0; IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA) or Prism (version 7.0; GraphPad Software, La Jolla, CA, USA). Descriptive statistics including mean, median, minimum, maximum, and standard deviation were calculated for patient- and tumor-related characteristics as well as doses and volumes investigated in the present study.

Conventional RT plans not taking nTMS motor maps into consideration ("no nTMS") were compared to RT plans with constraint to the nTMS motor maps ("nTMS cons"). Therefore, *t*-tests for paired samples with a level of significance set at $p < 0.05$ were performed. The Dmean of the nTMS motor maps, PTV, and OARs consisting of the optic chiasm, optical nerves, eye lenses, and brainstem were selected as comparison criteria. In addition, motor map volumes receiving specific doses were compared accordingly.

RESULTS

Patients and Clinical Information

Eleven patients harboring motor-eloquent supratentorial brain metastases were considered for RT plan recalculations (**Table 1**, **Supplementary Table 1**). The maximum follow-up was 13.1 ± 10.8 months on average (1.3–36.0 months), with a mean progression-free survival of 11.7 ± 10.1 months. One male patient died before the regular 3-months follow-up examination, all others completed at least follow-up at this time point.

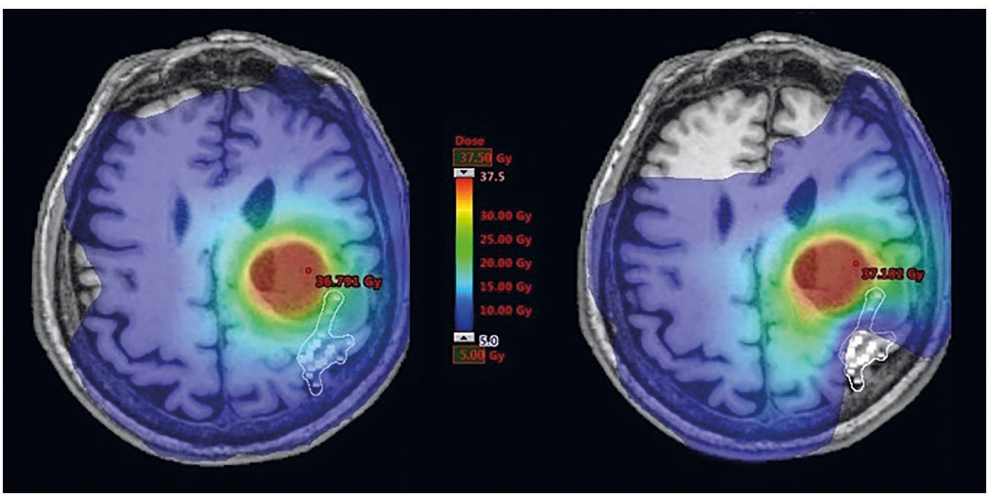


FIGURE 2 | Dose distribution within motor maps. This figure illustrates radiotherapy (RT) planning in one exemplary patient with a brain metastasis affecting the left central region. The navigated transcranial magnetic stimulation (nTMS) motor-positive points (white squares) are shown on respective contrast-enhanced, T1-weighted magnetic resonance imaging (MRI) and were contoured as an organ at risk (OAR) in the RT plan. Dose distributions covering the range of 5–37.5 Gy are visualized in color-wash mode showing high doses in red and low doses in blue colors. Constraining dose to nTMS motor maps resulted in a shift of dose distributions to lower values.

TABLE 1 | Patient characteristics.

Gender (number of patients)	Females	6
	Males	5
Age at primary treatment (mean and range)		55.9 years (21.1–76.7 years)
Primary tumor (number of patients)	Breast cancer	3
	Non-small cell lung cancer	2
	Ewing sarcoma	2
	Adenocarcinoma	2
	Testicular non-seminoma	1
	Malignant melanoma	1
Tumor-affected hemisphere (number of patients)	Right	4
	Left	7
Extent of resection (number of patients)	>90%	10
	>80%	1
Tumor volume (mean and range)		19.3 cm^3 (2.8 – 62.1 cm^3)
Maximum tumor diameter (mean and range)		3.4 cm (1.9 – 5.2 cm)
Distance tumor—nTMS motor maps (mean and range)		0 mm (0 – 2 mm)
Preoperative motor deficits (number of patients)	BMRC 5/5	3
	4/5	5
	≤3/5	3
Postoperative motor deficits (number of patients)	BMRC 5/5	2
	4/5	6
	≤3/5	3
Motor deficits at 3-months follow-up (number of patients)	BMRC 5/5	6
	4/5	3
	≤3/5	1
Motor deficits at follow-up before tumor progression (number of patients)	BMRC 5/5	5
	4/5	5
	≤3/5	1
Motor deficits at maximum follow-up (number of patients)	BMRC 5/5	5
	4/5	4
	≤3/5	2

This table gives an overview of patient and tumor characteristics for the eleven patients with radiotherapy (RT) plan recalculations. Grading of motor deficits was conducted preoperatively, postoperatively, at 3-months follow-up, at follow-up before progression, and at maximum follow-up according to the British Medical Research Council (BMRC) scale and with respect to the initial side of symptoms, if any. One male patient died before the regular 3-months follow-up examination.

Detailed clinical information including details on the motor status at different time points is shown in **Table 1**. When comparing the preoperative to the postoperative motor status according to the British Medical Research Council (BMRC) scale, two patients declined in motor strength, whereas one patient improved. When comparing the preoperative motor status to the status during 3-months follow-up examinations, no patient showed worsening of motor strength, while four patients showed improved motor strength.

Furthermore, four patients suffered from preoperative paresthesia, two patients from impairment of fine motor skills, and two patients from aphasia. During 3-months follow-up examinations, paresthesia was still found in four patients, while only one patient showed deficits regarding fine motor skills and another patient presented with aphasia.

Tumor recurrence occurring at the site of initial surgery and RT was observed in two patients (4.5 and 22.2 months after surgery, respectively), with both patients undergoing surgical re-resection. Histopathological evaluation of surgically removed tissue confirmed tumor recurrence in both patients without evidence of radiation necrosis in examined tissue probes.

Integration of Navigated Transcranial Magnetic Stimulation During Radiotherapy Planning

Integration of nTMS motor maps in RT planning was feasible in all of the included patients. nTMS motor maps were covered by the PTV by 18.7% on average (**Table 2**). Regarding conventional RT plans, the Dmean of nTMS motor maps was 23.0 Gy (16.9–30.4 Gy; **Figure 3**). With a constraint of 15 Gy to the motor area, the Dmean of nTMS motor maps was 18.9 Gy (13.5–28.8 Gy), thus reducing the dose to nTMS motor maps by 4.1 ± 2.1 Gy (18.1%, $p < 0.05$; **Table 3**, **Figure 3**). The Dmean of the PTV slightly increased by 0.62 ± 0.31 Gy from 35.4 ± 0.1 Gy to 36.0 ± 0.3 Gy (1.7%, $p < 0.05$; **Figure 4**).

Proportional volumes of nTMS motor maps receiving doses equal to or more than 10, 15, 20, 25, 30, and 35 Gy are shown in DVHs (**Figure 5**). The average volume of nTMS motor maps receiving at least 10, 15, and 20 Gy could be reduced by 24.7% ($p < 0.05$), 29.8% ($p < 0.05$), and 26.3% ($p = 0.059$) by constraining the dose applied to the nTMS motor maps outside the PTV (**Supplementary Figure 2**). The Dmean of the anatomical OARs was not affected.

Regarding the 19 patients not considered eligible for recalculation of RT plans, the Dmean was only 9.7 Gy (2.1–18.0 Gy), and the minimum distance between the edge of the tumor and the nTMS motor maps was 8 mm (0–24 mm; **Supplementary Table 1**). These values were significantly different from the respective measurements among the patients considered for RT recalculations ($p < 0.05$).

DISCUSSION

Potential Side Effects of Radiotherapy to Eloquent Brain Areas

In the treatment of brain metastases, whole-brain RT (WBRT), gamma knife radiosurgery, stereotactic radiosurgery, and HFSRT are current treatment strategies, with the choice of the exact treatment approach depending on several factors such as the number and size of metastases, spatial lesion extents, the activity of the systemic disease, and the age and performance status of the individual patient (3, 25). For patients suffering from single, large brain metastases like the patients in this study, surgery combined with HFSRT to the resection cavity is a common treatment strategy (24, 26).

However, all above-mentioned RT options can come at cost of specific side effects. Late neurocognitive deficits are a feared complication especially in WBRT; therefore, local control by stereotactic radiosurgery and fractionated stereotactic RT is often preferred (27–29). Such impairment of neurocognitive function is caused by damage to neural progenitor cells located

TABLE 2 | Spatial relation of motor maps to isodose levels.

	TMS motor maps ∩ PTV	nTMS motor maps ∩ 90% isodose level	nTMS motor maps ∩ 80% isodose level	nTMS motor maps ∩ 70% isodose level	nTMS motor maps ∩ 50% isodose level	nTMS motor maps ∩ 20% isodose level
Mean	18.7%	28.6%	36.7%	43.8%	66.0%	96.5%
Minimum	2.4%	8.3%	13.8%	19.3%	35.1%	83.8%
Maximum	61.7%	70.6%	75.4%	78.1%	89.5%	100.0%
Median	16.6%	29.3%	36.7%	44.7%	68.9%	99.2%

This table shows the spatial relation of the navigated transcranial magnetic stimulation (nTMS) motor maps and the planning target volume (PTV). nTMS motor maps were covered by the PTV by 18.7% (2.4–61.7%) on average and covered by the 90, 80, 70, 50, and 20% isodose levels in 28.6, 36.7, 43.8, 66.0, and 96.5%.

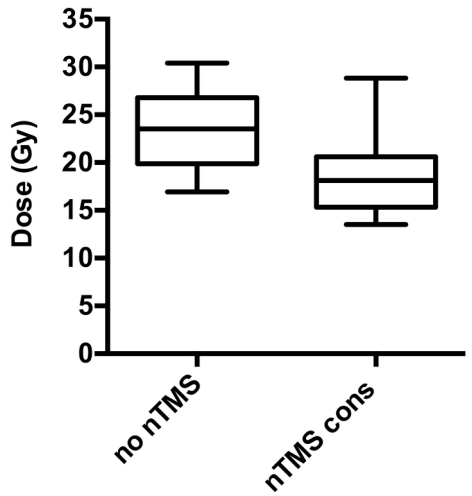


FIGURE 3 | Change of dose to motor maps. Radiation dose to the navigated transcranial magnetic stimulation (nTMS) motor maps can be significantly reduced in radiotherapy (RT) planning. The box plots represent the dosage applied to the nTMS motor maps. Regarding conventional RT plans not taking nTMS motor maps into account ("no nTMS"), the mean dose (Dmean) is 23.0 Gy compared to 18.9 Gy ($p < 0.001$) for RT plans with constraints to the nTMS motor maps ("nTMS cons").

TABLE 3 | Relative and absolute dose applied to motor maps.

nTMS motor maps	Absolute change of Dmean nTMS cons	Relative change of Dmean nTMS cons
Mean	−4.1 *Gy*	−18.1%
Minimum	−1.4 *Gy*	−5.2%
Maximum	−9.0 *Gy*	−33.2%
Median	−4.1 *Gy*	−20.0%

This table depicts the absolute and relative changes of the mean dose (Dmean) in navigated transcranial magnetic stimulation (nTMS) motor maps. Radiotherapy (RT) plans with constraints to the nTMS motor maps ("nTMS cons") achieved an average dose reduction of 4.1 Gy (18.1%) compared to conventional RT plans not taking nTMS motor maps into consideration ("no nTMS").

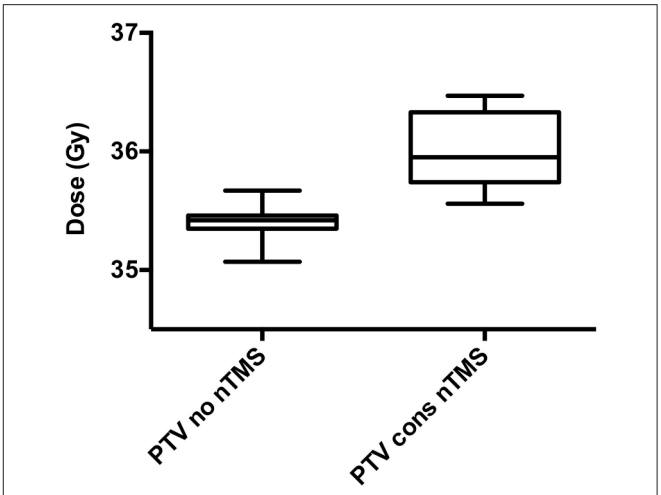


FIGURE 4 | Dose to the planning target volume (PTV). The mean dose (Dmean) to the PTV for conventional radiotherapy (RT) plans not taking nTMS motor maps into consideration ("PTV no nTMS") and with dose constraints to nTMS motor areas ("PTV cons nTMS") is depicted in these box plots. A minor but significant increase of the Dmean from 35.4 ± 0.1 Gy to 36.0 ± 0.3 Gy was observed ($p < 0.001$).

in the subgranular zone of the hippocampus; therefore, it should be spared during RT planning (30). Further treatment-related cerebral injuries are radiation necrosis and white matter injuries that can occur months to years after RT (16, 31). Radiation necrosis may cause motor deficits, sensor deficits, or seizures, depending on the extent and location of the lesion. It occurs in up to 17% of patients treated by stereotactic radiosurgery (32, 33). Risk factors are dose volumes, radiation doses, and fraction sizes (34–36). Tumor location near eloquent areas bears an increased risk of complications in radiosurgical treatment (37). For gamma knife radiosurgery near motor-eloquent areas, the risk of neurological deficits was significantly higher for doses above 20 Gy (38).

Identifying eloquent brain areas by means of nTMS and integrating nTMS data into the radiosurgical planning procedure improved the risk-benefit balancing and led to dose plan modifications as well as a change in radiation dosage for the majority of patients in previous studies (17, 39). For lesions at high risk due to larger size or vicinity to critical structures including motor-eloquent areas, HFSRT is often preferred over radiosurgery (40, 41). However, even in patients treated with fractioned stereotactic RT, radiation necrosis occurred in

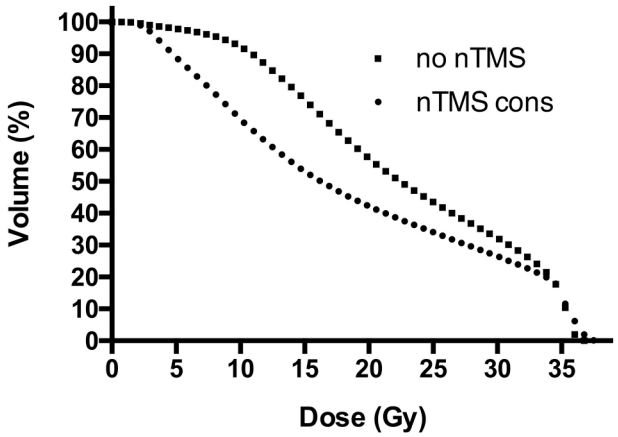


FIGURE 5 | Dose-volume histograms (DVHs) for motor maps. This figure shows the proportional volume of motor maps by navigated transcranial magnetic stimulation (nTMS) receiving a specific dose, represented by DVHs. Radiotherapy (RT) plans with constraint to the nTMS motor maps ("nTMS cons") reduced nTMS motor map volumes receiving doses >2 Gy, as represented by a steeper gradient of DHV curves compared to conventional RT plans not taking nTMS motor maps into consideration ("no nTMS"). The most optimal effect can be observed in a dose range from 5 to 25 Gy. The effect is ceasing for higher doses due to partially high overlap of the planning target volume (PTV) and nTMS motor maps.

eloquent brain areas like the primary motor cortex (14). This points out the need of sparing eloquent brain areas in RT, including HFSRT. However, anatomical imaging is currently regarded as the clinical standard for delineation of the target volumes and OARs. Thus, functionally eloquent brain areas are not considered routinely, although they are crucial in terms of risk-benefit balancing and RT planning to minimize neurological deficits. Several methods of functional assessment like fMRI, magnetoencephalography (MEG), and nTMS have been used to identify motor-eloquent areas in the past (39, 42, 43). However, there are currently no established standards in HFSRT regarding functional imaging and dose constraints to eloquent brain structures like the primary motor cortex.

Functional Imaging in Radiotherapy Planning

Lately, nTMS has been implemented as an accurate tool to non-invasively generate preoperative motor maps of the cortex for surgery, resulting in a lower rate of residual tumor and less surgery-related deficits in patients suffering from motor-eloquent metastases (11). In this context, favorable clinical outcome has also been suggested for patients with other intracranial lesions when nTMS motor maps are available for preoperative planning and intraoperative resection guidance (44–46). In terms of RT planning of brain metastases, this is the first study to apply preoperative nTMS with the purpose of decreasing the radiation dose applied to the primary motor cortex.

Currently, eloquent brain areas like the primary motor cortex are commonly not defined as OARs and, hence, not integrated in the process of contouring target volumes in RT planning. Applying diffusion tensor tractography for dose reductions to the corticospinal tract in radiosurgical treatment of cerebral arteriovenous malformations significantly reduced the risk of motor complications (47). Witt et al. integrated eloquent brain areas identified by fMRI into planning of stereotactic radiosurgery by keeping these structures outside the 30% isodose level (42). Furthermore, Aoyama et al. integrated functional brain imaging by MEG and magnetic resonance axonography into stereotactic irradiation treatment planning in regard of the volume receiving more or equal to 10 Gy and more or equal to 15 Gy (43). A majority of treatment plans was modified, achieving a significant reduction of the volume receiving more or equal to 15 Gy (43). Conti et al. applied functional imaging including fMRI, tractography, and nTMS in radiosurgery (39). Integrating nTMS motor maps in radiosurgery treatment planning of 12 patients with malignant brain tumors achieved an average dose reduction of 25% to these structures (39).

Because nTMS has already been successfully applied in radiosurgery, this study focused on adjuvant RT of supratentorial brain metastases. In our setting, the dose applied to the nTMS motor maps outside the PTV was constrained to 15 Gy. The treatment strategy was HFSRT of 35 Gy subscribed in seven fractions applied to the resection cavity, with a safety margin of 2 mm (24). Due to the small size of the safety margin compared to RT of other brain tumors like glioblastoma, there is a steep gradient of radiation dosage toward circumjacent brain areas. Therefore, in most of the cases, high radiation doses are only applied to a small fraction of the nTMS motor areas. Because this results in a low Dmean of the OARs, these cases were not considered eligible for RT plan recalculations.

The PTV and the 80% isodose level were covered by nTMS motor areas by 18.7 and 36.7% on average. This increases the potential of dose reductions. The Dmean significantly decreased by 18.1% on average, and the volumes of nTMS motor maps receiving at least 10 and 15 Gy were significantly reduced by 24.7 and 29.8%, respectively.

Limitations and Perspectives

This study analyzed eleven patients and applied dose constraints only to cortical motor-eloquent brain areas, not taking tractography into account. Integrating the corticospinal tract by means of diffusion tensor tractography and including a larger number of patients should be considered as the next step. Furthermore, preoperative nTMS motor maps were fused with RT plans based on postoperative imaging. Therefore, shifting of motor areas due to cortical plasticity and perioperative brain shift has not been taken into account for dosimetric analyses. For this retrospective approach, postoperative nTMS motor mapping was categorically not available because only preoperative mapping is currently performed in the context of clinical diagnostics as a method to facilitate preoperative neurosurgical planning and intraoperative resection guidance. Thus, future prospective studies incorporating postoperative nTMS motor maps are highly needed to validate the results of the present study.

As tumor progression mostly occurs shortly after treatment and overall median survival is limited, motor deficits induced by RT might be masked. In the treatment of recurrent or progressive

brain metastases, repeated RT by stereotactic RT or radiosurgery are favorable options, together with new treatment strategies like neoadjuvant radiosurgery before surgical resection; however, repeated treatment once again bears the risk of neurologic impairment for patients with tumors near the motor cortex (48, 49). Overall, survival of patients with brain metastases is limited and motor function is essential for the quality of life; thus, sparing of the motor cortex from higher radiation dosage in selected cases seems reasonable, even in consideration of the unclear distinct impact of photon radiation on the cortex (50, 51).

CONCLUSIONS

Integrating nTMS motor maps in the standard process of RT planning is feasible and valuable in patients harboring motor-eloquent supratentorial metastases. nTMS motor maps considered as OARs in the process of target contouring enable a significant dose reduction to the motor area for selected cases, without impairing the therapeutically crucial dose to the PTV covering the tumor itself. Based on these preliminary results, further prospective studies have to be conducted in order to evaluate the potential benefit, especially the impact on the clinical outcome.

AUTHOR CONTRIBUTIONS

NS, CD, SK, and SC designed the study. MS, NS, CD, MO, BM, SK, and SC coordinated subject inclusion, data handling, and data storage. MS, NS, CD, and MO were responsible for data analysis and performed statistics. MS, NS, CD, SK, and SC were involved in literature research. MS, NS, CD, MO, BM, SK, and SC drafted the manuscript. The study was supervised by BM, SK, and SC. All authors reviewed the manuscript before submission.

FUNDING

The study was completely financed by institutional grants from the Department of Neurosurgery and the Department of Radiation Oncology. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00424/full#supplementary-material

REFERENCES

1. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer* (1996) 78:1781–8.
2. Taillibert S, Le Rhun E. [Epidemiology of brain metastases]. *Cancer Radiother.* (2015) 19:3–9. doi: 10.1016/j.canrad.2014.11.001
3. Gallego Perez-Larraya J, Hildebrand J. Brain metastases. *Handb Clin Neurol.* (2014) 121:1143–57. doi: 10.1016/B978-0-7020-4088-7.00077-8
4. Keller A, Dore M, Cebula H, Thillays F, Proust F, Darie I, et al. Hypofractionated stereotactic radiation therapy to the resection bed for intracranial metastases. *Int J Radiat Oncol Biol Phys.* (2017) 99:1179–89. doi: 10.1016/j.ijrobp.2017.08.014
5. Pessina F, Navarria P, Cozzi L, Ascolese AM, Maggi G, Riva M, et al. Outcome evaluation of oligometastatic patients treated with surgical resection followed by Hypofractionated Stereotactic Radiosurgery (HSRS) on the tumor bed, for single, large brain metastases. *PLoS ONE* (2016) 11:e0157869. doi: 10.1371/journal.pone.0157869
6. Kamp MA, Rapp M, Buhner J, Slotty PJ, Reichelt D, Sadat H, et al. Early postoperative magnet resonance tomography after resection of cerebral metastases. *Acta Neurochir.* (2015) 157:1573–80. doi: 10.1007/s00701-015-2479-4
7. Wengenroth M, Blatow M, Guenther J, Akbar M, Tronnier VM, Stippich C. Diagnostic benefits of presurgical fMRI in patients with brain tumours in the primary sensorimotor cortex. *Eur Radiol.* (2011) 21:1517–25. doi: 10.1007/s00330-011-2067-9
8. Kamada K, Todo T, Masutani Y, Aoki S, Ino K, Takano T, et al. Combined use of tractography-integrated functional neuronavigation and direct fiber stimulation. *J Neurosurg.* (2005) 102:664–72. doi: 10.3171/jns.2005.102.4.0664
9. Sanai N, Berger MS. Mapping the horizon: techniques to optimize tumor resection before and during surgery. *Clin Neurosurg.* (2008) 55:14–9.
10. Ottenhausen M, Krieg SM, Meyer B, Ringel F. Functional preoperative and intraoperative mapping and monitoring: increasing safety and efficacy in glioma surgery. *Neurosur Focus* (2015) 38:E3. doi: 10.3171/2014.10.FOCUS14611
11. Krieg SM, Picht T, Sollmann N, Bahrend I, Ringel F, Nagarajan SS, et al. Resection of motor eloquent metastases aided by preoperative nTMS-based motor maps-comparison of two observational cohorts. *Front Oncol.* (2016) 6:261. doi: 10.3389/fonc.2016.00261
12. Scoccianti S, Detti B, Gadda D, Greto D, Furfaro I, Meacci F, et al. Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. *Radiother Oncol.* (2015) 114:230–8. doi: 10.1016/j.radonc.2015.01.016
13. Kirkpatrick JP, Marks LB, Mayo CS, Lawrence YR, Bhandare N, Ryu S. Estimating normal tissue toxicity in radiosurgery of the CNS: application and limitations of QUANTEC. *J Radiosurg SBRT* (2011) 1:95–107.
14. Kim YZ, Kim DY, Yoo H, Yang HS, Shin SH, Hong EK, et al. Radiation-induced necrosis deteriorating neurological symptoms and mimicking progression of brain metastasis after stereotactic-guided radiotherapy. *Cancer Res Treat.* (2007) 39:16–21. doi: 10.4143/crt.2007.39.1.16
15. Luther N, Kondziolka D, Kano H, Mousavi SH, Flickinger JC, Lunsford LD. Motor function after stereotactic radiosurgery for brain metastases in the region of the motor cortex. *J Neurosurg.* (2013) 119:683–8. doi: 10.3171/2013.6.JNS122081
16. Duffey P, Chari G, Cartlidge NE, Shaw PJ. Progressive deterioration of intellect and motor function occurring several decades after cranial irradiation. A new facet in the clinical spectrum of radiation encephalopathy. *Arch Neurol.* (1996) 53:814–8.
17. Picht T, Schilt S, Frey D, Vajkoczy P, Kufeld M. Integration of navigated brain stimulation data into radiosurgical planning: potential benefits and dangers. *Acta Neurochir.* (2014) 156:1125–33. doi: 10.1007/s00701-014-2079-8
18. Krieg SM. *Navigated Transcranial Magnetic Stimulation in Neurosurgery*. Cham: Springer International Publishing AG 2017 (2017).
19. Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. *Neurophysiol Clin.* (2010) 40:7–17. doi: 10.1016/j.neucli.2010.01.006
20. Krieg SM, Lioumis P, Makela JP, Wilenius J, Karhu J, Hannula H, et al. Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. *Acta Neurochir.* (2017) 159:1187–95. doi: 10.1007/s00701-017-3187-z
21. Krieg SM, Shiban E, Buchmann N, Gempt J, Foerschler A, Meyer B, et al. Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. *J Neurosurg.* (2012) 116:994–1001. doi: 10.3171/2011.12.JNS111524
22. Sollmann N, Goblirsch-Kolb MF, Ille S, Butenschoen VM, Boeckh-Behrens T, Meyer B, et al. Comparison between electric-field-navigated and line-navigated TMS for cortical motor mapping in patients with brain tumors. *Acta Neurochir.* (2016) 158:2277–89. doi: 10.1007/s00701-016-2970-6
23. Sollmann N, Tanigawa N, Bulubas L, Sabih J, Zimmer C, Ringel F, et al. Clinical factors underlying the inter-individual variability of the resting motor threshold in navigated transcranial magnetic stimulation motor mapping. *Brain Topogr.* (2016) 30:98–121. doi: 10.1007/s10548-016-0536-9

24. Specht HM, Kessel KA, Oechsner M, Meyer B, Zimmer C, Combs SE. HFSRT of the resection cavity in patients with brain metastases. *Strahlenther Onkol.* (2016) 192:368–76. doi: 10.1007/s00066-016-0955-2
25. Lu-Emerson C, Eichler AF. Brain metastases. *Continuum* (2012) 18:295–311. doi: 10.1212/01.CON.0000413659.12304.a6
26. Croker J, Chua B, Bernard A, Allon M, Foote M. Treatment of brain oligometastases with hypofractionated stereotactic radiotherapy utilising volumetric modulated arc therapy. *Clin Exp Metastasis* (2016) 33:125–32. doi: 10.1007/s10585-015-9762-x
27. Tallet AV, Azria D, Barlesi F, Spano JP, Carpentier AF, Goncalves A, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. *Radiat Oncol.* (2012) 7:77. doi: 10.1186/1748-717X-7-77
28. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1049–60. doi: 10.1016/S1470-2045(17)30441-2
29. Habets EJ, Dirven L, Wiggenraad RG, Verbeek-de Kanter A, Lycklama ANGJ, Zwinkels H, et al. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. *Neuro Oncol.* (2016) 18:435–44. doi: 10.1093/neuonc/nov186
30. Gondi V, Tome WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol.* (2010) 97:370–6. doi: 10.1016/j.radonc.2010.09.013
31. Valk PE, Dillon WP. Radiation injury of the brain. *AJNR Am J Neuroradiol.* (1991) 12:45–62.
32. Terakedis BE, Jensen RL, Boucher K, Shrieve DC. Tumor control and incidence of radiation necrosis after reirradiation with stereotactic radiosurgery for brain metastases. *J Radiosurg SBRT* (2014) 3:21–8.
33. Minniti G, D'Angelillo RM, Scaringi C, Trodella LE, Clarke E, Matteucci P, et al. Fractionated stereotactic radiosurgery for patients with brain metastases. *J Neurooncol.* (2014) 117:295–301. doi: 10.1007/s11060-014-1388-3
34. Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* (2010) 77:996–1001. doi: 10.1016/j.ijrobp.2009.06.006
35. Ruben JD, Dally M, Bailey M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. *Int J Radiat Oncol Biol Phys.* (2006) 65:499–508. doi: 10.1016/j.ijrobp.2005.12.002
36. Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol.* (2011) 6:48. doi: 10.1186/1748-717X-6-48
37. Williams BJ, Suki D, Fox BD, Pelloski CE, Maldaun MV, Sawaya RE, et al. Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications. *J Neurosurg.* (2009) 111:439–48. doi: 10.3171/2008.11.JNS08984
38. Park CY, Choi HY, Lee SR, Roh TH, Seo MR, Kim SH. Neurological change after gamma knife radiosurgery for brain metastases involving the motor cortex. *Brain Tumor Res Treat.* (2016) 4:111–5. doi: 10.14791/btrt.2016.4.2.111
39. Conti A, Pontoriero A, Ricciardi GK, Granata F, Vinci S, Angileri FF, et al. Integration of functional neuroimaging in CyberKnife radiosurgery: feasibility and dosimetric results. *Neurosurg Focus* (2013) 34:E5. doi: 10.3171/2013.2.FOCUS12414
40. Kim YJ, Cho KH, Kim JY, Lim YK, Min HS, Lee SH, et al. Single-dose versus fractionated stereotactic radiotherapy for brain metastases. *Int J Radiat Oncol Biol Phys.* (2011) 81:483–9. doi: 10.1016/j.ijrobp.201005.033
41. Ernst-Stecken A, Ganslandt O, Lambrecht U, Sauer R, Grabenbauer G. Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: results and toxicity. *Radiother Oncol.* (2006) 81:18–24. doi: 10.1016/j.radonc.2006.08.024
42. Witt TC, Kondziolka D, Baumann SB, Noll DC, Small SL, Lunsford LD. Preoperative cortical localization with functional MRI for use in stereotactic radiosurgery. *Stereotact Funct Neurosurg.* (1996) 66:24–9. doi: 10.1159/000099663
43. Aoyama H, Kamada K, Shirato H, Takeuchi F, Kuriki S, Iwasaki Y, et al. Integration of functional brain information into stereotactic irradiation treatment planning using magnetoencephalography and magnetic resonance axonography. *Int J Radiat Oncol Biol Phys.* (2004) 58:1177–83. doi: 10.1016/j.ijrobp.2003.08.034
44. Krieg SM, Sollmann N, Obermueller T, Sabih J, Bulubas L, Negwer C, et al. Changing the clinical course of glioma patients by preoperative motor mapping with navigated transcranial magnetic brain stimulation. *BMC Cancer* (2015) 15:231. doi: 10.1186/s12885-015-1258-1
45. Frey D, Schilt S, Strack V, Zdunczyk A, Rosler J, Niraula B, et al. Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations. *Neuro Oncol.* (2014) 16:1365–72. doi: 10.1093/neuonc/nou110
46. Krieg SM, Sabih J, Bulubasova L, Obermueller T, Negwer C, Janssen I, et al. Preoperative motor mapping by navigated transcranial magnetic brain stimulation improves outcome for motor eloquent lesions. *Neuro Oncol.* (2014) 16:1274–82. doi: 10.1093/neuonc/nou007
47. Koga T, Shin M, Maruyama K, Kamada K, Ota T, Itoh D, et al. Integration of corticospinal tractography reduces motor complications after radiosurgery. *Int J Radiat Oncol Biol Phys.* (2012) 83:129–33. doi: 10.1016/j.ijrobp.2011.05.036
48. Ammirati M, Cobbs CS, Linskey ME, Paleologos NA, Ryken TC, Burri SH, et al. The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* (2010) 96:85–96. doi: 10.1007/s11060-009-0055-6
49. Asher AL, Burri SH, Wiggins WF, Kelly RP, Boltes MO, Mehrlich M, et al. A new treatment paradigm: neoadjuvant radiosurgery before surgical resection of brain metastases with analysis of local tumor recurrence. *Int J Radiat Oncol Biol Phys.* (2014) 88:899–906. doi: 10.1016/j.ijrobp.2013.12.013
50. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A european organisation for research and treatment of cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol.* (2013) 31:65–72. doi: 10.1200/JCO.2011.41.0639
51. Maringwa J, Quinten C, King M, Ringash J, Osoba D, Coens C, et al. Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. *Ann Oncol.* (2011) 22:2107–12. doi: 10.1093/annonc/mdq726

Conflict of Interest Statement: NS received honoraria from Nexstim Plc (Helsinki, Finland). SK is consultant for Nexstim Plc (Helsinki, Finland) and received honoraria from Medtronic (Meerbusch, Germany) and Carl Zeiss Meditec (Oberkochen, Germany). SK and BM received research grants and are consultants for Brainlab AG (Munich, Germany). BM received honoraria, consulting fees, and research grants from Medtronic (Meerbusch, Germany), icotec ag (Altstätten, Switzerland), and Relievant Medsystemy Inc., (Sunnyvale, CA, USA), honoraria and research grants from Ulrich Medical (Ulm, Germany), honoraria and consulting fees from Spineart Deutschland GmbH (Frankfurt, Germany) and DePuy Synthes (West Chester, PA, USA), and royalties from Spineart Deutschland GmbH (Frankfurt, Germany).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Schwendner, Sollmann, Diehl, Oechsner, Meyer, Krieg and Combs. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neurology

MINI REVIEW
published: 28 September 2018
doi: 10.3389/fneur.2018.00758

Prevention of Brain Metastases

*Joseph A. Bovi**

Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, United States

The incidence of brain metastases is projected to rise because survival rates of lung cancer, breast cancer, and melanoma continue to improve (1). The brain is being identified as a sanctuary site for harboring metastases despite excellent control of extracranial disease. This is thought to occur because the drug therapies that control extracranial disease have limited central nervous system (CNS) penetration. The development of brain metastases is a devastating diagnosis affecting both quality of life (QOL) and survival. Symptoms after diagnosis can include headache, nausea, vomiting, seizure, neurocognitive decline, and focal neurologic deficit. Some of these symptoms can be irreversible even after successful treatment of intracranial disease. Treatment of brain metastases often necessitates surgery and radiation. There have been some reports of systemic therapies offering an intracranial response however long-term data is lacking. These treatments for CNS metastases can also lead to neurocognitive sequelae impacting quality of life. Therefore, preventing disease from spreading to the brain is a topic that has generated much interest in oncology. Prophylactic cranial Irradiation (PCI) has been used in leukemia, small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC). While showing effectiveness in preventing intracranial disease development, its carries with it side effects of neurocognitive decline that can affect QOL. There are Clinical trials exploring novel delivery of PCI and concurrent neuroprotective drug therapy to try to mitigate these neurocognitive sequelae. These will be important trials to complete, as PCI has shown promise in controlling disease and prolonging survival in select patient populations. There are also drug therapies that have shown efficacy in preventing CNS metastases development. This review will explore the current therapies available to prevent CNS metastases.

Keywords: CNS metastases, prevention, SRS, WBRT, immunotherapy, targeted therapy (TT)

OPEN ACCESS

Edited by:
Sunit Das,
St. Michael's Hospital, Canada

Reviewed by:
Riccardo Soffietti,
Università degli Studi di Torino, Italy
Arjun Sahgal,
University of Toronto, Canada
Kaisorn Chaichana,
Mayo Clinic, United States

***Correspondence:**
Joseph A. Bovi
jbovi@mcw.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *29 June 2018*
Accepted: *21 August 2018*
Published: *28 September 2018*

Citation:
Bovi JA (2018) Prevention of Brain Metastases. Front. Neurol. 9:758. doi: 10.3389/fneur.2018.00758

STANDARD BRAIN METS TREATMENT

Standard therapies for brain metastases often include surgery, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or a combination of these treatment modalities. The decision for utilizing these therapies are often dependent upon the number of lesions, their location, and the severity of patients' symptoms.

The routine use of WBRT has been challenged with recent publications showing improved cognitive outcomes and equivalent survival in patients treated with SRS compared to SRS and WBRT in patients with limited brain metastases (2). In addition, SRS is also being favored over WBRT following resection of metastases as recent data has also shown good local control and equivalent survival with less neurocognitive decline in patients where WBRT following surgery was

omitted (3, 4). Regardless of the reduction in neurocognitive sequelae when WBRT is withheld, it's important to recognize that patients still experienced neurocognitive decline even when focused radiotherapy was administered. This is a fact that is frequently omitted in the discussion of the results of these trials. The mere presence of metastatic disease can lend itself to neurocognitive symptoms. These may not be outwardly apparent to the patient or clinician but in trials where pre-treatment cognitive assessments were performed, pre-WBRT neurocognitive symptoms were uncovered with testing (5, 6). This underscores the need for prevention of brain metastases as opposed treatment after the development of intracranial disease.

PCI IN THE MANAGEMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

PCI was initially introduced in order to address metastatic disease to the CNS in childhood leukemia. The CNS was known to be a sanctuary site for leukemic cells and CNS relapses were common and carried with it a poor prognosis (7–9). Early studies had shown that patients with high risk features (young age at diagnosis, T cell phenotype, WBC count >50,000–100,000, extra-medullary disease, presence of Philadelphia chromosome ,and poor response to induction chemotherapy) had poor survival even after they had achieved remission, and this was attributed to CNS relapses (7–9). In high risk populations, PCI has been shown to decrease the rate of CNS recurrences from 42 to 100% down to 6% (10). These impressive results have been seen in both the pediatric and adult populations (11).

The unfortunate result of delivering radiation therapy to the brain in this disease process is the long-term repercussions of CNS radiation toxicity. Some of the side effects that children developed as a result of these therapies were neurocognitive decline, mood disturbances, short stature, abnormal skull growth, endocrinopathies, and secondary malignancies. As a result of these side effects the radiotherapy dose has been aggressively decreased from 24 to 12 Gy in the hopes of avoiding some or all of these long-term toxicities (12–14).

Currently, leukemia CNS prophylaxis without PCI has been the preferred approach. As an example, the Berlin-Franfurt-Munster (NHL-BFM 95) trial showed that in Stage III–IV lymphoblastic leukemia who received high dose systemic methotrexate, including intrathecal (IT) methotrexate, had very low rates of CNS relapse comparable to historic control who had received PCI (15). Additionally, the Children's Leukemia Group showed that even in patients with CNS involvement at diagnosis had high rates of cure and low rates of CNS relapse with appropriate systemic and IT therapies (16).

Current management of ALL, even with high risk features, excludes PCI. However, the early use of this treatment modality was the initial pioneering effort that led to cures of childhood ALL and paved the way for this treatment modality to be utilized in other malignancies where metastases can be harbored in the CNS and shielded from effective systemic chemotherapies.

PCI IN SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) is an additional malignancy where CNS failure rates are approximated to be 50–60% at 2 years following diagnosis (17). CNS failure in SCLC carries with it a poor prognosis (18). As a result of these high rates of CNS failure, consideration of delivering PCI to improve local CNS control was considered.

Initial early trials did not show a clear benefit to the delivery of PCI in SCLC (19). These early trials did not separate patients into limited disease (LD) or extensive disease (ED) or perform appropriate re-staging for response to chemotherapy prior to the delivery of PCI. The failure to show improvements in survival was likely due to the competing risk of death from systemic disease progression or the presence of CNS disease prior to the delivery of "prophylactic" CNS radiation. What became evident was that patients who had a complete response to systemic chemotherapy in LD SCLC and were re-staged prior to the delivery of PCI benefitted from PCI with both local control and survival (**Table 1**). The Aurperin meta-analysis demonstrated that the use of PCI at varying dose and fractionation schedules who had a complete response to systemic chemotherapies had a 50% reduction in the development of brain metastases and an improvement in overall survival (20.7% PCI vs. 15% observation) (25). A more recent analysis of 12 trials by Meert et al. showed similar results. PCI decreased brain metastases and improved survival in patients achieving a complete response (CR) after chemotherapy with hazard ratio [HR] of 0.48 (95% CI 0.39–0.60) for incidence of brain metastases, and HR of 0.82 (95% CI 0.71–0.96) for survival. However, when patients with less than a CR to chemotherapy were included in this analysis, the benefit of PCI on survival became non-significant (HR 0.94, 0.87–1.02) (27).

Recommendations for PCI in patients with ED-SCLC is less clear. Auperin's meta-analysis included a small number of patients with ED-SCLC and in those patients who achieved a complete response (CR) to systemic chemotherapy there was better survival and lower rates of brain metastases when PCI was administered (25).

In addition to this data, the European Organization for Research and Treatment of Cancer (EORTC) performed a Phase III trial investigating the role of PCI in patients with ED SCLC who had partial response (PR) or CR to chemotherapy (28). The risk of brain metastases at 1-year was significantly reduced in the PCI group (14.6% PCI vs. 40.4% No PCI), and the 1-year survival rate was also superior (27.1% PCI and 13.3% No PCI). A criticism of this study was its lack of re-staging brain MRI in asymptomatic patients which may have led to inclusion of patients who may have harbored brain metastases.

More evidence in support of PCI in ED-SCLC came from a North Central Cancer Treatment Group analysis examining patients with LD and ED-SCLC with stable disease following chemotherapy and thoracic radiotherapy. Three hundred eighteen patients were enrolled, and this showed improvement in survival at 1 and 3 years with limited toxicity using traditional radiation dose fractionation (29).

There are other studies that question the routine use of PCI in ED-SCLC. The Japanese closed their phase III trial early due to

TABLE 1 | Randomized trials of PCI in SCLC.

Trial	Years	Patients (*n*)	PCI dose (Gy# of fractions)	Brain metastasis rate (%) (PCI vs. no PCI)	*p*-value	Survival (PCI vs. no PCI)	*p*-value	References
UMCC	1977–1980	29	30/10	0 vs. 36	0.02			(20)
Okayama	1981–1986	46	40/20	22 vs. 52	<0.05	Median 21 months vs. 15 months	0.097	(21)
PCI-85	1985–1993	300	24/8	40 vs. 67 (2 year rate)	$<10^{-13}$	29 vs. 21.5 (2 year)	0.14	(18)
UKCCCR-RORTC	1987–1995	314	Variable	38 vs. 54 (3 year rate)	0.00004	21 vs. 11 (3 year)	0.25	(22)
PCI-88	1988–1994	211	Variable	44 vs. 51 (4 year rate)	0.14	22 vs. 16 (4 year)	0.25	(23)
ECOG-RTOG	1991–1994	32	25/10	24 vs. 53	NS	Median 15.3 months vs. 8.8 months	0.25	(24)
Auperin meta-analysis	1977–1995	987	Variable	33.3 vs. 58.6 (3 year rate)	<0.0001	20.7 vs. 15.3(3 year)	0.01	(25)

Adapted from Prophylactic cranial irradiation: recent outcomes and innovations (26).

the lack of survival seen in patients who received PCI (25 Gy in 10 fractions). Median survival was shown to be 10.1 months in those receiving PCI compared to 15.1 months without PCI ($p = 0.091$). However, there was a significant reduction in the development of brain metastases (32% PCI vs. 58% No PCI) which matches the 50% reduction in brain metastases development seen in patients with LD-SCLC where PCI is administered (30).

There is a clear role for PCI in LD-SCLC who demonstrate a CR to systemic chemotherapy with improvements in both local control and survival. The routine use of PCI in ED-SCLC is less clear. However, it seems very reasonable to consider administering this therapy in patients with ED-SCLC who show response to initial systemic chemotherapies and who have not developed brain metastases upon restaging of the CNS prior to PCI delivery.

ROLL OF PCI IN NON-SMALL CELL LUNG CANCER (NSCLC)

Brain metastases occur with frequency in patients diagnosed with NSCLC and are also one of the first sites of relapse. Patient with early stage (I–II) disease are less likely to be diagnosed with brain metastases compared to those with more advanced disease (Stage III) (31–37).

The role of PCI in NSCLC is not as well established as it is in those with SCLC. However, there are some older studies that demonstrated PCI reduced development of CNS metastases and prolonged the time to develop intracranial disease. Cox et al. had shown that PCI decreased the incidence of CNS metastases from 13% to 6% ($p = 0.038$) (38). Umsawasdi et al. showed a decrease in CNS metastases from 27% (No PCI) to 4% (PCI) ($p = 0.002$) with an increase in CNS metastases free survival (39).

However, the biggest criticism of PCI in NSCLC is that, while this treatment modality demonstrates reductions in the development of brain metastases, there is not a corresponding improvement in overall survival. As an example, the RTOG tried to demonstrate a benefit of PCI in Stage II and III NSCLC. With 187 patients enrolled, there were non-significant reductions in the development of brain metastases but also a non-significant reduction in survival in the PCI arm (40). There was however one trial that showed a significant benefit in brain metastases reduction and survival (41).

Based upon these mixed results, the RTOG tried to definitively answer the question of the benefit of PCI in NSCLC with RTOG 0214. This was a Phase III trial with Stage IIIA and IIIB NSCLC. Three hundred fifty-six patients were accrued to this study. After definitive treatment, patients were randomized to PCI, 30 Gy in 15 fractions or observation. This study closed early due to poor accrual. Unfortunately, it failed to show a difference in overall survival between the two arms, however, there was a statistically significant reduction in the development of brain metastases (18.0% No PCI vs. 7.7% PCI, p =0.004) (42).

Based upon these trials, the routine use of PCI in NSCLC is not routinely recommended. (**Table 2**).

SIDE EFFECTS AND QOL

Cranial radiation can cause significant neurologic toxicity that can negatively impact QOL. This argument is used for forgoing PCI especially in settings where a survival benefit is not realized. However, when PCI is omitted, the competing risk of neurologic sequelae caused by the emergence of CNS metastases must also be considered (28).

Earlier studies reporting on the neurocognitive impact of PCI were small, retrospective, and did not establish a pre-treatment baseline (43). The absence of a pre-treatment baseline is critical because there are many factors that can lead to neurocognitive decline in patients other than the presence of metastatic disease or radiotherapy. Age, smoking, paraneoplastic syndromes, and depression are just a few factors that can lead to neurocognitive symptoms in the absence of radiotherapy. This is why it is absolutely necessary to perform neurocognitive assessments on patients at baseline to truly measure the impact that radiotherapy can have on posttreatment neurocognition.

Modern series assessing the efficacy of PCI have included more robust and reliable assessments of cognitive function assessed both before and after the administration of radiotherapy like mini mental status exam (MMSE), Hopkins Verbal Learning

TABLE 2 | Randomized trials evaluating PCI in NSCLC.

Trial	Year of publication	Patients (*n*)	PCI dose (Gy# of fractions)	Brain metastasis rate (%) (PCI vs. no PCI)	*p*-value	Survival (PCI vs. no PCI)	*p*-value	References
VALG	1981	281	20/10	6 vs. 13	0.038	Median 8.2 months vs. 9.7 months	0.5	(38)
MDACC	1984	97	30/10	4 vs. 27	0.02			(39)
RTOG 8403	1991	187	30/10	9 vs. 19	0.10	Median 8.4 months vs. 8.1 months	NS	(40)
SWOG	1998	254	37.5/15 or 30/10	1 vs. 11	0.003	Median 8 months vs. 11 months	0.004	(41)
RTOG 0214	2011	356	30/15	7.7 vs. 18 (1 year rate)	0.004	75.6 vs. 76.9 (1 year)	0.86	(42)

Adapted from Prophylactic cranial irradiation: recent outcomes and innovations (26).

Test (HVLT) and Controlled Oral Word Association (COWA). Cognitive evaluation of RTOG 0212 showed a correlation between higher-dose PCI and increased, chronic neurological toxicity, but this was not associated with an impact on HVLT score (44).

Pooled analysis of RTOG 0212 and RTOG 0214 reported that patients treated with PCI had a greater risk of self-reported neurocognitive decline at 6 months (odds ratio [OR] 3.60, 95% CI 2.34–6.37; $p < 0.0001$) and 12 months (OR 3.44, 1.84–6.44; $p < 0.0001$) in addition to a decline in HVLT recall score at 6 and 12 months compared with the observation group (6, 44, 45).

QOL was also assessed in RTOG 0214 and showed that while global cognitive function and QOL was preserved between PCI and no PCI cohorts, there was decline in memory as measured by the HVLT in the group that received radiotherapy (6). Therefore, robust cognitive assessments may show neurocognitive decline in those receiving PCI, however, this does not always translate into patient's QOL being impacted.

There are currently efforts underway to try to deliver PCI in a way to try to mitigate cognitive effects. NRG Oncology CC003 *"Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer"* is currently accruing patients in the hopes of enhancing the therapeutic ratio of PCI[1]; improve intracranial control while limiting neurocognitive toxicity. It has been hypothesized that radiation-induced injury to proliferating neuronal progenitor cells in the sub granular zone of the hippocampi may be responsible for the radiation induced NCF decline, thus, avoiding the hippocampal region of the brain may reduce cognitive side effects (46–48). The addition of neurocognitive protective agents is also being considered to further reduce the cognitive side effects of cranial irradiation (49).

SYSTEMIC TARGETED OR IMMUNOTHERAPIES THERAPIES FOR BRAIN METASTASES PREVENTION

An interesting approach to the treatment of brain metastases to try to mitigate the deleterious effect of radiotherapy to the brain has been to consider targeted or immunotherapies upfront to treat intracranial disease. The Chinese Thoracic Oncology Group conducted a randomized trial looking at patients with NSCLC with epidermal growth factor receptor (EGFR) mutations, who were naive to treatment with EGFR-tyrosine kinase inhibitors (TKI) or radiotherapy and had at least three metastatic brain lesions to either icotinib or WBRT (30 Gy in ten fractions of 3 Gy) plus concurrent or sequential chemotherapy for 4–6 cycles. In patients with EGFR-mutant NSCLC and multiple brain metastases, icotinib had significantly longer intracranial PFS than WBI plus chemotherapy. Therefore, icotinib might be a better first-line therapeutic option for this patient population (50).

In another recently published trial, 303 patients with untreated, advanced ALK-positive NSCLC were treated with alectinib (600 mg twice daily) or crizotinib (250 mg twice daily). The primary end point was PFS. Secondary end points were time to CNS progression, objective CNS response rate, and overall survival. A CNS response was appreciated in 17 of 21 patients in the alectinib group (CNS response rate, 81%; 95% CI, 58 to 95) and in 11 of 22 patients in the crizotinib group (CNS response rate, 50%; 95% CI, 28 to 72). Eight patients (38%) in the alectinib group had a CNS complete response (CR), compared to 1 patient (5%) in the crizotinib group. The median duration of intracranial response was 17.3 months in the alectinib group (95% CI, 14.8 to not estimable) and 5.5 months in the crizotinib group (95% CI, 2.1 to 17.3), respectively. A CNS response occurred in 38 of 64 patients in the alectinib group (CNS response rate, 59%; 95% CI, 46 to 71) and in 15 of 58 patients in the crizotinib group (CNS response rate, 26%; 95% CI, 15 to 39) in patients who had measurable disease. Twenty-nine patients (45%) in the alectinib group had a CNS CR, as compared with 5 patients (9%) in the crizotinib group. This was an important trial as it showed that in patients who harbor an ALK-mutation, targeted therapies can be effective in treating and *preventing* CNS progression (51).

Similar studies have also been performed in patients with metastatic melanoma. In a recently published trial, patients with asymptomatic melanoma brain metastases with no prior local CNS therapy were randomly assigned to cohort A (nivolumab plus ipilimumab, $n = 36$) or cohort B (nivolumab, $n = 27$). With a median follow up of 17 months (IQR 8–25), intracranial responses were achieved by 16 (46%; 95% CI 29–63) of 35 patients in cohort A and five (20%; 7–41) of 25 in cohort B. Intracranial CR occurred in six (17%) patients in cohort A and three (12%) in cohort B. The effectiveness of these therapies came at the cost of

treatment-related adverse events which occurred in 34 (97%) of 35 patients in cohort A and 17 (68%) of 25 in cohort B. Grade 3 or 4 treatment-related adverse events occurred in 19 (54%) patients in cohort A and four (16%) in cohort B indicating that the combination therapy was more toxic (52).

Another EGFR-TKI Lapatinib has also shown effectiveness in the treatment of metastatic HER2 positive breast cancer to the brain based upon 2, Phase II clinical trials (53, 54). Addition studies have also shown that Lapatinib in combination with chemotherapy can decrease the rate of CNS relapse of Her2 positive disease from 6% down the 1–2%. Currently, the Radiation Therapy Oncology Group (RTOG) 1119 is evaluating the complete response rate in the brain at 12 weeks post WBRT based upon MRI with the addition of Lapatinib and WBRT compared to WBRT alone in women with Her2 positive disease that has metastasized to the brain[1]. Another agent that has shown activity in the treatment of HER2 positive metastatic breast cancer to the brain is neratinib. There are trials currently accruing to determine if neratinib combined with other systemic chemotherapies will show activity against CNS metastases (55).

An interesting concept based upon these promising results is whether systemic targeted or immunotherapies could be used in the prevention of disease as opposed to treatment of metastases that have already developed. Trial concepts are currently being generated at the cooperative group level to address this question.

[1]https://www.rtog.org/ClinicalTrials/Welcome.aspx

CONCLUSION

The prevention of metastases spreading to the CNS would have a significant benefit in preventing debilitating side effects. PCI has shown promise in preventing CNS metastases in ALL, LD and ED-SCLC, and NSCLC. However, a survival benefit has only been firmly established in ALL and SCLC. Some argue that in the absence of a survival benefit PCI should be omitted because of the neurologic and QOL sequelae that can occur in some patients. However, consideration needs to be given to the competing decline in cognition and QOL that can arise because of the development of CNS metastases. Novel radiation delivery techniques and targeted and immunotherapies may provide some hope of preventing CNS metastases without the negative impact on cognition and QOL.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Posner JB, Chernik NL. Intracranial metastases from systemic cancer. *Adv Neurol.* (1978) 19:579–92.
2. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi: 10.1001/jama.2016.9839
3. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1049–60. doi: 10.1016/S1470-2045(17)30441-2
4. Soliman H, Ruschin M, Angelov L, Brown PD, Chiang VLS, Kirkpatrick JP, et al. Consensus contouring guidelines for postoperative completely resected cavity stereotactic radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* (2018) 100:436–42. doi: 10.1016/j.ijrobp.2017.09.047
5. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol.* (2007) 25:1260–6. doi: 10.1200/JCO.2006.09.2536
6. Sun A, Bae K, Gore EM, Movsas B, Wong SJ, Meyers CA, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. *J Clin Oncol.* (2011) 29:279–86. doi: 10.1200/JCO.2010.29.6053
7. Aur RJ, Hustu HO, Verzosa MS, Wood A, Simone JV. Comparison of two methods of preventing central nervous system leukemia. *Blood* (1973) 42:349–57.
8. Aur RJ, Simone JV, Husto HO, Verzosa MS, Pinkel D. Cessation of therapy during complete remission of childhood acute lymphocytic leukemia. *N Engl J Med.* (1974) 291:1230–4. doi: 10.1056/NEJM197412052912306
9. Pinkel, D. (1987). Curing children of leukemia. *Cancer* 59:1683–91. doi: 10.1002/1097-0142(19870515)59:10<1683::AID-CNCR2820591002>3.0.CO;2-G
10. Hustu HO, Aur RJ. Extramedullary leukaemia. *Clin Haematol.* (1978) 7:313–37. doi: 10.1016/S0308-2261(78)80008-3
11. Hoelzer D, Gökbuget N, Digel W, Faak T, Kneba M, Reutzel R, et al. Outcome of adult patients with T-lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. *Blood* (2002) 99:4379–85. doi: 10.1182/blood-2002-01-0110
12. Bongers ME, Francken AB, Rouwé C, Kamps WA, Postma A. Reduction of adult height in childhood acute lymphoblastic leukemia survivors after prophylactic cranial irradiation. *Pediatr Blood Cancer* (2005) 45:139–43. doi: 10.1002/pbc.20334
13. Glover DA, Byrne J, Mills JL, Robison LL, Nicholson HS, Meadows A, et al. Impact of CNS treatment on mood in adult survivors of childhood leukemia: a report from the Children's Cancer Group. *J Clin Oncol.* (2003) 21:4395–401. doi: 10.1200/JCO.2003.04.089
14. Langer T, Martus P, Ottensmeier H, Hertzberg H, Beck JD, Meier W. CNS late-effects after ALL therapy in childhood. Part III: neuropsychological performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. *Med Pediatr Oncol.* (2002) 38:320–8. doi: 10.1002/mpo.10055
15. Burkhardt B, Woessmann W, Zimmermann M, Kontny U, Vormoor J, Doerffel W, et al. Impact of cranial radiotherapy on central nervous system prophylaxis in children and adolescents with central nervous system-negative stage III or IV lymphoblastic lymphoma. *J Clin Oncol.* (2006) 24:491–9. doi: 10.1200/JCO.2005.02.2707
16. Uyttebroeck A, Suciu S, Laureys G, Robert A, Pacquement H, Ferster A, et al. Treatment of childhood T-cell lymphoblastic lymphoma according to the strategy for acute lymphoblastic leukaemia, without radiotherapy: long term results of the EORTC CLG 58881 trial. *Eur J Cancer* (2008) 44:840–6. doi: 10.1016/j.ejca.2008.02.011
17. Komaki R, Cox JD, Whitson W. Risk of brain metastasis from small cell carcinoma of the lung related to length of survival and prophylactic irradiation. *Cancer Treat Rep.* (1981) 65:811–4.
18. Arriagada R, Le Chevalier T, Borie F, Rivière A, Chomy P, Monnet I, et al. Prophylactic cranial irradiation for patients with small-cell lung

cancer in complete remission. *J Natl Cancer Inst.* (1995) 87:183–90. doi: 10.1093/jnci/87.3.183
19. Kristjansen PE, Kristensen CA. The role of prophylactic cranial irradiation in the management of small cell lung cancer. *Cancer Treat Rev.* (1993) 19:3–16. doi: 10.1016/0305-7372(93)90023-K
20. Aroney RS, Aisner J, Wesley MN, Whitacre MY, Van Echo DA, Slawson RG, et al. Value of prophylactic cranial irradiation given at complete remission in small cell lung carcinoma. *Cancer Treat Rep.* (1983) 67:675–82.
21. Ohonoshi T, Ueoka H, Kawahara S, Kiura K, Kamei H, Hiraki Y, et al. Comparative study of prophylactic cranial irradiation in patients with small cell lung cancer achieving a complete response: a long-term follow-up result. *Lung Cancer* (1993) 10:47–54. doi: 10.1016/0169-5002(93)90308-K
22. Gregor A, Cull A, Stephens RJ, Kirkpatrick JA, Yarnold JR, Girling DJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer* (1997) 33:1752–8. doi: 10.1016/S0959-8049(97)00135-4
23. Laplanche A, Monnet I, Santos-Miranda JA, Bardet E, Le Péchoux C, Tarayre M, et al. Controlled clinical trial of prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *Lung Cancer* (1998) 21:193–201. doi: 10.1016/S0169-5002(98)00056-7
24. Wagner HKK, Turrisi A. A randomized Phase III study of prophylactic cranial irradiation vs observationin patient with small cell lung cancerachieving a complete response: final report of an incomplete trial by the ECOG and RTOG. *Proc Am Soc Clin Oncol.* (1996) 15:376.
25. Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. prophylactic cranial irradiation overview collaborative group *N Engl J Med.* (1999) 341:476–84. doi: 10.1056/NEJM199908123410703
26. Snider JW, Gondi V, Brown PD, Tome W, Mehta MP. Prophylactic cranial irradiation: recent outcomes and innovations. *CNS Oncol.* (2014) 3:219–30. doi: 10.2217/cns.14.22
27. Meert AP, Paesmans M, Berghmans T, Martin B, Mascaux C, Vallot F, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer* (2001) 1:5. doi: 10.1186/1471-2407-1-5
28. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med.* (2007) 357:664–72. doi: 10.1056/NEJMoa071780
29. Schild SE, Foster NR, Meyers JP, Ross HJ, Stella PJ, Garces YI, et al. Prophylactic cranial irradiation in small-cell lung cancer: findings from a North Central Cancer Treatment Group Pooled Analysis. *Ann Oncol.* (2012) 23:2919–24. doi: 10.1093/annonc/mds123
30. Seto T, Takahashi T, Yamanaka T. Prophylactic cranial irradiation has a detrimental effect on the overall survival of patients with extensive disease small cell lung cancer:results of a Japanese randomized Phase III trial. *Proc Am Soc Clin Oncol.* (2014) 32:663–71. doi: 10.1016/S1470-2045(17)30230-9
31. Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT, Weick JK, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol.* (1995) 13:1880–92. doi: 10.1200/JCO.1995.13.8.1880
32. Andre F, Grunenwald D, Pujol JL, Girard P, Dujon A, Brouchet L, et al. Patterns of relapse of N2 nonsmall-cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered. *Cancer* (2001) 91:2394–400. doi: 10.1002/1097-0142(20010615)91:12<2394::AID-CNCR1273>3.0.CO;2-6
33. Carolan H, Sun AY, Bezjak A, Yi QL, Payne D, Kane G, et al. Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection. *Lung Cancer* (2005) 49:109–15. doi: 10.1016/j.lungcan.2004.12.004
34. Gaspar LE, Chansky K, Albain KS, Vallieres E, Rusch V, Crowley JJ, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol.* (2005) 23:2955–61. doi: 10.1200/JCO.2005.08.026
35. Komaki R, Scott CB, Byhardt R, Emami B, Asbell SO, Russell AH, et al. Failure patterns by prognostic group determined by recursive partitioning analysis (RPA) of 1547 patients on four radiation therapy oncology group (RTOG) studies in inoperable nonsmall-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys.* (1998) 42:263–7. doi: 10.1016/S0360-3016(98)00213-2
36. Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. *J Clin Oncol.* (2001) 19:1344–9. doi: 10.1200/JCO.2001.19.5.1344
37. Strauss GM, Herndon JE, Sherman DD, Mathisen DJ, Carey RW, Choi NC, et al. Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIA non-small-cell carcinoma of the lung: report of a Cancer and Leukemia Group B phase II study. *J Clin Oncol.* (1992) 10:1237–44. doi: 10.1200/JCO.1992.10.8.1237
38. Cox JD, Stanley K, Petrovich Z, Paig C, Yesner R. Cranial irradiation in cancer of the lung of all cell types. *JAMA* (1981) 245:469–72. doi: 10.1001/jama.1981.03310300023013
39. Umsawasdi T, Valdivieso M, Chen TT, Barkley HT, Booser DJ, Chiuten DF, et al. Role of elective brain irradiation during combined chemoradiotherapy for limited disease non-small cell lung cancer. *J Neurooncol* .(1984) 2:253–9. doi: 10.1007/BF00253278
40. Russell AH, Pajak TE, Selim HM, Paradelo JC, Murray K, Bansal P, et al. Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys.* (1991) 21:637–43. doi: 10.1016/0360-3016(91)90681-S
41. Miller TP, Canwell JJ, Mira J. A randomized trial of chemotherapy and radiotherapy for stage III non-small cell lung cancer. *Cancer Ther.* (1998) 1:229–36.
42. Gore EM, Bae K, Wong SJ, Sun A, Bonner JA, Schild SE, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. *J Clin Oncol.* (2011) 29:272–8. doi: 10.1200/JCO.2010.29.1609
43. Le Péchoux C, Arriagada R. Prophylactic cranial irradiation in small cell lung cancer. *Hematol Oncol Clin North Am.* (2004) 18:355–72. doi: 10.1016/j.hoc.2003.12.004
44. Wolfson AH, Bae K, Komaki R, Meyers C, Movsas B, Le Pechoux C, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* (2011) 81:77–84. doi: 10.1016/j.ijrobp.2010.05.013
45. Mizumatsu S, Monje ML, Morhardt DR, Rola R, Palmer TD, Fike JR. Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res.* (2003) 63:4021–7.
46. Ghia A, Tomé WA, Thomas S, Cannon G, Khuntia D, Kuo JS, et al. Distribution of brain metastases in relation to the hippocampus: implications for neurocognitive functional preservation. *Int J Radiat Oncol Biol Phys.* (2007) 68:971–7. doi: 10.1016/j.ijrobp.2007.02.016
47. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol.* (2014) 32:3810–6. doi: 10.1200/JCO.2014.57.2909
48. Raber J, Rola R, LeFevour A, Morhardt D, Curley J, Mizumatsu S, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res.* (2004) 162:39–47. doi: 10.1667/RR3206
49. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.* (2013) 15:1429–37. doi: 10.1093/neuonc/not114
50. Yang JJ, Zhou C, Huang Y, Feng J, Lu S, Song Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. *Lancet Respir Med.* (2017) 5:707–16. doi: 10.1016/S2213-2600(17)30262-X

51. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* (2017) 377:829–38. doi: 10.1056/NEJMoa1704795
52. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol.* (2018) 19:672–81. doi: 10.1016/S1470-2045(18)30139-6
53. Lin NU, Carey LA, Liu MC, Younger J, Come SE, Ewend M, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol.* (2008) 26:1993–9. doi: 10.1200/JCO.2007.12.3588
54. Lin NU, Diéras V, Paul D, Lossignol D, Christodoulou C, Stemmler HJ, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res.* (2009) 15:1452–9. doi: 10.1158/1078-0432.CCR-08-1080
55. Freedman RA, Gelman RS, Wefel JS, Melisko ME, Hess KR, Connolly RM, et al. Translational Breast Cancer Research Consortium (TBCRC) 022: a phase II trial of neratinib for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol.* (2016) 34:945–52. doi: 10.1200/JCO.2015.63.0343

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Bovi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

REVIEW
published: 09 October 2018
doi: 10.3389/fonc.2018.00415

Strategies to Preserve Cognition in Patients With Brain Metastases: A Review

*Tyler P. Robin and Chad G. Rusthoven**

Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO, United States

Brain metastases are common to the natural history of many advanced malignancies. Historically, whole brain radiation therapy (WBRT) has played a key role in the management of brain metastases, especially for patients with multiple lesions. However, prospective trials have demonstrated consistent neurocognitive toxicities after WBRT, and various pharmacologic and anatomic strategies designed to mitigate these toxicities have been studied in recent years. Memantine, an NMDA receptor antagonist, taken during and after WBRT improved cognitive preservation in a randomized trial over placebo. Deliberate reductions in radiation dose to the hippocampus, via hippocampal-avoidance (HA)-WBRT, resulted in improved cognition over historic controls in a phase II trial, and follow-up randomized trials are now ongoing to evaluate cognitive outcomes with HA vs. conventional brain radiation techniques. Nevertheless, some of the most promising strategies currently available to reduce the cognitive effects of brain radiation may be found in efforts to avoid or delay WBRT administration altogether. Stereotactic radiosurgery (SRS), involving focused, high-dose radiation to central nervous system (CNS) lesions with maximal sparing of normal brain parenchyma, has become the standard for limited brain metastases (classically 1–3 or 4 lesions) in the wake of multiple randomized trials demonstrating equivalent survival and improved cognition with SRS alone compared to SRS plus WBRT. Today, there is growing evidence to support SRS alone for multiple (≥4) brain metastases, with comparable survival to SRS alone in patients with fewer lesions. In patients with small-cell lung cancer, the routine use of prophylactic cranial irradiation (PCI) for extensive-stage disease has been also been challenged following the results of a randomized trial supporting an alternative strategy of MRI brain surveillance and early salvage radiation for the development of brain metastases. Moreover, new systemic agents are demonstrating increasing CNS penetration and activity, with the potential to offer greater control of widespread and microscopic brain disease that was previously only achievable with WBRT. In this review, we endeavor to put these clinical data on cognition and brain metastases into historical context and to survey the evolving landscape of strategies to improve future outcomes.

Keywords: brain metastases (BM), radiosurgery, cognition, neurocognition, whole brain radiation therapy (WBRT), hippocampus, memantine, tyrosine kinase inhibitor

OPEN ACCESS

Edited by:
Sunit Das,
St. Michael's Hospital, Canada

Reviewed by:
Riccardo Soffietti,
Università degli Studi di Torino, Italy
David M. Peereboom,
Cleveland Clinic Lerner College of Medicine, United States

****Correspondence:***
Chad G. Rusthoven
chad.rusthoven@ucdenver.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *29 June 2018*
Accepted: *07 September 2018*
Published: *09 October 2018*

Citation:
Robin TP and Rusthoven CG (2018) Strategies to Preserve Cognition in Patients With Brain Metastases: A Review. Front. Oncol. 8:415. doi: 10.3389/fonc.2018.00415

INTRODUCTION

Paradigms for the management of brain metastases are evolving, with increasing treatment options and a greater focus on cognitive preservation. In an effort to mitigate the neurocognitive effects of whole brain radiation (WBRT) and prophylactic cranial irradiation (PCI), both anatomic and pharmacologic strategies have been studied in recent years, including hippocampal-avoidance radiation and the concomitant use of the drug memantine for neuroprotection (1, 2). In addition, one of the most promising neurocognitive preservation strategies has been the more limited use of WBRT and PCI altogether (3). There is growing evidence to support the use of stereotactic radiosurgery (SRS) for patients with multiple brain metastases, and guideline statements have been adapted to reduce strict reliance on lesion number for selection of SRS candidates (4–6). The contemporary role of PCI for small-cell lung cancer in the era of MRI staging and surveillance has also been challenged by a recent randomized trial (7). Concurrently, a number of emerging systemic therapies have shown increasing CNS penetration and activity, blurring the historic lines of distinction between anticipated CNS and extra-CNS disease response rates to systemic therapy (8–20). Herein, we review the emerging clinical data on neuroprotective strategies and attempt to place these data into the historical context of brain metastases management.

WBRT: CNS DISEASE CONTROL, COGNITION, AND SURVIVAL

WBRT has been the historic standard for the management of brain metastases and, prior to the more widespread availability of SRS, WBRT often represented the only means for treating unresected brain metastases in cases ranging from diffuse to solitary CNS lesions. As access to SRS technology increased a number of trials began comparing strategies of SRS alone to SRS plus WBRT for limited (1–3 or 4) brain metastases (21–25). The results of these trials, detailed below, would ultimately make SRS alone the contemporary standard of care for limited brain metastases; however, the role of SRS alone in multiple (often defined as $\geq$4) lesions remains somewhat controversial due to the exclusion of these patients from the landmark randomized trials (5). In addition, WBRT delivered in the form of PCI for patients without evidence of brain metastases remains the standard of care for patients with limited-stage small-cell lung cancer (LS-SCLC) following a response to first-line therapy, and is an option for patients with extensive-stage (ES) disease (26). Thus, the neurocognitive impact of WBRT and PCI remain highly relevant to contemporary clinical practice.

Multiple randomized trials of SRS alone vs. SRS plus WBRT for patients with limited metastases have demonstrated that, overall, the addition of WBRT is associated with (1) objective declines in neurocognitive function, (2) improved CNS disease control rates, but (3) no benefit in terms of OS (21–25). The first major trial published was a multicenter Japanese study reported by Aoyama et al. in 2006. That study randomized 132 patients with 1–4 brain metastases to WBRT and SRS or SRS alone and found an improvement in CNS control rates with no differences in OS with the addition of WBRT (21). Similarly, an EORTC trial enrolled patients with 1–3 brain metastases treated initially with SRS or surgical resection (local therapy was at the physician's discretion) and randomized them to WBRT or observation. This trial also observed a reduction in CNS progression events with WBRT, but no differences in OS (23). While these trials clearly demonstrated that WBRT did not significantly affect OS outcomes, the collection of rigorous cognitive data was limited. In a single-institution phase III trial at MD Anderson, Chang et al. randomized patients with 1–3 brain metastases to SRS alone vs. SRS plus WBRT with a primary endpoint of neurocognitive function. This study was stopped early by the data safety monitoring committee due to increased cognitive decline on the Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months with WBRT. For SRS plus WBRT, the mean probability of decline in total recall, delayed recall, and delayed recognition, was 52, 22, and 11%, respectively, compared with 24, 6, and 0% for patients treated with SRS alone (22). In an NCCTG study, Brown et al. reported the results of a randomized trial comparing SRS alone to SRS plus WBRT for 1–3 brain metastases with a primary endpoint of cognitive function using a rigorous battery of cognitive tests including the HVLT-R, controlled oral word association (COWA) test, Trial-making test (TMT) A and B, and Grooved Pegboard Test. Cognitive deterioration was defined as a decline of more than one standard deviation from baseline in at least one cognitive test. There was less cognitive deterioration at 3 months after SRS alone compared with SRS plus WBRT (63.5 vs. 91.7%, $p < 0.001$). Importantly, cognitive deterioration was also assessed at 12 months in long-term survivors, and the difference in cognitive decline persisted (60 vs. 94.4%, $p = 0.04$) (24). A subsequent study from the NCCTG, also reported by Brown et al. and using a similar cognitive testing battery, compared WBRT vs. SRS to the surgical cavity in patients with resected brain metastases. This study reported a decrease in cognitive-deterioration-free survival with WBRT (3.7 vs. 3.0 months, HR 0.47, 95% CI 0.35–0.63, $p < 0.0001$), as well as an increase in 6-month cognitive deterioration among patients that received WBRT (52 vs. 85%, $p < 0.001$). Consistent with the aforementioned studies, there was no difference in OS (median 12.2 months for SRS vs. 11.6 months for WBRT, HR 1.07, 95% CI 0.76–1.50, $p = 0.70$) (25).

Together the randomized trials above have detailed consistent improvements in CNS control rates with WBRT that do not translate into OS benefits, but are associated with objective declines in cognitive performance. Notably, an unplanned subgroup analysis of the Japanese trial by Aoyama et al. suggested that WBRT might improve OS in a subgroup of patients of patients with favorable prognoses; however, separate secondary analyses from both the NCCTG and EORTC trials have since refuted this finding (27–29). Moreover, a meta-analysis of three of these trials reported by Saghal et al. found no benefit in OS overall and, provocatively, suggested a decrement in OS with WBRT among patients <50 years of age (30). The apparent disconnect between improved CNS control without an accompanying improvement in OS with WBRT may be attributable to the observation that most contemporary patients

with brain metastases do not die of CNS progression (4, 31), and that subsequent CNS progression events are often salvageable without WBRT when identified in the context of brain MRI surveillance (32). In response to the consistency of these data, the contemporary NCCN CNS guidelines advocate SRS alone as the preferred treatment for limited brain metastases (5). These guideline recommendations underscore the clinical importance of cognitive decline after WBRT, and suggests that improved CNS control in the absence of an OS benefit fails to justify routine administration in patients with limited CNS disease (5).

One of the largest analyses of the cognitive impact of PCI was reported by Gondi et al. who performed a pooled analysis of the RTOG 0212 and 0214 trials (33). The RTOG 0212 enrolled patients with LS-SCLC who achieved a response to 1st-line therapy and randomized them to PCI with 25 vs. 36 Gy, while the RTOG 0214 was a trial in stage III non-small cell lung cancer (NSCLC) patients who had completed curative-intent therapy and then were randomized to PCI vs. observation (34, 35). In the pooled analysis comparing PCI vs. no-PCI outcomes, declines in tested cognitive function were observed at both 6 and 12 months, and a more than three-fold decrease in patient-reported cognitive outcomes were reported with PCI (33). Moreover, a dedicated analysis of the RTOG 0212 demonstrated increased cognitive decline with higher PCI radiation doses, and the RTOG 0212 and intergroup trials found greater declines in cognition and QOL after PCI in association with older patient age (35, 36).

The consistent neurocognitive effects of WBRT and PCI are also accompanied by a variety of characteristic anatomic and pathophysiologic correlates. Moderate doses of radiation to the entire brain common to WBRT and PCI have been associated with cortical thinning, demyelination, attenuated capillary density, damage to the vascular endothelium, disruption of the blood-brain barrier, oxidative and pro-inflammatory stress, and impairment of neurogenesis (28, 37–42). In a notable illustrative study, Monaco et al. analyzed longitudinal brain MRI findings in lung cancer patients treated SRS plus WBRT vs. SRS alone and found dramatic increases in the incidence and severity of white matter changes at 1 and 2 years among patients who received WBRT (**Figure 1**) (39).

ATTENUATING THE NEUROCOGNITIVE EFFECTS OF WBRT WITH PHARMACOTHERAPY

For patients requiring WBRT, there has been interest in the use of neuroprotective drugs to preserve cognitive function. Memantine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which has important roles in learning and memory. In the setting of vascular dementia, ischemia is associated with excessive NMDA receptor activation and excitotoxicity, and inhibition of the NMDA receptor with memantine represents a neuroprotective strategy (1, 43–45). The RTOG 0614 explored the hypothesis that memantine could be protective in the setting of radiation-induced excitotoxicty and neurocognitive decline. This study was a randomized controlled trial in patients undergoing WBRT for brain metastases, of placebo vs. memantine concurrent with WBRT and for an additional 6 months. Memantine was well tolerated and although the trend toward delayed recall (the primary endpoint) did not reach statistical significance ($p = 0.059$), memantine did delay time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed (1). As a result, the NCCN CNS and small-cell lung cancer guidelines acknowledge the potential role of memantine to promote cognitive preservation for patients undergoing both WBRT and PCI, although the latter has not yet been tested in a randomized control trial (5, 26).

A separate phase II trial enrolling patients treated with partial brain radiation or WBRT (66% with primary brain tumors, 26% with brain metastases, 8% receiving PCI) randomized 198 patients to placebo or donepezil, a reversible acetylcholine esterase inhibitor. Although donepezil did not improve cognitive composite scores (the primary endpoint), donepezil did result in modest improvements in memory (46). Donepezil, however, is not advocated for cognitive preservation in the context of brain radiation by the contemporary national guidelines (5, 26). In addition to memantine and donepezil, there is lower-level clinical and pre-clinical evidence investigating a variety of other pharmacologic agents (47). For example, one single-arm phase II study evaluated the botanical agent, *Ginkgo biloba*, in 34 patients receiving partial or whole brain radiation and reported improved neurocognitive function assessments over time (48).

Overall, the improved cognitive preservation with pharmacotherapy in the randomized RTOG 0614 represents a unique success in the radiation oncology literature, demonstrating proof of principle that radiation-induced cognitive decline can be attenuated with pharmacotherapy. It is also important to acknowledge, however, that the rates of cognitive decline after WBRT in the RTOG 0614 study remained suboptimal (cognitive preservation at 24 weeks was 31% with memantine vs. 20% with placebo), and further research into novel neuroprotective agents is warranted.

REDUCING WBRT TOXICITY ANATOMICALLY: HIPPOCAMPAL-AVOIDANCE

A separate strategy to potentially mitigate neurocognitive toxicity in patients undergoing WBRT and PCI involves a reduction in radiation exposure to the hippocampus using conformal intensity-modulated radiation therapy (IMRT). It has been proposed that injury to the neural stem-cell compartment of the hippocampal dentate gyrus may represent an important pathophysiologic mechanism of radiation-induced cognitive decline (2, 49, 50). Providing preliminary data in support of this hypothesis, the multi-institutional single-arm phase II RTOG 0933 demonstrated superior cognitive preservation on the HVLT-R with hippocampal avoidance WBRT (HA-WBRT) as compared to historical WBRT controls (2). As a result, two separate NRG Oncology trials have been launched to evaluate the impact of HA-WBRT in the randomized setting. The phase III NRG CC001 (NCT02360215) is randomizing patients requiring

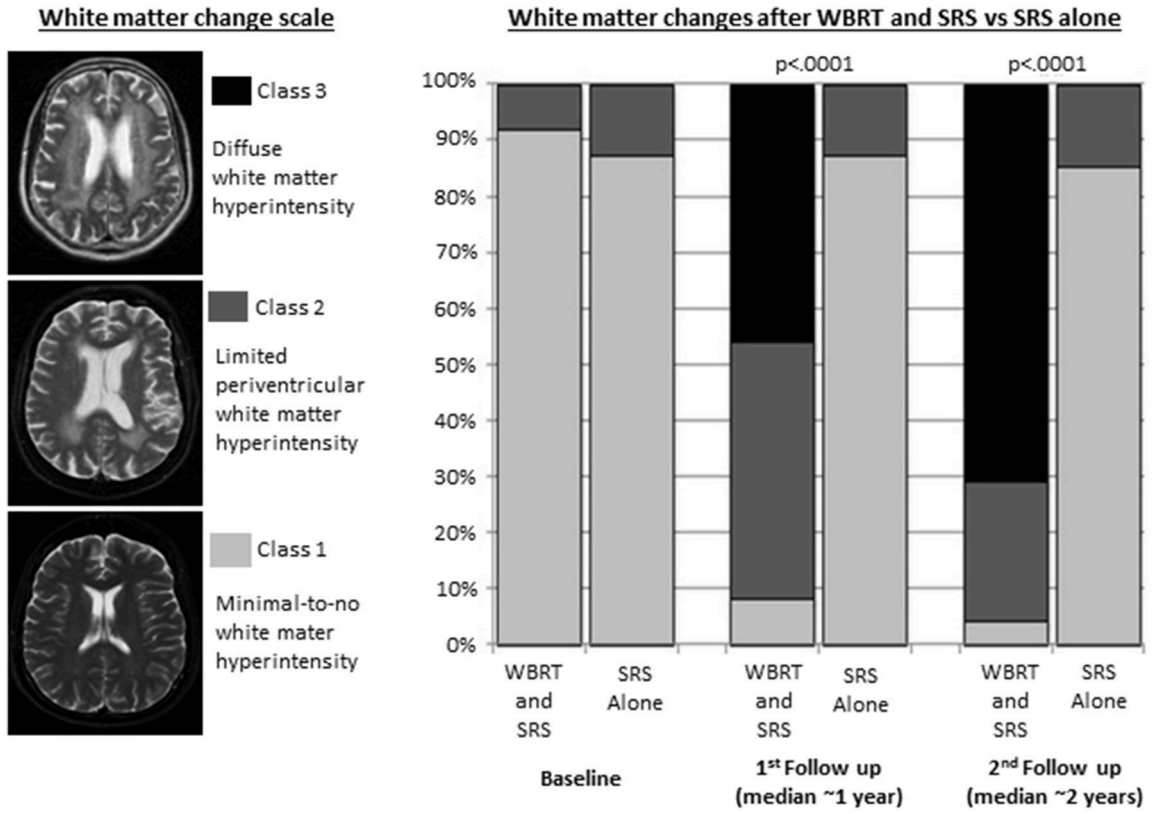


FIGURE 1 | White matter changes in patients with non-small cell lung cancer brain metastases treated with whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) ($n = 37$) or SRS alone ($n = 31$). Adapted from Monaco et al. (39) with permission from the publisher.

WBRT for brain metastases from various histologies to HA-WBRT vs. conventional WBRT, with a primary endpoint of cognitive preservation on a testing battery including the HVLT-R, COWA, and TMT A and B. All patients in this trial will receive concurrent and adjuvant memantine for 6 months. The phase II/III NRG CC003 (NCT02635009) is randomizing patients with LS and ES-SCLC to PCI with and without hippocampal avoidance, with optional memantine administration. The phase II portion is designed to confirm a non-inferior 12-month intracranial relapse rate with HA-PCI vs. conventional PCI, and the phase III portion will test whether HA-PCI can reduce the rate of 6-month deterioration on the HVLT-R delayed recall.

THE EXPANSION OF SRS AND NARROWING OF WBRT INDICATIONS

While WBRT remains an appropriate treatment for contemporary patients with diffuse brain metastases, there is a wealth of randomized evidence indicating that avoiding WBRT in favor of SRS for suitable candidates can offer superior cognitive preservation and equivalent OS (21–25). SRS alone does, however, come at the cost of higher rates of new brain metastases and greater need for subsequent brain treatments, often in the form of further SRS (4, 21–24, 32). This trade-off between superior cognitive preservation but higher rates of retreatment after SRS has largely been accepted for patients with limited brain metastases, and is now increasingly being studied and supported for patients with ≥4 brain lesions (4, 5, 32).

The strongest current evidence in support of SRS for multiple metastases comes from a Japanese single-arm, multi-institutional prospective study of SRS alone in 1,194 patients with 1–10 brain metastases reported by Yamamoto et al. (4, 51) This study stratified patients into groups of 1, 2–4, and 5–10 brain lesions. OS was superior among patients with a single brain lesion. The key finding, however, was that there were no significant differences in OS, toxicity, or subsequent CNS failure rates among patients with 2–4 vs. 5–10 brain lesions. Moreover, the rates of death from causes related to CNS progression were similarly low (6–10%) in all three cohorts (4). A recent follow up analysis to this study also found no differences in cognitive preservation rates between the cohorts; although, it should be acknowledged that this analysis was limited by its reliance on the mini-mental status exam, which is known to be a less sensitive metric for radiation-induced cognitive deterioration (51). Historically, SRS alone has been considered a reasonable strategy for 1–3 or 4 lesions based primarily on the inclusion criteria of the aforementioned randomized trials of SRS with and without WBRT (21–24); however, this large prospective trial by Yamamoto et al. suggests that SRS for 5–10 brain metastases may

be just as safe and effective as SRS for 2–4 lesions, where SRS alone is already widely accepted (4). In response to this data, the NCCN now acknowledges the use of SRS alone as an option for carefully selected patients with "extensive" (a strict number criteria has been intentionally omitted) brain metastases (5).

Along the lines of the Japanese data, our group from the University of Colorado recently reviewed the outcomes of patients with ALK and EGFR driven NSCLC brain metastases treated with SRS alone for ≥4 lesions (range 4–26) (32). The median OS was 3 years (4.2 for ALK and 2.4 for EGFR patients), emphasizing the encouraging prognoses and importance of cognitive preservation strategies in these subsets. OS was comparable regardless of the number of SRS courses and number of brain metastases treated either in a single session or overall. The 5-year freedom from neurologic death and freedom from WBRT rates were 84 and 97%, respectively. Of note, the mean hippocampal and whole-brain doses were exceedingly low even among patient treated to more than 10 lesions in a single session (1.2 G and 0.8 Gy, respectively), as compared to representative plans of conventional WBRT (30.3 and 30.9 Gy) and HA-WBRT (10.6 and 31.9 Gy). These dosimetric findings suggest that SRS alone even for numerous metastases may provide superior hippocampal sparing compared to HA-WBRT and that treating multiple lesions with SRS does not equate to *de facto* WBRT from a dosimetric standpoint (32).

These data, along with a variety of other institutional reports (52–55), provide increasing support for SRS in carefully selected patients with multiple brain lesions. Several randomized trials are ongoing or in development to evaluate WBRT vs. SRS in patients with multiple brain metastases (NCT02353000; NCT03550391; NCT01592968; NCT02953717).

While the role of SRS has been expanded for increasing numbers of brain metastases, the accepted indications for WBRT have also begun to shrink for patients with more limited prognoses. The QUARTZ trial enrolled a population of 538 poor-prognosis NSCLC patients (median OS 9 weeks overall) with brain metastases who were not considered candidates for SRS and randomized them to WBRT or best supportive care. This trial found no significant difference in quality-adjusted life years (primary endpoint) or OS, suggesting that omission of WBRT may be a reasonable recommendation in this population (56).

TREATING BRAIN METASTASES WITH CNS-ACTIVE SYSTEMIC THERAPIES

Historically, for patients with metastatic disease, the CNS and extra-CNS have largely been viewed as distinct compartments, at least in terms of anticipated response rates to systemic therapy. This division has primarily been attributed to the blood brain barrier, which can reduce conventional chemotherapy concentrations in the CSF to levels much lower than the peripheral blood, making the CNS a potential pharmacologic sanctuary for disease progression. As result, strategies for spatially cooperative combined-modality therapy emerged, with systemic therapy being used conceptually for extra-CNS control and radiation for the treatment of the brain. These historic lines of distinction, however, are now beginning to blur as emerging molecularly-targeted and immunotherapy agents have begun demonstrating encouraging CNS response and control rates in prospective trials (8–20). Below we highlight some of the recent data with an emphasis on some contemporary studies in lung cancer and melanoma (**Table 1**).

In ALK gene-rearranged lung cancer, a pooled analysis of two single arm phase 2 studies of alectinib, with a median follow-up of 12.4 months, demonstrated objective CNS response rates of 64% in patients with measurable CNS disease, and a median duration of response of 10.8 months (12). In a phase 3 study that randomized patients with ALK-rearranged NSCLC to alectinib vs. crizotinib, the CNS response rate and median duration of response for patients with baseline CNS metastases was 81% and 17.3 months, vs. 50% and 5.5 months, for alectinib vs. crizotinib, respectively (17). Similarly, in an exploratory analysis of 2 trials of brigatinib for ALK-positive NSCLC, the objective response rates were 53, 46, and 67%, in patients with measurable brain metastases, from the phase I/II study, ALTA arm A (brigatinib 90 mg daily), and ALTA arm B (brigatinib 180 mg daily), respectively (18). In patients with EGFR TKI-sensitive lung cancer, a pooled analysis of two phase II trials of osimertinib demonstrated CNS response rates of 54% in patients with measurable CNS disease; the median duration of response was not reached with 75% of patients estimated to remain in response at 9 months (15). Similarly, 46 patients included in the AURA3 randomized study of osimertinib or platinum-pemetrexed, had baseline measurable brain metastases. The CNS response rate was 70% in patients randomized to osimertinib vs. 31% in those randomized to platinum-pemetrexed (20).

In BRAF-mutated melanoma, a phase II study of dabrafenib and trametinib for patients with brain metastases demonstrated intracranial response rates of 44–59% in cohorts stratified by BRAF mutation type, prior CNS therapy, symptoms, and performance status. Importantly, however, the durability of response appeared to be suboptimal, with median durations of CNS response of only 4.5–8.3 months across the cohorts (14).

In evaluation of single-agent vs. combination immunotherapy, a randomized phase 2 study of patients with melanoma brain metastases reported objective intracranial responses with a median of 17 months follow-up in 16 of 35 (46%) patients treated with ipilumumab/nivolumab and 5 of 25 (20%) treated with nivolumab alone (19). A separate single-arm, single-institution phase II study of pembrolizumab enrolled patients with untreated brain metastases and reported response in 4 of 18 (22%) patients with melanoma in 6 of 18 (33%) with NSCLC, which appear similar to expected extracranial response rates (13). Intracranial responses were also generally durable, with all but one patient showing continued response at a median of 11.6 and 6.8 months of follow-up in the melanoma and NSCLC cohorts, respectively (13).

The emerging data on systemic agents with enhanced CNS activity are encouraging and have generated appropriate optimism regarding the expanding arsenal for the treatment and prevention of brain metastases. It is important to acknowledge, however, that there is limited prospective data comparing CNS-penetrant agents to strategies incorporating

TABLE 1 | Selected studies supporting CNS efficacy for systemic agents in melanoma, lung, and breast cancer.

References	Eligibility	No. of pts	Drug	Methods	Outcomes
Margolin et al. (9)	Metastatic melanoma with BM (divided into cohorts for symptomatic or asymptomatic)	72	Ipi	Phase II	CNS disease control: 24% in asymptomatic cohort 10% in symptomatic cohort
Goldberg et al. (13)	Untreated asymptomatic BM from melanoma or NSCLC	36	Pembro	Phase II	CNS response: melanoma: 22% NSCLC: 33%
Long et al. (19)	Untreated asymptomatic melanoma BM with no previous local brain therapy	79	Nivo OR Ipi/Nivo	Randomized Phase II	CNS response: Ipi/Nivo: 46% Nivo: 20% Nivo (after failed local therapy, symptomatic, or with LMD): 6%
Davies et al. (14)	Metastatic melanoma with BM cohorts: (A)$BRAF^{V600E}$/asymptomatic/no prior local brain therapy/ECOG 0/1 (B) $BRAF^{V600E}$/asymptomatic/prior local brain therapy/ECOG 0/1 (C) $BRAF^{V600D/K/R}$/asymptomatic/ with or without prior local brain therapy/ECOG 0/1 (D) $BRAF^{V600D/E/K/R}$/symptomatic/ with or without prior local brain therapy/ECOG 0/1/2	125	D/T	Phase II	CNS response: (A) 58% (B) 56% (C) 44% (D) 59% Duration of response (median): (A) 6.5 months (B) 7.3 months (C) 8.3 months (D) 4.5 months
Gadgeel et al. (12)	ALK-positive NSCLC after prior crizotinib (Pts with measurable CNS disease were pooled from two single-arm phase II studies)	50 pts with measurable CNS lesions	Alectinib	Pooled analysis of 2 Phase II studies	CNS response: 64.0% Duration of response (median): 10.8 mo
Peters et al. (17)	Previously untreated advanced ALK-positive NSCLC	Total: 303 BM: 43 pts with measurable CNS lesions	Crizotinib OR alectinib	Phase III	CNS response: crizotinib: 50% alectinib: 81% Duration of response (median): crizotinib: 5.5 months alectinib: 17.3 months
Goss et al. (15)	T790M-positive advanced NSCLC after progression on other EGFR-TKI with >1 measurable CNS lesion (pooled analysis of two phase II trials)	50	Osi	Pooled analysis of 2 Phase II studies	CNS response: 54.0% Duration of response (median): NR Est duration of response: 75% at 9 mo
Wu et al. (20)	T790M-positive advanced NSCLC after progression on other EGFR-TKI. Planned subgroup analysis of AURA3 for patients with baseline CNS lesions.	46 pts with measurable CNS lesions	Osi	Planned subgroup analysis of phase III	CNS response: osimertinib: 70% Platinum-pemetrexed: 31%
Camidge et al. (18)	ALK-positive NSCLC (Exploratory analysis of pts with baseline brain metastases from two prospective studies): (1) phase I/II (NCT01449461) (2) phase II ATLA (NCT02094573) arm A (3) phase II ATLA (NCT02094573) arm B	Measurable (>10 mm) (1) 15 (2) 26 (3) 18	brigatinib	Exploratory analysis of a phase I/II and subsequent phase II study	CNS response (among pts with measurable (>10 mm) brain metastases: (1) 53% (2) 46% (3) 67%
Lin et al. (8)	HER2+ breast cancer after prior trastuzumab and progressive BM after prior WBRT or SRS	242	L	Phase II	CNS response: 6% (20% in patients on capecitabine-lapatinib expansion)
Bachelot et al. (10)	HER2+ breast cancer with BM not previously treated with WBRT, capecitabine, or lapatinib	45	X/L	Phase II	CNS response: 65.9%
Krop et al. (11)	Her2+ breast cancer after prior trastuzumab and a taxane (exploratory analysis of EMILIA limited to patients with pre-existing BM)	95	TDM-1 OR X/L	Exploratory analysis of Phase III study	CNS progression: TDM-1: 22.2%; XL: 16.0% Median overall survival: TDM-1: 26.8 mo; XL: 12.9 mo

BM, brain metastases; L, lapatinib; X, capecitabine; X/L, capecitabine and lapatinib; TDM-1, trastuzumab emtansine; Ipi, ipilimumab; Pembro, pembrolizumab; Nivo, nivolumab; LMD, leptomeningeal disease; D, abrafenib; T, trametinib; Osi, osimertinib; pem, pemetrexed; platinum, cisplatin or carboplatin; NR, not reached.

CNS radiotherapy. One recent trial compared icotinib alone, a first generation EGFR-TKI with modest CNS activity, to radiation and chemotherapy for brain metastases and found improved CNS control outcomes with icotinib (57). This trial was notably limited by a lack of detailed information of CNS failure patterns (e.g., existing vs. new lesions) and the use of a non-standard control arm of 1st line chemotherapy in EGFR-sensitive NSCLC. It is probable in this setting, and many others, that a strategy incorporating CNS active agents with a combination of radiation therapy would offer superior CNS disease control outcomes to either therapy alone, and some cautionary retrospective analyses have been reported to that end (58). Moreover, while it may be presumed that drugs with increased activity across the blood-brain barrier will have a lesser impact on cognition than therapies like WBRT, high-level evidence is still lacking. In addition, drugs with prospective data characterizing encouraging objective CNS response rates are still only applicable for a subset patients with metastatic cancer. Nevertheless, the CNS activity of emerging systemic agents is already relevant to contemporary practice and should open the door to new strategies to improve both CNS control and cognitive preservation. Future trials will be needed to assess optimal multidisciplinary integration of local and systemic therapy for brain metastases.

EVOLVING CNS MANAGEMENT STRATEGIES IN SMALL-CELL LUNG CANCER (SCLC)

Although SRS alone for limited brain metastases has been accepted across most histologies, SCLC represents a notable exception where WBRT remains a guideline recommendation in cases ranging from diffuse to solitary CNS lesions, as well as in patients without radiographic brain metastases in the form of PCI (26). Historic objections to the use of SRS in SCLC have generally included the concern for diffuse interval CNS progression and the potential for a resulting decrease in survival in such cases. There is, however, growing evidence to suggest that SRS alone may be appropriate for some patients with SCLC (**Table 2**) (32, 59–62). Notably, Serizawa et al. compared the outcomes of SCLC ($N = 34$) and NSCLC ($N = 211$) patients with brain metastases treated with SRS alone and found comparable rates of OS, CNS control, and neurologic mortality in SCLC and NSCLC patients (59). Yomo and Hayashi reported on 70 SCLC patients treated with SRS (46 patients underwent SRS alone without prior PCI or WBRT), with median OS of 7.8 months and encouraging one- and two-year neurologic mortality-free survival of 94 and 84%, respectively (61). Recently, our group reported a National Cancer Database (NCDB) analysis of upfront SRS ($N = 200$) vs. WBRT for brain metastases, and observed favorable survival outcomes with SRS overall and on propensity-score matched analyses (6). While these retrospective data are subject to confounding from selection bias, they do suggest that a subset of patients with SCLC might be safely and effectively managed with SRS alone and point to the need for prospective investigation. One recently opened randomized phase II trial (ENCEPHALON) is comparing SRS to WBRT for SCLC patients with 1–10 brain metastases (NCT03297788).

For patients with a response to first-line therapy, PCI remains a guideline endorsed therapy for LS-SCLC patients and a treatment option for those with ES-SCLC (26). PCI was accepted in SCLC management after a 1999 meta-analysis of 7 trials of primarily LS-SCLC patients (86%) reported a 5% improvement in OS at 3 years, and a subsequent 2007 EORTC randomized trial in ES-SCLC reported a 14% OS benefit at 12-months and a 1.3 month (6.7 vs. 5.4) improvement in median survival (63, 64). The OS advantage of PCI in the contemporary MRI era, however, was recently challenged by a phase III randomized trial in Japan that, unlike the EORTC or trials included in the aforementioned meta-analysis, required brain MRI staging and surveillance (every 3 months in year-1 and every 6 months in year-2) (7). This trial found a similar reduction in brain metastases to prior PCI

TABLE 2 | Studies of first-line SRS (no prior PCI or WBRT) for SCLC brain metastases.

References	No. of patients	Methods	Outcomes
Serizawa et al. (59)	34 (compared with 211 NSCLC pts)	Retrospective comparison of SRS outcomes for SCLC vs. NSCLC	No significant difference in any outcome, including local control, overall survival, and neurologic survival
Jo et al. (60)	50 (first-line SRS: 12)	Retrospective	Median overall survival for first line SRS group: 4.6 months
Yomo and Hayashi (61)	70 (first-line SRS: 46)	Retrospective	Median overall survival: 7.8 months One-year neurologic death-free survival: 94% Two-year neurologic death-free survival: 84%
Ozawa et al. (62)	94 (LS-SCLC, managed with strategy of PCI omission, MRI surveillance, and SRS salvage)	Retrospective	Median overall survival: 34 months 30.8% of patients developed brain metastases within 2 years of diagnosis *No significant difference in outcomes when compared to 29 patients that received PCI
Robin et al. (6)	200	Retrospective/ US national cancer registry database	Median overall survival: 10.8 months *Compared with matched cohort of patients that received WBRT, superior OS observed with SRS

SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer; PCI, prophylactic cranial irradiation.

studies, but reported no difference in PFS and, provocatively, a trend toward improved OS (median 13.7 vs. 11.6 months) with omission of PCI (7).

Reconciling the conflicting OS outcomes from the ES-SCLC PCI trials from the EORTC and Japan requires some consideration of the key differences in their respective designs. First, the Japanese trial mandated MRI staging, whereas the EORTC trial only obtained CNS imaging for neurologic symptoms. It is estimated that up to 25% of SCLC may have brain metastases when staged with MRI at diagnosis (65), and one study found that up to one-third without brain metastases developed them during first-line therapy (66). Thus, a meaningful but unknown percentage of patients in the EORTC trial were actually randomized to WBRT for brain metastases vs. observation until symptoms. Second, the MRI surveillance in the Japanese trial allowed for more patients to receive salvage radiation, presumably because metastases were identified at earlier and, thus, more treatable stages. Among patients who ultimately developed brain metastases in the no-PCI arms of these trials, 83% successfully underwent salvage radiation in the Japanese trial vs. only 59% in the EORTC study (7, 64). Additionally, it is important to note that, in all, only 58% of patients in the no-PCI arm of the Japanese trial (64 of 111 total patients) ultimately required brain radiation and a clinically meaningful 42% did not (7), indicating that the trial was not simply comparing early vs. late radiation, as has sometimes been a suggested.

Overall, the results of the Japanese ES-SCLC trial are important to contemporary clinical practice because they suggest that (1) brain metastases identified earlier in the context of MRI surveillance may be salvaged without negatively impacting survival and (2) that a meaningful subset of patients with SCLC who do not develop brain metastases can be spared the neurocognitive sequela of PCI altogether. Moreover, the design of the Japanese trial also points to the need for new studies in LS-SCLC comparing PCI to MRI surveillance strategies, as the trials included in the 1999 meta-analysis of LS-SCLC were all in the pre-MRI era and the majority of patients did not undergo brain CT staging or surveillance in those studies (67, 68). In response to this data, the NCCN has now changed PCI from recommended to optional in ES-SCLC and has endorsed MRI surveillance for any patient that does not receive PCI (26).

CONCLUSIONS AND FUTURE DIRECTIONS

The management of brain metastases remains a complex and highly-individualized discipline in oncology. As prognoses continue to improve for patients with brain metastases, efforts to minimize the cognitive sequelae of therapy will only become increasingly important. Numerous clinical trials have characterized the deleterious effects of moderate doses of radiation to the entire brain common to WBRT and PCI, challenging investigators to develop new strategies to attenuate, avoid, or delay the neurocognitive effects of these therapies. Pharmacotherapy and anatomic avoidance strategies are actively being investigated, as is the expansion of SRS candidacy to patients with increasing burdens of CNS disease. It is also clear that management of brain metastases will become increasingly multidisciplinary in the context of emerging systemic agents with enhanced CNS activity. A new generation of combined-modality trials involving local and systemic therapies will be needed to evaluate the optimal strategies for durable CNS disease control, neurocognitive function, and survival in the rapidly evolving landscape of therapies for metastatic disease.

AUTHOR CONTRIBUTIONS

TR and CR: Conception and design, writing, and final approval of manuscript.

REFERENCES

1. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro-oncology* (2013) 15:1429–37. doi: 10.1093/neuonc/not114
2. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol.* (2014) 32:3810. doi: 10.1200/JCO.2014.57.2909
3. Trifiletti DM, Sheehan JP, Grover S, Dutta SW, Rusthoven CG, Kavanagh BD, et al. National trends in radiotherapy for brain metastases at time of diagnosis of non-small cell lung cancer. *J Clin Neurosci.* (2017) 45:48–53. doi: 10.1016/j.jocn.2017.08.028
4. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol.* (2014) 15:387–95. doi: 10.1016/S1470-2045(14)70061-0
5. NCCN Org. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Central Nervous System Cancers version 1.2018 [Online]* (2018). Available: http://www.nccn.org (Accessed 17 April, 2018).
6. Robin TP, Jones BL, Amini A, Koshy M, Gaspar LE, Liu AK, et al. Radiosurgery alone is associated with favorable outcomes for brain metastases from small-cell. *Lung Cancer* (2018) 120:88–90. doi: 10.1016/j.lungcan.2018.03.027
7. Takahashi T, Yamanaka T, Seto T, Harada H, Nokihara H, Saka H, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* (2017) 18:663–71. doi: 10.1016/S1470-2045(17)30230-9
8. Lin NU, Diéras V, Paul D, Lossignol D, Christodoulou C, Stemmler H-J, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res.* (2009) 15:1452–9. doi: 10.1158/1078-0432.CCR-08-1080
9. Margolin K, Ernstoff MS, Hamid O, Lawrence D, Mcdermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol.* (2012) 13:459–65. doi: 10.1016/S1470-2045(12)70090-6
10. Bachelot T, Romieu G, Campone M, Diéras V, Cropet C, Dalenc F, et al. Lapatinib plus capecitabine in patients with previously

untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol.* (2013) 14:64–71. doi: 10.1016/S1470-2045(12)70432-1

11. Krop I, Lin N, Blackwell K, Guardino E, Huober J, Lu M, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol.* (2014) 26:113–9. doi: 10.1093/annonc/mdu486
12. Gadgeel SM, Shaw AT, Govindan R, Gandhi L, Socinski MA, Camidge DR, et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non–small-cell lung cancer. *J Clin Oncol.* (2016) 34:4079–85. doi: 10.1200/JCO.2016.68.4639
13. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol.* (2016) 17:976–83. doi: 10.1016/S1470-2045(16)30053-5
14. Davies MA, Saiag P, Robert C, Grob J-J, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol.* (2017) 18:863–73. doi: 10.1016/S1470-2045(17)30429-1
15. Goss G, Tsai C-M, Shepherd F, Ahn M-J, Bazhenova L, Crinò L, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. *Ann Oncol.* (2017) 29:687–93. doi: 10.1093/annonc/mdx820
16. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum–pemetrexed in EGFR T790M–positive lung cancer. *N Engl J Med.* (2017) 376:629–40. doi: 10.1056/NEJMoa1612674
17. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. *N Engl J Med.* (2017) 377:829–38. doi: 10.1056/NEJMoa1704795
18. Camidge DR, Kim D-W, Tiseo M, Langer CJ, Ahn M-J, Shaw AT, et al. Exploratory analysis of brigatinib activity in patients with anaplastic lymphoma kinase-positive non–small-cell lung cancer and brain metastases in two clinical trials. *J Clin Oncol.* (2018) 36:2693–701. doi: 10.1200/JCO.2017.77.5841
19. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol.* (2018). 19:672–81. doi: 10.1016/S1470-2045(18)30139-6
20. Wu Y-L, Ahn M-J, Garassino MC, Han J-Y, Katakami N, Kim HR, et al. CNS Efficacy of osimertinib in patients with T790M-positive advanced non–small-cell lung cancer: data from a randomized phase III trial (AURA3). *J Clin Oncol.* (2018) 36:2702–09. doi: 10.1200/JCO.2018.77.9363
21. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* (2006) 295:2483–91. doi: 10.1001/jama.295.21.2483
22. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet oncol.* (2009) 10:1037–44. doi: 10.1016/S1470-2045(09)70263-3
23. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol.* (2011) 29:134–41. doi: 10.1200/JCO.2010.30.1655
24. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316:401–9. doi: 10.1001/jama.2016.9839
25. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC· 3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* (2017) 18:1049–60. doi: 10.1016/S1470-2045(17)30441-2
26. NCCN.Org. *National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. Version 1.2018*. (2018). Available online at: www.nccn.org (Accessed 7 March, 2018).
27. Aoyama H, Tago M, Shirato H. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases: secondary analysis of the JROSG 99-1 randomized clinical trial. *JAMA Oncol.* (2015) 1:457–64. doi: 10.1001/jamaoncol.2015.1145
28. Churilla T, Handorf E, Collette S, Collette L, Dong Y, Aizer A, et al. Whole brain radiotherapy after stereotactic radiosurgery or surgical resection among patients with one to three brain metastases and favorable prognoses: a secondary analysis of EORTC 22952-26001. *Ann Oncol.* (2017) 28:2588–94. doi: 10.1093/annonc/mdx332
29. Churilla TM, Ballman KV, Brown PD, Twohy EL, Jaeckle K, Farace E, et al. Stereotactic radiosurgery with or without whole-brain radiation therapy for limited brain metastases: a secondary analysis of the north central cancer treatment group n0574 (alliance) randomized controlled trial. *Int J Radiat Oncol Biol Phys.* (2017) 99:1173–8. doi: 10.1016/j.ijrobp.2017.07.045
30. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys.* (2015) 91:710–7. doi: 10.1016/j.ijrobp.2014.10.024
31. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol.* (2017) 3:827–31. doi: 10.1001/jamaoncol.2016.3834
32. Robin TP, Camidge DR, Stuhr K, Nath SK, Breeze RE, Pacheco JM, et al. Excellent outcomes with radiosurgery for multiple brain metastases in ALK and EGFR driven non-small cell lung cancer. *J Thorac Oncol.* (2017) 13:715–20. doi: 10.1016/j.jtho.2017.12.006
33. Gondi V, Paulus R, Bruner DW, Meyers CA, Gore EM, Wolfson A, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of radiation therapy oncology group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys.* (2013) 86:656–64. doi: 10.1016/j.ijrobp.2013.02.033
34. Le Pechoux C, Dunant A, Senan S, Wolfson A, Quoix E, Faivre-Finn C, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol.* (2009) 10:467–74. doi: 10.1016/S1470-2045(09)70101-9
35. Wolfson AH, Bae K, Komaki R, Meyers C, Movsas B, Le Pechoux C, et al. Primary analysis of a phase II randomized trial radiation therapy oncology group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* (2011) 81:77–84. doi: 10.1016/j.ijrobp.2010.05.013
36. Le Pechoux C, Laplanche A, Faivre-Finn C, Ciuleanu T, Wanders R, Lerouge D, et al. Clinical neurological outcome and quality of life among patients with limited small-cell cancer treated with two different doses of prophylactic cranial irradiation in the intergroup phase III trial (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01). *Ann Oncol.* (2011) 22:1154–63. doi: 10.1093/annonc/mdq576
37. Welzel T, Niethammer A, Mende U, Heiland S, Wenz F, Debus J, et al. Diffusion tensor imaging screening of radiation-induced changes in the white matter after prophylactic cranial irradiation of patients with small cell lung cancer: first results of a prospective study. *Am J Neuroradiol.* (2008) 29:379–83. doi: 10.3174/ajnr.A0797
38. Lee YW, Cho HJ, Lee WH, Sonntag WE. Whole brain radiation-induced cognitive impairment: pathophysiological mechanisms and therapeutic targets. *Biomol Therapeutics* (2012) 20:357. doi: 10.4062/biomolther.2012.20.4.357
39. Monaco EA, Faraji AH, Berkowitz O, Parry PV, Hadelsberg U, Kano H, et al. Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. *Cancer* (2013) 119:226–32. doi: 10.1002/cncr.27504

40. Warrington JP, Ashpole N, Csiszar A, Lee YW, Ungvari Z, Sonntag WE. Whole brain radiation-induced vascular cognitive impairment: mechanisms and implications. *J Vascul Res.* (2013) 50:445–57. doi: 10.1159/000354227
41. Simó M, Vaquero L, Ripollés P, Gurtubay-Antolin A, Jové J, Navarro A, et al. Longitudinal brain changes associated with prophylactic cranial irradiation in lung cancer. *J Thoracic Oncol.* (2016) 11:475–86. doi: 10.1016/j.jtho.2015.12.110
42. Makale MT, Mcdonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. *Nat Rev Neurol.* (2017) 13:52. doi: 10.1038/nrneurol.2016.185
43. Danysz W, Parsons CG, Karcz-Kubicha M, Schwaier A, Popik P, Wedzony K, et al. GlycineB antagonists as potential therapeutic agents. Previous hopes and present reality *Amino Acids* (1998) 14:235–9. doi: 10.1007/BF01345268
44. Lancelot E, Beal MF. Glutamate toxicity in chronic neurodegenerative disease. *Prog Brain Res.* (1998) 116:331–47. doi: 10.1016/S0079-6123(08)60446-X
45. Orgogozo J-M, Rigaud A-S, Stöffler A, Möbius H-J, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke* (2002) 33:1834–9. doi: 10.1161/01.STR.0000020094.08790.49
46. Rapp SR, Case LD, Peiffer A, Naughton MM, Chan MD, Stieber VW, et al. Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. *J Clin Oncol.* (2015) 33:1653. doi: 10.1200/JCO.2014.58.4508
47. Shaw MG, Ball DL. Treatment of brain metastases in lung cancer: strategies to avoid/reduce late complications of whole brain radiation therapy. *Curr Treatment Opt Oncol.* (2013) 14:553–67. doi: 10.1007/s11864-013-0258-0
48. Attia A, Rapp SR, Case LD, Dagostino R, Lesser G, Naughton1 M, et al. Phase II study of Ginkgo biloba in irradiated brain tumor patients: effect on cognitive function, quality of life, and mood. *J Neuro Oncol.* (2012) 109:357–63. doi: 10.1007/s11060-012-0901-9
49. Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn A-M, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. *Nat Med.* (1998) 4:1313. doi: 10.1038/3305
50. Gondi V, Tomé WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol.* (2010) 97:370–6. doi: 10.1016/j.radonc.2010.09.013
51. Yamamoto M, Serizawa T, Higuchi Y, Sato Y, Kawagishi J, Yamanaka K, et al. A Multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 Study Update): irradiation-related complications and long-term maintenance of mini-mental state examination scores. *Int J Radiat Oncol Biol Phys.* (2017) 99:31–40. doi: 10.1016/j.ijrobp.2017.04.037
52. Grandhi R, Kondziolka D, Panczykowski D, Monaco Iii EA, Kano H, Niranjan A, et al. Stereotactic radiosurgery using the leksell gamma knife perfexion unit in the management of patients with 10 or more brain metastases. *J Neurosurg.* (2012) 117:237–45. doi: 10.3171/2012.4.JNS11870
53. Hunter GK, Suh JH, Reuther AM, Vogelbaum MA, Barnett GH, Angelov L, et al. Treatment of five or more brain metastases with stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* (2012) 83:1394–8. doi: 10.1016/j.ijrobp.2011.10.026
54. Raldow AC, Chiang VL, Knisely JP, James BY. Survival and intracranial control of patients with 5 or more brain metastases treated with gamma knife stereotactic radiosurgery. *Am J Clin Oncol.* (2013) 36:486–90. doi: 10.1097/COC.0b013e31825494ef
55. Rava P, Leonard K, Sioshansi S, Curran B, Wazer DE, Cosgrove GR, et al. Survival among patients with 10 or more brain metastases treated with stereotactic radiosurgery. *J Neurosurg.* (2013) 119:457–62. doi: 10.3171/2013.4.JNS121751
56. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, Mccoll E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* (2016) 388:2004–14. doi: 10.1016/S0140-6736(16)30825-X
57. Yang J-J, Zhou C, Huang Y, Feng J, Lu S, Song Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. *Lancet Respir Med.* (2017) 5:707–16. doi: 10.1016/S2213-2600(17)30262-X
58. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, et al. Management of brain metastases in tyrosine kinase inhibitor–naïve epidermal growth factor receptor–mutant non–small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol.* (2017) 35:1070–7. doi: 10.1200/JCO.2016.69.7144
59. Serizawa T, Ono J, Iichi T, Matsuda S, Sato M, Odaki M, et al. Gamma knife radiosurgery for metastatic brain tumors from lung cancer: a comparison between small cell and non—small cell carcinoma. *J Neurosurg.* (2002) 97:484–8. doi: 10.3171/jns.2002.97.supplement
60. Jo KW, Kong DS, Do Hoon Lim YCA, Nam D-H, Lee J-I. The role of radiosurgery in patients with brain metastasis from small cell lung carcinoma. *J Korean Neurosurg Soc.* (2011) 50:99. doi: 10.3340/jkns.2011.50.2.99
61. Yomo S, Hayashi M. Is stereotactic radiosurgery a rational treatment option for brain metastases from small cell lung cancer? a retrospective analysis of 70 consecutive patients. *BMC Cancer* (2015) 15:95. doi: 10.1186/s12885-015-1103-6
62. Ozawa Y, Omae M, Fujii M, Matsui T, Kato M, Sagisaka S, et al. Management of brain metastasis with magnetic resonance imaging and stereotactic irradiation attenuated benefits of prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. *BMC Cancer* (2015) 15:589. doi: 10.1186/s12885-015-1593-2
63. Aupérin A, Arriagada R, Pignon J-P, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Engl J Med.* (1999) 341:476–84. doi: 10.1056/NEJM199908123410703
64. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med.* (2007) 357:664–72. doi: 10.1056/NEJMoa071780
65. Seute T, Leffers P, Ten Velde GP, Twijnstra A. Detection of brain metastases from small cell lung cancer. *Cancer* (2008) 112:1827–34. doi: 10.1002/cncr.23361
66. Manapov F, Klautke G, Fietkau R. Prevalence of brain metastases immediately before prophylactic cranial irradiation in limited disease small cell lung cancer patients with complete remission to chemoradiotherapy: a single institution experience. *J Thoracic Oncol.* (2008) 3:652–5. doi: 10.1097/JTO.0b013e3181757a76
67. Rusthoven CG, Kavanagh BD. Prophylactic cranial irradiation (pci) versus active mri surveillance for small cell lung cancer: the case for equipoise. *J Thoracic Oncol.* (2017) 12:1746–54. doi: 10.1016/j.jtho.2017.08.016
68. Rusthoven CG, Kavanagh BD. Prophylactic cranial irradiation in small-cell lung cancer. *Lancet Oncol* (2017) 18:e365. doi: 10.1016/S1470-2045(17)30378-9

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Robin and Rusthoven. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Oncology

MINI REVIEW
published: 28 September 2018
doi: 10.3389/fonc.2018.00395

Diagnosis and Management of Radiation Necrosis in Patients With Brain Metastases

Balamurugan Vellayappan[1], Char Loo Tan[2], Clement Yong[3], Lih Kin Khor[4], Wee Yao Koh[1], Tseng Tsai Yeo[5], Jay Detsky[6], Simon Lo[7] and Arjun Sahgal[6]*

[1] Department of Radiation Oncology, National University Cancer Institute, National University Health System, Singapore, Singapore, [2] Department of Pathology, National University Hospital, Singapore, Singapore, [3] Department of Diagnostic Imaging, National University Hospital, Singapore, Singapore, [4] Nuclear Medicine, Advanced Medicine Imaging, Singapore Institute of Advanced Medicine Holdings, Singapore, Singapore, [5] Department of Neurosurgery, National University Hospital, Singapore, Singapore, [6] Department of Radiation Oncology, Sunnybrook Health Sciences Center, University of Toronto, Toronto, ON, Canada, [7] Department of Radiation Oncology, University of Washington School of Medicine, Seattle, WA, United States

The use of radiotherapy, either in the form of stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT), remains the cornerstone for the treatment of brain metastases (BM). As the survival of patients with BM is being prolonged, due to improved systemic therapy (i.e., for better extra-cranial control) and increased use of SRS (i.e., for improved intra-cranial control), patients are clinically manifesting late effects of radiotherapy. One of these late effects is radiation necrosis (RN). Unfortunately, symptomatic RN is notoriously hard to diagnose and manage. The features of RN overlap considerably with tumor recurrence, and misdiagnosing RN as tumor recurrence may lead to deleterious treatment which may cause detrimental effects to the patient. In this review, we will explore the pathophysiology of RN, risk factors for its development, and the strategies to evaluate and manage RN.

Keywords: brain metastases (BM), stereotactic radiosurgery, whole brain radiation therapy, radiation necrosis, MRI imaging techniques

OPEN ACCESS

Edited by:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil

Reviewed by:
Carsten Friedrich, University of Rostock, Germany
Alfredo Conti, Università degli Studi di Messina, Italy

****Correspondence:***
Balamurugan Vellayappan
bala_vellayappan@nuhs.edu.sg

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *29 June 2018*
Accepted: *31 August 2018*
Published: *28 September 2018*

Citation:
Vellayappan B, Tan CL, Yong C, Khor LK, Koh WY, Yeo TT, Detsky J, Lo S and Sahgal A (2018) Diagnosis and Management of Radiation Necrosis in Patients With Brain Metastases. Front. Oncol. 8:395. doi: 10.3389/fonc.2018.00395

INTRODUCTION

Radiotherapy is the cornerstone management for BM. Historically, WBRT was the only available modality for management. Although it provides palliation of symptoms, the survival of patients treated with WBRT alone remains poor (1, 2). Technological advancements have now made SRS widely available, and the effectiveness of SRS in controlling BM is well-documented (3).

Often a combination of these two approaches are used, either upfront or as salvage. Prior randomized controlled trials have shown that the addition of SRS to WBRT improves the local intra-cranial control and survival for patients with a single brain metastasis (4, 5). In contrast, patients treated with SRS (without WBRT), have a higher risk of distant intra-cranial relapse, but no detriment in survival (3). Therefore, National Comprehensive Cancer Network guidelines recommend that patients undergo routine surveillance MRI imaging every 2–3 monthly, especially if treated with SRS alone[1]. Often, treatment-related changes, detected on follow-up scans, are

[1]https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf (Accessed June 2018).

indistinguishable from tumor recurrence. This creates a diagnostic dilemma for many clinicians, as the management of each are vastly different. One of the feared complications of BM treatment is symptomatic RN; this often affects patient quality-of-life and can lead to significant morbidity.

In this review, we will explore the pathophysiology of RN, risk factors for its development, and the strategies to evaluate and manage RN.

INCIDENCE OF RN

Within the context of BM, the true incidence of RN is hard to estimate and probably lies between 5 and 25% (6–10). The definition of RN varies across studies, and only some required histological confirmation. Moreover, the wide variation may be attributable to improved quality and frequency of diagnostic imaging, increased awareness (leading to better reporting) within the oncology community and length of follow-up. For example, a study by Chin et al. where pathological confirmation or temporal resolution was required, the incidence was reported to be 7% (8). In contrast, using primarily imaging-based diagnosis, Minniti et al. reported a 24% incidence of RN (14% symptomatic, 10% asymptomatic), for which they relied on imaging features, such as increased contrast enhancement, non-progression of lesion over 4 months and reduced perfusion on dynamic MRI sequences (6).

PATHOPHYSIOLOGY OF RN

Early experiments were done on rats (11) and dogs (12) with single-fraction brain radiation(10–25 Gy). These experiments showed that the radiation tolerance of the brain was intricately linked to dose, volume of treatment and was a function of time elapsed since radiation. Histopathological analysis from these animal experiments demonstrated changes in vasculature, as well as demyelination, in the irradiated areas. Higher doses consistently led to demyelination and necrosis, as well as an earlier manifestation of necrosis.

There are two theories behind the pathophysiology of RN, however it is likely that the true cause is multi-factorial (13).

1. Vascular injury theory
    a. Radiation disrupts the blood-brain barrier, resulting in increased capillary leakiness and vascular permeability (14). Radiation, especially in large fraction sizes >8 Gy, activates acid sphingomyelinase and causes upregulation of ceramide, which in turn causes endothelial apoptosis (15). This leads to increased oxygen-free radicals, a pro-inflammatory milieu (through release of Tumor-necrosis factor and interleukin-1 beta) (16, 17), increased production of vascular-endothelial growth factor (VEGF) (18) and intercellular adhesion molecule (ICAM-1) (19). This cascade leads to vessel narrowing and fibrinoid necrosis of small vessels resulting in ischemia and cell death (20).
2. Glial cell theory
    a. Radiation can also damage glial cells. Damage to oligodendrocytes and their progenitors result in demyelination (21). Hypoxia caused by endothelial cell damage leads to liberation of hypoxia-inducible factor 1α and VEGF. VEGF induces neo-angiogenesis, but these tend to be leaky capillaries; resulting in perilesional edema and contrast extravasation.

RISK FACTORS FOR RN AND MITIGATION STRATEGIES

A direct cause-effect relationship for RN is hard to establish, but many risk factors have been identified. These include tumor volume, prescribed dose, fraction size, volume of normal brain irradiated, previous use of radiation and the use of concurrent systemic therapy (22). Many of these risk factors were established in patients being treated for arterio-venous malformations and gliomas, but can be extrapolated to BM.

1. Dose-volume interplay
    a. Early studies from RTOG 90-05 recommended the maximum safe radiation dose to be based on tumor volume (23). The 12-months cumulative incidence of RN was 8%, with larger tumors having increased rates of RN. For example, lesions below ≤20 mm were safely treated with 24 Gy, 21–30 mm with 18 Gy and 31–40 mm with 15 Gy. However, this data is based on a mixture of recurrent primary and secondary brain tumors, and all patients had prior radiation.
    b. For patients undergoing SRS (with or without WBRT), the volume of brain parenchyma receiving higher than 10 or 12 Gy (V10 and V12, respectively) has been correlated to RN. Blonigen et al reported that the risk of RN is higher when V10 > 10.5 cm^3 or V12 > 7.9 cm^3 (9). The use of V10 and V12 corroborates with studies in AVM (24) and other intracranial tumors (25). It remains unclear how this volume should be defined, in particular if the gross tumor volume should be excluded from normal brain parenchyma. Fractionated stereotactic radiotherapy has been proposed to mitigate this risk, but strong comparative evidence is still lacking (26, 27).
2. Prior radiation exposure
    a. The use of prior WBRT or SRS and the time interval between re-irradiation influences the risk of RN. For example, the risk of RN with SRS in the setting of prior SRS (to the same lesion) was reported to be 20% at 1 year, 4% when prior WBRT had been used and 8% when concurrent WBRT is used (22). The risk was reported to be 3% when no prior irradiation had been given (22). In the setting of prior WBRT, it is unclear if the fraction size of WBRT influences the risk.
3. Chemotherapy
    a. The use of chemotherapy in the setting of primary brain tumors increases the risk of RN (28). Within the context of

BM, the use of capecitabine within 1 month of SRS appeared to increase the risk of RN (22).

4. Location
   a. Extrapolating from AVM studies, certain locations within the brain may have higher risk of RN. The frontal cortex appears to carry the highest risk for RN while the brainstem is more resistant to developing RN (24).
   b. Japanese investigators suggest that superficial lesions are at a lower risk of RN, because of the dose spillage to extraparenchymal tissue (skull vault, skin, etc.) (29).
5. Histology
   a. Miller et al suggest certain histological subtypes to have a higher risk of RN (30). These include renal carcinoma, lung adenocarcinoma (ALK rearrangement specifically), HER2-amplied breast cancer, and BRAF V600 wild-type melanoma.
6. Planning Target Volume (PTV) margin
   a. While a larger GTV (gross tumor volume) to PTV margin would allow for setup and positional uncertainties, the consequence is that target volume increases significantly and larger volume of normal brain parenchyma is included in the prescription isodose. In a randomized trial, comparing 1 and 3 mm GTV-PTV expansion, the local control was similar in both groups, however the 3 mm group had a higher incidence of biopsy-proven RN (12.5 vs. 2.5%, $p = 0.1$) (31). Although clinically significant, statistical significance may not have been reached due to the low patient number.
7. Intrinsic radiosensitivity
   (a) Data from AVM treatment suggest that patients who developed RN had an increased sensitivity to radiation. This was demonstrated using survival curves (*in vitro*) from skin fibroblasts obtained from patients who developed RN (32). Although intrinsic radiosensitivity may be a risk factor, there are no practical methods to quantify this in the clinics.

DIAGNOSIS AND INVESTIGATIONS FOR PATIENTS WITH SUSPECTED RN

- Imaging

Magnetic resonance (MR) imaging is the most commonly used modality to investigate RN. However, the imaging features of radiation necrosis and tumor recurrence overlap considerably, with both entities demonstrating some degree of contrast enhancement and perilesional edema (33, 34). Most of the time, there is a combination of both entities (35).

Temporal changes alone (i.e., increase in size over time) is not specific to either entity. While certain enhancement patterns described in the literature as "Swiss cheese," "soap bubble," or "cut green pepper" were initially thought to favor radiation necrosis, these have only a 25% positive predictive value (36). Dequesada et al. noted that gyriform lesions and edema with marginal or solid enhancement suggested at least some viable tumor, adding that a lesion quotient (LQ) (which is the ratio of the nodule on T2 sequence to the total enhancing area on T1 sequence) of >0.6 was suggestive of tumor recurrence, while an LQ of <0.3 favored radiation necrosis alone (36). Other authors however found this feature to be only 8% sensitive (37).

In practice, the low predictive value of conventional MR features prompted the need for more advanced tools, such as MR spectroscopy (MRS), MR perfusion, and Positron Emission Tomography (PET) to help increase diagnostic confidence. These three advanced techniques are discussed below.

MR Perfusion

Viable tumor has intact vasculature and thus higher perfusion and blood volume than necrotic tissue. An increased relative cerebral blood volume (rCBV) based on dynamic susceptibility-weighted MRI has been used for differentiating tumor from necrosis (38–40). Unfortunately, published data have been inconsistent. Hu et al reported rCBV of <0.71 as 92% sensitivity and 100% specificity for radiation necrosis, while another suggested a rCBV cutoff of <2.1 (100% sensitivity and specificity) (38, 41). Barajas et al reported significant overlap in rCBV values and proposed using the percentage of signal-intensity recovery (PSR) (33). Furthermore, rCBV values vary between machines, depend on the acquisition methods and are confounded by signal-intensity pileup artifacts, and susceptibility artifacts from blood and contrast pooling within the lesions. Intravoxel incoherent motion (IVIM) is another method that provides quantitative diffusion and perfusion measurements based on a diffusion-weighted imaging (DWI) MR acquisition. IVIM has been shown to be superior to rCBV for distinguishing recurrent tumor from RN (42) and has been validated against gold standard histopathology (35).

MR Spectroscopy

Assessment of the metabolite composition within BM is another useful method that has published threshold values. Increased choline-creatinine (Cho:Cr) and choline–N-acetyl aspartate (Cho:NAA) ratios may favor tumor recurrence (43). Zeng et al found that when both Cho:Cr and Cho:NAA were above 1.71, sensitivity, specificity and diagnostic accuracy were 94.1%, 100%, and 96.2%, respectively (44). In contrast, an elevated lipid-lactate peak and generalized decrease in other metabolites supported radiation necrosis (45). MRS is limited by voxel size, often requiring the lesion to be larger than 1 cm^3, and is also affected by sampling errors within heterogeneous tumors. Chemical exchange saturation transfer (CEST) is a novel method that is sensitive to mobile proteins and peptides and has shown early promise as well in identifying recurrent tumor after SRS (46).

PET-CT

PET imaging has better spatial resolution and coverage than MRS and use of Fluorodeoxyglucose (FDG) PET in this clinical setting was first proposed in 1982, relying on the presumed increased glucose metabolism in tumors (47). However, multiple studies have shown FDG-PET unhelpful for diagnosing RN

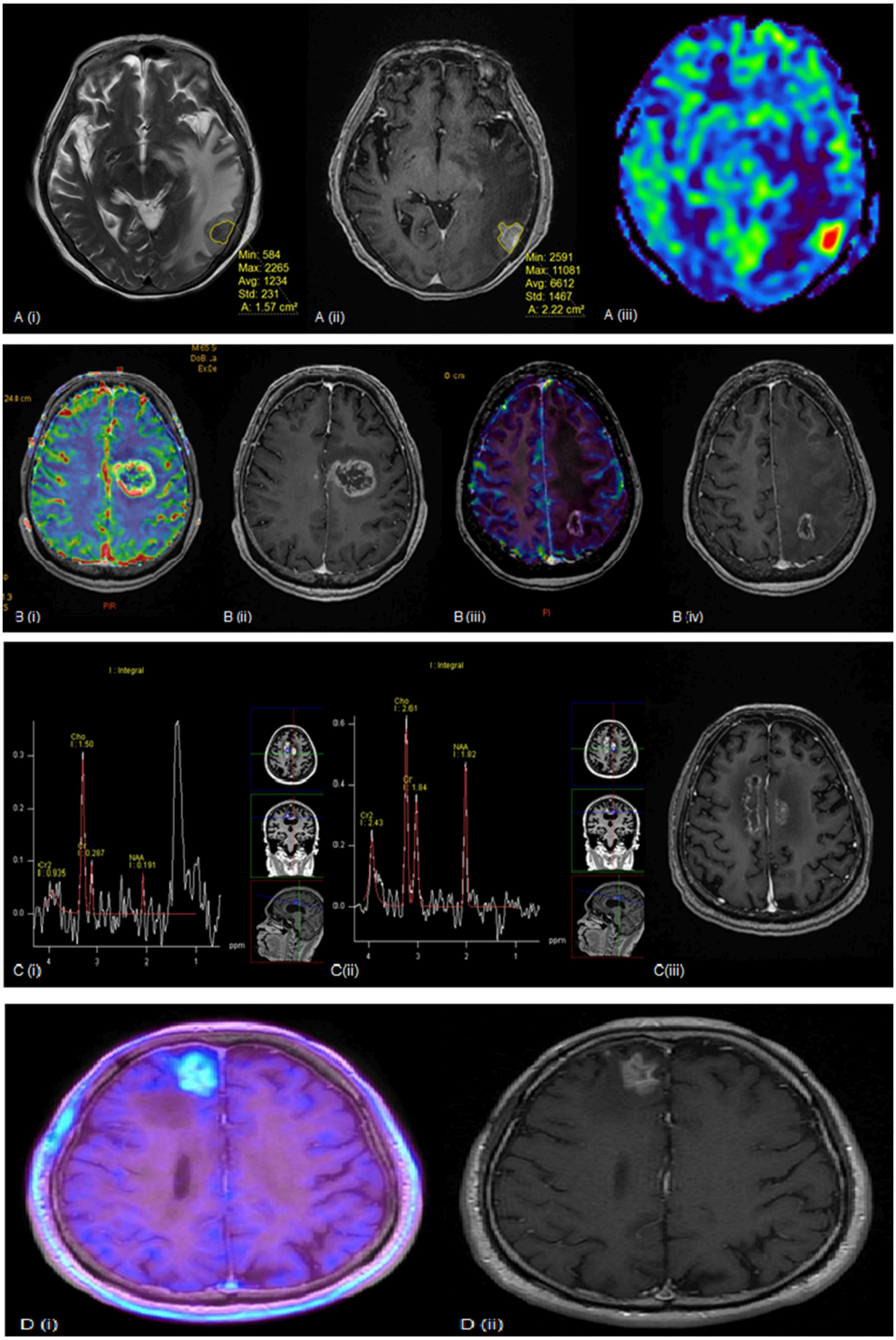


FIGURE 1 | (A) (i) T2 weighted (ii) post-contrast T1 weighted and (iii) rCBV MR perfusion sequences of a lesion seen within the left temporal lobe. The lesion quotient is calculated using the ratio of the hypointense nodule on T2W imaging to the total enhancing area on T1W imaging. This case showed a lesion quotient of 0.71 and increased rCBV is suggestive of tumor recurrence. **(B)** (i) rCBV and (ii) post-contrast T1 weighted sequences showing increased blood flow within the periphery of the lesion. This was a tumor recurrence proven by histopathology. (iii) rCBV and (iv) post-contrast T1W sequences of another patient showing no increased blood flow within the periphery in keeping with radiation necrosis. **(C)** (i, ii) MR spectroscopy and (iii) post-contrast T1 weighted sequences of a growing pericallosal lesion post-WBRT. (i) typical high lipid-lactate peak seen in radiation necrosis at the right cingulum while (ii) shows increased Cho:Cr and Cho:NAA ratios suggestive of tumor recurrence over the left cingulum. **(D)** (i) F-18 FET PET showing intense amino acid tracer uptake within the enhancing lesion seen in (ii) post-contrast T1 weighted sequence. This is suggestive of tumor recurrence and found to be recurrent RCC metastasis on histology.

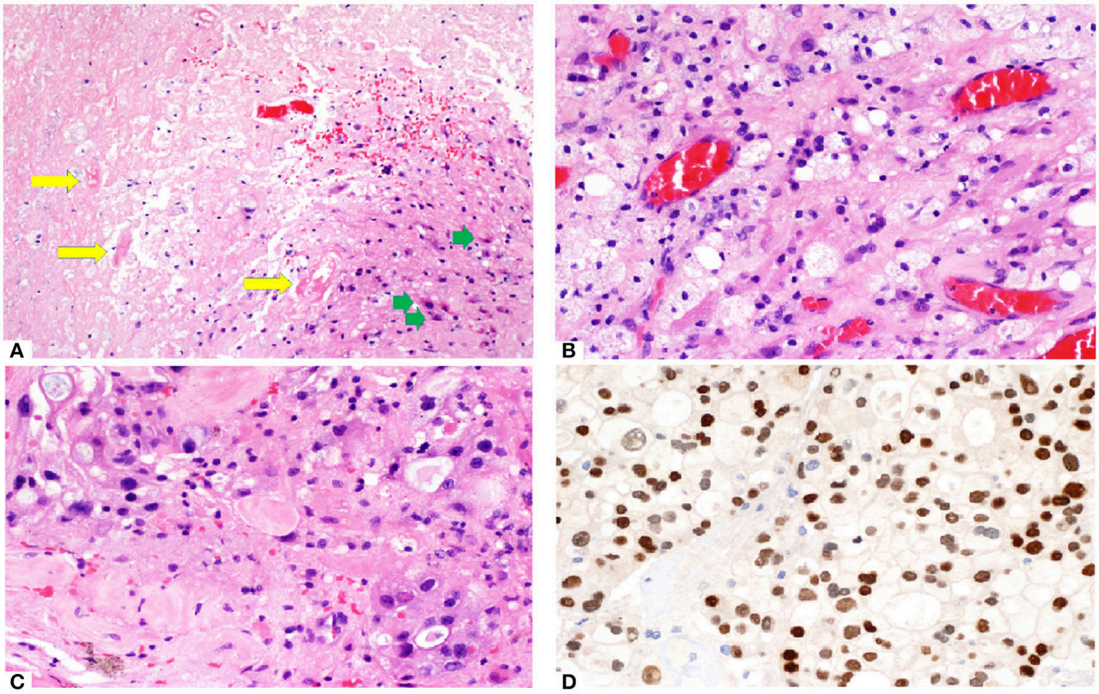


FIGURE 2 | (A) Brain tumor resection specimen from a patient with known metastatic breast carcinoma 6 months after Gamma knife SRS (20 Gy to 50% isodose line). The area of necrosis appears hypocellular and sharply demarcated from the surrounding gliotic brain. Few necrotic, hyalinized blood vessels (yellow arrows) are present, as well as scattered reactive astrocytes (green arrows). Overall features are those of a radiation necrosis. **(B)** Foamy macrophages are often present. The capillaries appear ectatic and congested. **(C)** Focal area shows increased cellularity with more nuclear pleomorphism in an otherwise hyalinised background, raising the possibility of residual viable tumor. **(D)** Immunostain (brown) with GATA3 labels numerous viable tumor cells. Nuclear pleomorphism appears more prominent and highlighted by this nuclear stain.

(48, 49). Amino acid tracers then became particularly useful in PET imaging because of high amino acid utilization in tumors for cell proliferation and extracellular matrix production (50). Moreover, normal brain tissue has relatively lower amino acid uptake, and this provides good tissue contrast. Tracers including Carbon-11 methionine (MET), Fluoro-l-thymidine (FLT) and Fluoroethyltyrosine (FET) have been used with promising results (51–54). Of particular interest is FET-PET, where the addition of dynamic data analysis reported a sensitivity of 100% and specificity of 93%, comparable to some MRS results (55).

Figure 1 illustrates several examples where the above modalities have been used to evaluate RN. For now, there is no single modality that has been shown to accurately differentiate tumor recurrence from radiation necrosis, and biopsy is still regarded as the diagnostic gold standard. In view of the limitations of each modality, a multi-modality approach may be warranted to improve diagnostic confidence.

- Pathological assessment

Histopathology from surgically resected lesions after SRS commonly shows a mix of residual tumor cells and RN (56–60). Endothelial cells, which are most susceptible to radiation damage, often manifest with fibrinoid necrosis, hemorrhage, hyalinization and thrombosis of the blood vessels, resulting in hypoxic injury to the surrounding tissue (61). The area of necrosis is usually paucicellular, surrounded by highly gliotic brain tissue consisting of GFAP-reactive astrocytes demonstrating prominent cytoplasmic ramification. Foamy macrophages and hemosiderophages are often encountered, occasionally with dystrophic calcification. In addition, radiation-induced cytologic atypia maybe seen, featuring cytomegaly with bizarre "bubbly" nuclei, maintaining an overall low nuclei-cytoplasmic ratio. In contrast, in recurrent tumor, tumor necrosis often appears cellular with ghost-outline of the tumor cells, demonstrating high nucleo-cytoplasmic ratio. Careful examination of the blood vessels is important as residual viable tumor maybe present around the Virchow Robin spaces or as intravascular clusters, reminiscing the hematogenous route taken by the tumor. In the setting of suspected tumor recurrence with superimposed radiation-induced damage, a limited panel of immunohistochemistry, depending on the known primary tumor types, can be helpful in highlighting the viable tumor which may not be obvious on hematoxylin-eosin stained slides. Histo-pathological assessment of a patient with RN is shown in **Figure 2**.

MANAGEMENT OF RN

The management of RN primarily depends on the presence of symptoms. Symptomatic patients may experience headaches,

nausea, cognitive impairment, seizures or focal deficits relating to the location of the lesion.

Data from patients with nasopharyngeal carcinoma with radiological RN suggest that one third or less of patients have spontaneous regression over time, and that it is not always an irreversible progressive process (62). As such, observation is a viable treatment option for small and/or asymptomatic RN. However, closer clinical and radiological monitoring is warranted (e.g., every 6–8 weeks, and then extending to 12–16 weeks once the lesion is stable/regressed). Patel et al. reported that approximately one-third of patients treated with SRS have increase in lesional size during follow-up (63), occurring between 6 weeks and 15 months post-SRS. Counterintuitively, patients with lesion progression had the longest survival compared to patients with stable or decreased lesional size. They hypothesized that post-SRS lesional growth may be due to brisk reactive immune response, rather than tumor recurrence. However, this has to be interpreted with caution, as there is an inherent selection bias.

For symptomatic patients, oral corticosteroids (such as dexamethasone) is the preferred first line. Corticosteroids reduce the inflammatory signals and cytokines produced by the necrotic tissue and reduce the leakiness of the blood-brain barrier (64). Due to resolution of the edema, most patients experience rapid improvement once steroids are initiated. There are no studies guiding the dose of steroids. In our practice, we prefer to use dexamethasone (4–8 mg per day), with a gradual taper of the dose. Unfortunately, many patients will require steroids for a long duration and are subject to steroid-toxicity, such as myopathy, iatrogenic Cushing's syndrome, gastric ulcers etc.

As VEGF has been shown to be a key mediator in RN (65), there is considerable interest in the use of bevacizumab (humanized monoclonal antibody against VEGF) to treat steroid-refractory RN. A pooled analysis involving 71 patients, showed that the use of bevacizumab had a radiographic response rate of 97% and clinical improvement rate of 79% with a mean decrease in dexamethasone of 6 mg (66). The median decrease in FLAIR signal and enhancing-volume was ∼60%. One small randomized study has been performed using bevacizumab for RN that allowed a cross-over from the placebo group (67). All 14 patients eventually ended up receiving bevacizumab, and all patients showed radiographic response. No differences could be demonstrated in symptomatology, however the majority of the patients on dexamethasone were able to reduce their doses. As such, bevacizumab appears to be a promising agent; however, the durability of response and toxicities associated with bevacizumab, such as hemorrhage, thrombosis and impaired wound healing must be taken into account.

Anticoagulants and medications which moderate perfusion have been tested in RN, but are not routinely used. For example, oral pentoxifylline and vitamin E were evaluated in 11 patients, with their MRI FLAIR volume changes recorded over time (68). Although there was an overall average decrease in edema, some patients had an increase in edema.

In another study, heparin and warfarin were evaluated in eight patients, with slightly over half showing some functional recovery (69). However, it is unclear if anticoagulation needs to be continued indefinitely.

Hyperbaric oxygen therapy (HBOT) is designed to promote perfusion and angiogenesis. The use of HBOT in RN is mostly limited to case reports where the efficacy is not well-documented (70–72). Investigators have also studied the use of HBOT as prophylaxis, and have shown promising results (73). However, HBOT is expensive, requires specialized facilities and involves a significant time commitment with prescribed treatment ranging from 20 to 40 sessions.

For patients who remain symptomatic despite conservative management, or in whom there is diagnostic uncertainty, surgical resection can be considered. The main advantages of surgical resection are relief of any mass effect and histological confirmation. This influences subsequent treatment decisions and can help with prognostication. Removing the nidus of necrotic tissue responsible for the peri-lesional edema will provide patients symptomatic relief, and allow weaning off steroids. Patient selection remains an important consideration, and includes surgical accessibility, overall performance status and life expectancy. Early reports suggest a high risk of morbidity with surgical resection, but it remains to be seen if these risks still persist in the modern era (74). In situations where there is necrotic tissue admixed with viable tumor, clinical judgment is required to decide on further management.

Novel techniques, such as laser interstitial thermal therapy (LITT) are emerging as treatment options. LITT is an image-guided approach which generates high temperatures using a laser fiber, and facilitates ablation of both tumor tissue, or VEGF-producing reactive glial cells (75). A prospective study has shown this to be safe and allow weaning of steroids in a third of patients (76).

CONCLUSION

RN will be increasingly encountered due to the widespread use of SRS. Symptomatic RN can cause significant morbidity and should be managed pro-actively. There is no single modality which can reliably distinguish RN from recurrent tumor, and a multi-modal approach is often required. For patients with symptomatic RN, oral corticosteroid therapy and bevacizumab are both effective. A minority of patients, with an unclear diagnosis, or refractory symptoms, will require surgical resection. As RN proves to be a challenging condition to diagnose and manage, risk factor mitigation becomes important in clinical decision making.

AUTHOR CONTRIBUTIONS

BV and AS substantial contributions to the conception or design of the work. BV, CT, CY, and JD drafting the work or revising it critically for important intellectual content. All authors provide approval for publication of the content. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. (1980) 6:1–9. doi: 10.1016/0360-3016(80)90195-9
2. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* (2016) 388:2004–14. doi: 10.1016/S0140-6736(16)30825-X
3. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys*. (2015) 91:710–7. doi: 10.1016/j.ijrobp.2014.10.024
4. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* (2004) 363:1665–72. doi: 10.1016/S0140-6736(04)16250-8
5. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys*. (1999) 45:427–34. doi: 10.1016/S0360-3016(99)00198-4
6. Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol.* (2011) 6:48. doi: 10.1186/1748-717X-6-48
7. Kohutek ZA, Yamada Y, Chan TA, Brennan CW, Tabar V, Gutin PH, et al. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases. *J Neurooncol.* (2015) 125:149–56. doi: 10.1007/s11060-015-1881-3
8. Chin LS, Ma L, DiBiase S. Radiation necrosis following gamma knife surgery: a case-controlled comparison of treatment parameters and long-term clinical follow up. *J Neurosurg.* (2001) 94:899–904. doi: 10.3171/jns.2001.94.6.0899
9. Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* (2010) 77:996–1001. doi: 10.1016/j.ijrobp.2009.06.006
10. Varlotto JM, Flickinger JC, Niranjan A, Bhatnagar AK, Kondziolka D, Lunsford LD. Analysis of tumor control and toxicity in patients who have survived at least one year after radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* (2003) 57:452–64. doi: 10.1016/S0360-3016(03)00568-6
11. Calvo W, Hopewell JW, Reinhold HS, Yeung TK. Time- and dose-related changes in the white matter of the rat brain after single doses of X rays. *Br J Radiol.* (1988) 61:1043–52. doi: 10.1259/0007-1285-61-731-1043
12. Benczik J, Tenhunen M, Snellman M, Joensuu H, Farkkila M, Joensuu R, et al. Late radiation effects in the dog brain: correlation of MRI and histological changes. *Radiother Oncol.* (2002) 63:107–20. doi: 10.1016/S0167-8140(02)00028-2
13. Rahmathulla G, Marko NF, Weil RJ. Cerebral radiation necrosis: a review of the pathobiology, diagnosis and management considerations. *J Clin Neurosci.* (2013) 20:485–502. doi: 10.1016/j.jocn.2012.09.011
14. Remler MP, Marcussen WH, Tiller-Borsich J. The late effects of radiation on the blood brain barrier. *Int J Radiat Oncol Biol Phys*. (1986) 12:1965–9. doi: 10.1016/0360-3016(86)90133-1
15. Fuks Z, Kolesnick R. Engaging the vascular component of the tumor response. *Cancer Cell* (2005) 8:89–91. doi: 10.1016/j.ccr.2005.07.014
16. Daigle JL, Hong JH, Chiang CS, McBride WH. The role of tumor necrosis factor signaling pathways in the response of murine brain to irradiation. *Cancer Res.* (2001) 61:8859–65. Available online at: http://cancerres.aacrjournals.org/content/61/24/8859.article-info
17. Nordal RA, Wong CS. Molecular targets in radiation-induced blood-brain barrier disruption. *Int J Radiat Oncol Biol Phys.* (2005) 62:279–87. doi: 10.1016/j.ijrobp.2005.01.039
18. Nordal RA, Nagy A, Pintilie M, Wong CS. Hypoxia and hypoxia-inducible factor-1 target genes in central nervous system radiation injury: a role for vascular endothelial growth factor. *Clin Cancer Res.* (2004) 10:3342–53. doi: 10.1158/1078-0432.CCR-03-0426
19. Nordal RA, Wong CS. Intercellular adhesion molecule-1 and blood-spinal cord barrier disruption in central nervous system radiation injury. *J Neuropathol Exp Neurol.* (2004) 63:474–83. doi: 10.1093/jnen/63.5.474
20. Burger PC, Mahley MS Jr., Dudka L, Vogel FS. The morphologic effects of radiation administered therapeutically for intracranial gliomas: a postmortem study of 25 cases. *Cancer* (1979) 44:1256–72. doi: 10.1002/1097-0142(197910)44:4<1256::AID-CNCR2820440415>3.0.CO;2-T
21. Panagiotakos G, Alshamy G, Chan B, Abrams R, Greenberg E, Saxena A, et al. Long-term impact of radiation on the stem cell and oligodendrocyte precursors in the brain. *PLoS ONE* (2007) 2:e588. doi: 10.1371/journal.pone.0000588
22. Sneed PK, Mendez J, Vemer-van den Hoek JG, Seymour ZA, Ma L, Molinaro AM, et al. Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. *J Neurosurg.* (2015) 123:373–86. doi: 10.3171/2014.10.JNS141610
23. Shaw E, Scott C, Souhami L, Dinapoli R, Bahary JP, Kline R, et al. Radiosurgery for the treatment of previously irradiated recurrent primary brain tumors and brain metastases: initial report of radiation therapy oncology group protocol (90-05). *Int J Radiat Oncol Biol Phys.* (1996) 34:647–54. doi: 10.1016/0360-3016(95)02106-X
24. Flickinger JC, Kondziolka D, Lunsford LD, Kassam A, Phuong LK, Liscak R, et al. Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients. Arteriovenous Malformation Radiosurgery Study Group. *Int J Radiat Oncol Biol Phys*. (2000) 46:1143–8. doi: 10.1016/S0360-3016(99)00513-1
25. Korytko T, Radivoyevitch T, Colussi V, Wessels BW, Pillai K, Maciunas RJ, et al. 12 Gy gamma knife radiosurgical volume is a predictor for radiation necrosis in non-AVM intracranial tumors. *Int J Radiat Oncol Biol Phys.* (2006) 64:419–24. doi: 10.1016/j.ijrobp.2005.07.980
26. Minniti G, D'Angelillo RM, Scaringi C, Trodella LE, Clarke E, Matteucci P, et al. Fractionated stereotactic radiosurgery for patients with brain metastases. *J Neurooncol*. (2014) 117:295–301. doi: 10.1007/s11060-014-1388-3
27. Wegner RE, Leeman JE, Kabolizadeh P, Rwigema JC, Mintz AH, Burton SA, et al. Fractionated stereotactic radiosurgery for large brain metastases. *Am J Clin Oncol.* (2015) 38:135–9. doi: 10.1097/COC.0b013e31828aadac
28. Ruben JD, Dally M, Bailey M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. *Int J Radiat Oncol Biol Phys*. (2006) 65:499–508. doi: 10.1016/j.ijrobp.2005.12.002
29. Ohtakara K, Hayashi S, Nakayama N, Ohe N, Yano H, Iwama T, et al. Significance of target location relative to the depth from the brain surface and high-dose irradiated volume in the development of brain radionecrosis after micromultileaf collimator-based stereotactic radiosurgery for brain metastases. *J Neurooncol.* (2012) 108:201–9. doi: 10.1007/s11060-012-0834-3
30. Miller JA, Bennett EE, Xiao R, Kotecha R, Chao ST, Vogelbaum MA, et al. Association between radiation necrosis and tumor biology after stereotactic radiosurgery for brain metastasis. *Int J Radiat Oncol Biol Phys*. (2016) 96:1060–9. doi: 10.1016/j.ijrobp.2016.08.039
31. Kirkpatrick JP, Wang Z, Sampson JH, McSherry F, Herndon JE II, Allen KJ, et al. Defining the optimal planning target volume in image-guided stereotactic radiosurgery of brain metastases: results of a randomized trial. *Int J Radiat Oncol Biol Phys*. (2015) 91:100–8. doi: 10.1016/j.ijrobp.2014.09.004
32. Raaphorst GP, Malone S, Alsbeih G, Souhani L, Szumacher E, Girard A. Skin fibroblasts *in vitro* radiosensitivity can predict for late complications following AVM radiosurgery. *Radiother Oncol*. (2002) 64:153–6. doi: 10.1016/S0167-8140(02)00076-2
33. Barajas RF, Chang JS, Sneed PK, Segal MR, McDermott MW, Cha S. Distinguishing recurrent intra-axial metastatic tumor from radiation necrosis following gamma knife radiosurgery using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *AJNR Am J Neuroradiol.* (2009) 30:367–72. doi: 10.3174/ajnr.A1362
34. Forsyth PA, Kelly PJ, Cascino TL, Scheithauer BW, Shaw EG, Dinapoli RP, et al. Radiation necrosis or glioma recurrence: is computer-assisted stereotactic biopsy useful? *J Neurosurg*. (1995) 82:436–44. doi: 10.3171/jns.1995.82.3.0436

35. Detsky JS, Keith J, Conklin J, Symons S, Myrehaug S, Sahgal A, et al. Differentiating radiation necrosis from tumor progression in brain metastases treated with stereotactic radiotherapy: utility of intravoxel incoherent motion perfusion MRI and correlation with histopathology. *J Neurooncol.* (2017) 134:433–41. doi: 10.1007/s11060-017-2545-2
36. Dequesada IM, Quisling RG, Yachnis A, Friedman WA. Can standard magnetic resonance imaging reliably distinguish recurrent tumor from radiation necrosis after radiosurgery for brain metastases? A radiographic-pathological study. *Neurosurgery* (2008) 63:898–903; discussion 904. doi: 10.1227/01.NEU.0000333263.31870.31
37. Chao ST, Ahluwalia MS, Barnett GH, Stevens GH, Murphy ES, Stockham AL, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys.* (2013) 87:449–57. doi: 10.1016/j.ijrobp.2013.05.015
38. Hu LS, Baxter LC, Smith KA, Feuerstein BG, Karis JP, Eschbacher JM, et al. Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements. *AJNR Am J Neuroradiol.* (2009) 30:552–8. doi: 10.3174/ajnr.A1377
39. Cha S, Neuroimaging in neuro-oncology. *Neurotherapeutics* (2009) 6:465–77. doi: 10.1016/j.nurt.2009.05.002
40. Alexiou GA, Tsiouris S, Kyritsis AP, Voulgaris S, Argyropoulou MI, Fotopoulos AD. Glioma recurrence versus radiation necrosis: accuracy of current imaging modalities. *J Neurooncol.* (2009) 95:1–11. doi: 10.1007/s11060-009-9897-1
41. Muto M, Frauenfelder G, Senese R, Zeccolini F, Schena E, Giurazza F, et al. Dynamic susceptibility contrast (DSC) perfusion MRI in differential diagnosis between radionecrosis and neoangiogenesis in cerebral metastases using rCBV, rCBF and K2. *Radiol Med.* (2018) 123:545–52. doi: 10.1007/s11547-018-0866-7
42. Kim DY, Kim HS, Goh MJ, Choi CG, Kim SJ. Utility of intravoxel incoherent motion MR imaging for distinguishing recurrent metastatic tumor from treatment effect following gamma knife radiosurgery: initial experience. *AJNR Am J Neuroradiol.* (2014) 35:2082–90. doi: 10.3174/ajnr.A3995
43. Matsusue E, Fink JR, Rockhill JK, Ogawa T, Maravilla KR. Distinction between glioma progression and post-radiation change by combined physiologic MR imaging. *Neuroradiology* (2010) 52:297–306. doi: 10.1007/s00234-009-0613-9
44. Zeng QS, Li CF, Zhang K, Liu H, Kang XS, Zhen JH. Multivoxel 3D proton MR spectroscopy in the distinction of recurrent glioma from radiation injury. *J Neurooncol.* (2007) 84:63–9. doi: 10.1007/s11060-007-9341-3
45. Shah R, Vattoth S, Jacob R, Manzil FF, O'Malley JP, Borghei P, et al. Radiation necrosis in the brain: imaging features and differentiation from tumor recurrence. *Radiographics* (2012) 32:1343–59. doi: 10.1148/rg.325125002
46. Mehrabian H, Desmond KL, Soliman H, Sahgal A, Stanisz GJ. Differentiation between radiation necrosis and tumor progression using chemical exchange saturation transfer. *Clin Cancer Res.* (2017) 23:3667–75. doi: 10.1158/1078-0432.CCR-16-2265
47. Patronas NJ, Di Chiro G, Brooks RA, DeLaPaz RL, Kornblith PL, Smith BH, et al. Work in progress: [18F] fluorodeoxyglucose and positron emission tomography in the evaluation of radiation necrosis of the brain. *Radiology* (1982) 144:885–9. doi: 10.1148/radiology.144.4.6981123
48. Ricci PE, Karis JP, Heiserman JE, Fram EK, Bice AN, Drayer BP. Differentiating recurrent tumor from radiation necrosis: time for re-evaluation of positron emission tomography? *AJNR Am J Neuroradiol.* (1998) 19:407–13.
49. Thompson TP, Lunsford LD, Kondziolka D. Distinguishing recurrent tumor and radiation necrosis with positron emission tomography versus stereotactic biopsy. *Stereotact Funct Neurosurg.* (1999) 73:9–14. doi: 10.1159/000029743
50. Isselbacher KJ. Sugar and amino acid transport by cells in culture–differences between normal and malignant cells. *N Engl J Med.* (1972) 286:929–33. doi: 10.1056/NEJM197204272861707
51. Terakawa Y, Tsuyuguchi N, Iwai Y, Yamanaka K, Higashiyama S, Takami T, et al. Diagnostic accuracy of 11C-methionine PET for differentiation of recurrent brain tumors from radiation necrosis after radiotherapy. *J Nucl Med.* (2008) 49:694–9. doi: 10.2967/jnumed.107.048082
52. Park J, Byun BH, Lim I, Kim BI, Choi CW, Lim SM. Comparison of diagnostic performances of F-18 FDG, F-18 FLT, and F-18 FET brain PET/CT for differentiating recurrent glioma from post-treatment change. *J Nucl Med.* (2014) 55:526. Available online at: http://jnm.snmjournals.org/citmgr?gca=jnumed%3B55%2Fsupplement_1%2F526
53. Miyake K, Shinomiya A, Okada M, Hatakeyama T, Kawai N, Tamiya T. Usefulness of FDG, MET and FLT-PET studies for the management of human gliomas. *J Biomed Biotechnol.* (2012) 2012:205818. doi: 10.1155/2012/205818
54. Galldiks N, Stoffels G, Filss CP, Piroth MD, Sabel M, Ruge MI, et al. Role of O-(2-(18)F-fluoroethyl)-L-tyrosine PET for differentiation of local recurrent brain metastasis from radiation necrosis. *J Nucl Med.* (2012) 53:1367–74. doi: 10.2967/jnumed.112.103325
55. Rachinger W, Goetz C, Popperl G, Gildehaus FJ, Kreth FW, Holtmannspotter M, et al. Positron emission tomography with O-(2-[18F]fluoroethyl)-l-tyrosine versus magnetic resonance imaging in the diagnosis of recurrent gliomas. *Neurosurgery* (2005) 57:505–11; discussion 505–11. doi: 10.1227/01.NEU.0000171642.49553.B0
56. Truong MT, St Clair EG, Donahue BR, Rush SC, Miller DC, Formenti SC, et al. Results of surgical resection for progression of brain metastases previously treated by gamma knife radiosurgery. *Neurosurgery* (2006) 59:86–97; discussion 86–97. doi: 10.1227/01.NEU.0000219858.80351.38
57. Telera S, Fabi A, Pace A, Vidiri A, Anelli V, Carapella CM, et al. Radionecrosis induced by stereotactic radiosurgery of brain metastases: results of surgery and outcome of disease. *J Neurooncol.* (2013) 113:313–25. doi: 10.1007/s11060-013-1120-8
58. Szeifert GT, Atteberry DS, Kondziolka D, Levivier M, Lunsford LD. Cerebral metastases pathology after radiosurgery: a multicenter study. *Cancer* (2006) 106:2672–81. doi: 10.1002/cncr.21946
59. Jagannathan J, Bourne TD, Schlesinger D, Yen CP, Shaffrey ME, Laws ER Jr., et al. Clinical and pathological characteristics of brain metastasis resected after failed radiosurgery. *Neurosurgery* (2010) 66:208–17. doi: 10.1227/01.NEU.0000359318.90478.69
60. Vecil GG, Suki D, Maldaun MV, Lang FF, Sawaya R. Resection of brain metastases previously treated with stereotactic radiosurgery. *J Neurosurg.* (2005) 102:209–15. doi: 10.3171/jns.2005.102.2.0209
61. Perry A. *21–Therapy-Associated Neuropathology, Practical Surgical Neuropathology: A Diagnostic Approach*. 2nd ed. Philadelphia, PA: Elsevier (2018). p. 493–503. Available online at: https://www.elsevier.com/books/practical-surgical-neuropathology-a-diagnostic-approach/9780323449410
62. Wang YX, King AD, Zhou H, Leung SF, Abrigo J, Chan YL, et al. Evolution of radiation-induced brain injury: MR imaging-based study. *Radiology* (2010) 254:210–8. doi: 10.1148/radiol.09090428
63. Patel TR, McHugh BJ, Bi WL, Minja FJ, Knisely JP, Chiang VL. A comprehensive review of MR imaging changes following radiosurgery to 500 brain metastases. *AJNR Am J Neuroradiol.* (2011) 32:1885–92. doi: 10.3174/ajnr.A2668
64. Kotsarini C, Griffiths PD, Wilkinson ID, Hoggard N. A systematic review of the literature on the effects of dexamethasone on the brain from *in vivo* human-based studies: implications for physiological brain imaging of patients with intracranial tumors. *Neurosurgery* (2010) 67:1799–815; discussion 1815. doi: 10.1227/NEU.0b013e3181fa775b
65. Kim JH, Chung YG, Kim CY, Kim HK, Lee HK. Upregulation of VEGF and FGF2 in normal rat brain after experimental intraoperative radiation therapy. *J Korean Med Sci.* (2004) 19:879–86. doi: 10.3346/jkms.2004.19.6.879
66. Tye K, Engelhard HH, Slavin KV, Nicholas MK, Chmura SJ, Kwok Y, et al. An analysis of radiation necrosis of the central nervous system treated with bevacizumab. *J Neurooncol.* (2014) 117:321–7. doi: 10.1007/s11060-014-1391-8
67. Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys.* (2011) 79:1487–95. doi: 10.1016/j.ijrobp.2009.12.061
68. Williamson R, Kondziolka D, Kanaan H, Lunsford LD, Flickinger JC. Adverse radiation effects after radiosurgery may benefit from oral vitamin E and pentoxifylline therapy: a pilot study. *Stereotact Funct Neurosurg.* (2008) 86:359–66. doi: 10.1159/000163557
69. Glantz MJ, Burger PC, Friedman AH, Radtke RA, Massey EW, Schold SC Jr. Treatment of radiation-induced nervous system injury with heparin and warfarin. *Neurology* (1994) 44:2020–7. doi: 10.1212/WNL.44.11.2020

70. Chuba PJ, Aronin P, Bhambhani K, Eichenhorn M, Zamarano L, Cianci P, et al. Hyperbaric oxygen therapy for radiation-induced brain injury in children. *Cancer* (1997) 80:2005–12. doi: 10.1002/(SICI)1097-0142(19971115)80:10<2005::AID-CNCR19>3.0.CO;2-0
71. Kohshi K, Imada H, Nomoto S, Yamaguchi R, Abe H, Yamamoto H. Successful treatment of radiation-induced brain necrosis by hyperbaric oxygen therapy. *J Neurol Sci.* (2003) 209:115–7. doi: 10.1016/S0022-510X(03)00007-8
72. Leber KA, Eder HG, Kovac H, Anegg U, Pendl G. Treatment of cerebral radionecrosis by hyperbaric oxygen therapy. *Stereotact Funct Neurosurg.* (1998) 70:229–36. doi: 10.1159/000056426
73. Ohguri T, Imada H, Kohshi K, Kakeda S, Ohnari N, Morioka T, et al. Effect of prophylactic hyperbaric oxygen treatment for radiation-induced brain injury after stereotactic radiosurgery of brain metastases. *Int J Radiat Oncol Biol Phys.* (2007) 67:248–55. doi: 10.1016/j.ijrobp.2006.08.009
74. McPherson CM, Warnick RE. Results of contemporary surgical management of radiation necrosis using frameless stereotaxis and intraoperative magnetic resonance imaging. *J Neurooncol.* (2004) 68:41–7. doi: 10.1023/B:NEON.0000024744.16031.e9
75. Rahmathulla G, Recinos PF, Valerio JE, Chao S, Barnett GH. Laser interstitial thermal therapy for focal cerebral radiation necrosis: a case report and literature review. *Stereotact Funct Neurosurg.* (2012) 90:192–200. doi: 10.1159/000338251
76. Ahluwalia M, Barnett GH, Deng D, Tatter SB, Laxton AW, Mohammadi AM, et al. Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. *J Neurosurg.* (2018) 4:1-8. doi: 10.3171/2017.11.JNS171273.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Vellayappan, Tan, Yong, Khor, Koh, Yeo, Detsky, Lo and Sahgal. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership