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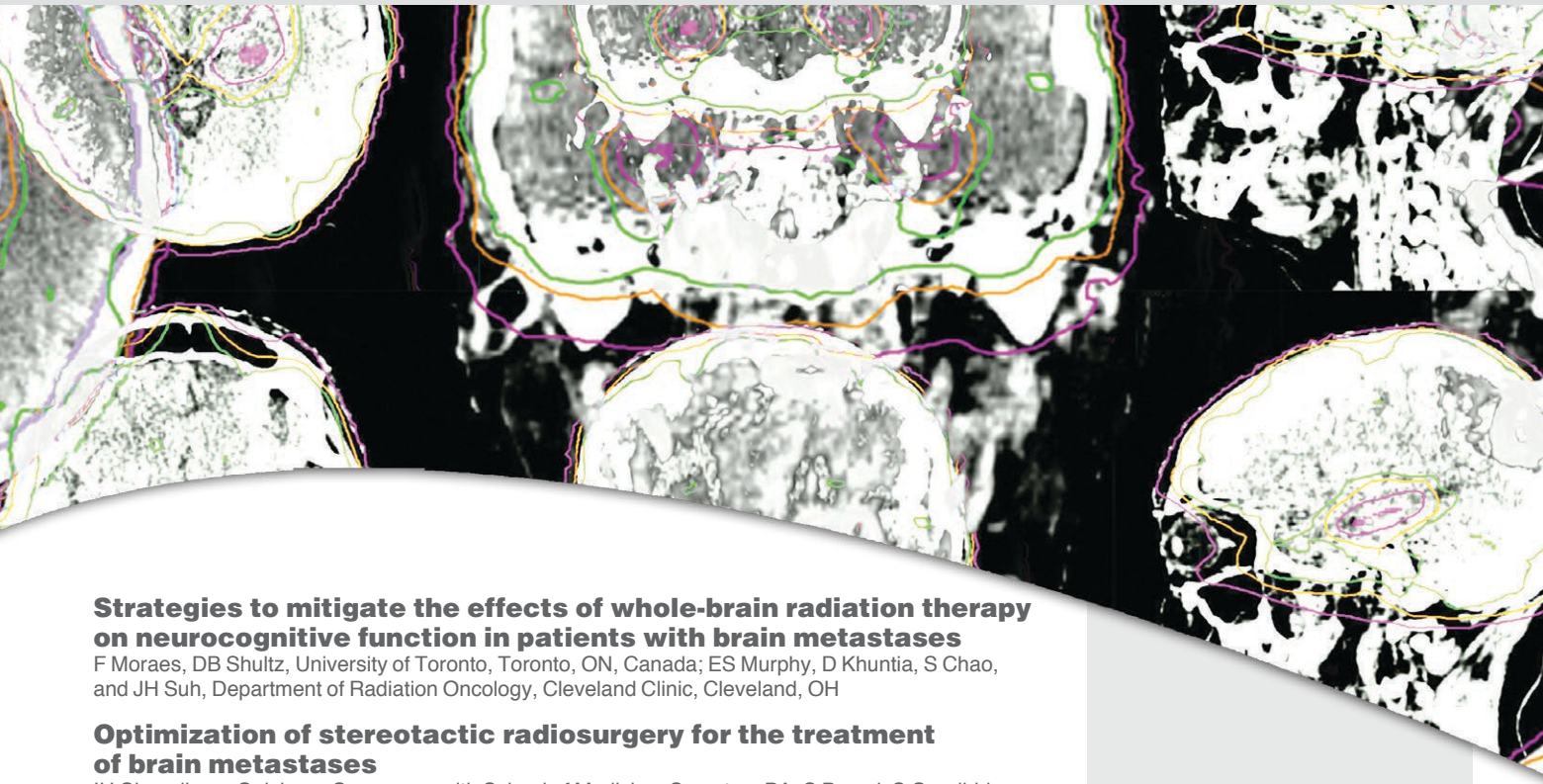

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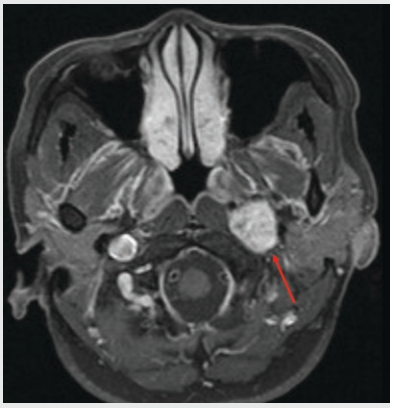

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BRAIN METASTASES FOCUS

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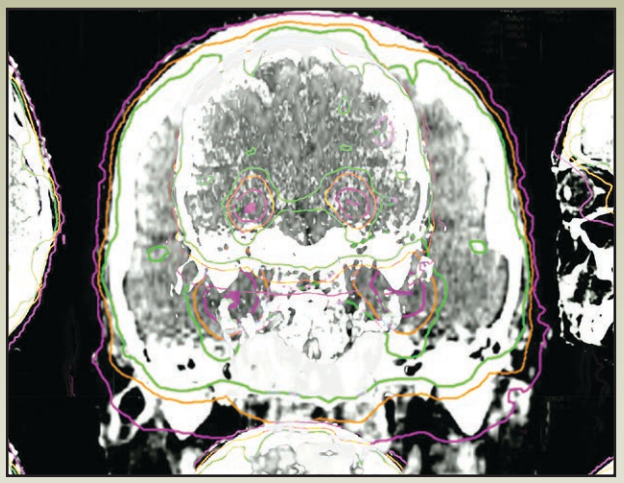

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EDITORIAL

John Suh, MD, FASTRO
Editor-in-Chief

Gray Matters: Advances in Brain Metastases Treatment

Brain metastases (BM) comprise the clear majority of intracranial neoplasms and represent one of the most controversial areas in oncology given the wide array of effective options, strong advocacy for certain treatments, and knowledge that biology influences outcomes. Despite controversies, outcomes for some patients have improved with a greater number of long-term survivors, which has increased the focus on side effects, in particular neurocognitive function. Unfortunately, the prevalence of BM is increasing, and prognosis and survival remain poor for the majority of these patients.

In this month's focus on BM, the review article, *Strategies to mitigate the effects of whole-brain radiation therapy (WBRT) on neurocognitive function in patients with brain metastases,* stresses the importance of balancing treatment approaches for tumor control and survival with preservation of neurocognitive function, a major focus of BM research and trials. Authors describe the use of hippocampal avoidance (HA)-WBRT, memantine, renin angiotensin-aldosterone system blockers, donepezil/lithium, peroxisomal proliferator-activated receptor agonists, and two ongoing cooperative group studies to test whether HA-WBRT and memantine use can decrease risk for neurocognitive decline for some patients.

For patients undergoing stereotactic radiosurgery (SRS), which has emerged as the preferred treatment for many patients with BM, *Optimization of stereotactic radiosurgery for the treatment of brain metastases* reviews methods to achieve better local control, reduced toxicity, and improved patient survival for some patients. This review article discusses the use of targeted agents, treatment planning strategies, radiation necrosis, imaging criteria, and future investigations.

We also have a paper from the University of Virginia, Charlottesville on whether SRS could result in obstructive hydrocephalus with tumor edema or progression, and if resection could minimize this risk. Results, presented in *Stereotactic radiosurgery for cerebellar metastases and the risk of obstructive hydrocephalus,* demonstrate encouraging findings that SRS is a safe treatment option following surgical resection, in properly selected patients.

In addition are the case reports, *Long-term outcome after two-stage low-dose Gamma Knife radiosurgery for large recurrent petroclival meningioma* and *Paraganglioma of the skull base treated with intensity-modulated radiation therapy*. These interesting cases will be entered into ARO's new annual Clinical Case Contest featuring a $500 grand prize. And if you haven't heard, we have introduced a Research Article of the Year in addition to our Review Article of the Year, with grand prizes of $1,000 each (details at http://appliedradiationoncology.com/contests).

As always, we look forward to your submissions and suggestions for topics, as we want *Applied Radiation Oncology* to be a journal that you look forward to reading in print or online. I hope you enjoy the March issue and its focus on brain metastases!

Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

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Strategies to mitigate the effects of whole-brain radiation therapy on neurocognitive function in patients with brain metastases

Fabio Y. Moraes, MD; David B. Shultz, MD; Erin S. Murphy, MD; Deepak Khuntia, MD; Samuel T. Chao, MD; and John H. Suh, MD, FASTRO

Brain metastases (BM) account for the vast majority of intracranial malignancies in adults, occurring in 20% to 40% of all patients with malignant tumors (mostly from lung and breast cancers).[1,2] Due to improved local and systemic therapies and increased utilization of MR imaging, the incidence of BM is rising. Despite technological advances and more treatment options for these patients, unselected populations with BM continue to have a poor prognosis and survival.[2,3]

The use of prognostic systems such as the recursive partitioning analysis (RPA) and graded prognostic assessment (GPA) have helped to categorize BM patients based on several factors, such as age at diagnosis, Karnofsky Performance Status (KPS), status of the primary cancer, number of brain lesions, and absence or presence of extracranial disease.[4,5] Disease-specific GPAs have been developed,[6] including the incorporation of molecular markers.[7] Nomograms have also been generated to provide individual survival estimates and help decide on treatment options.[8]

The most common treatment for patients with > 5 BM is whole-brain radiation therapy (WBRT). Currently, use of stereotactic radiosurgery, especially for patients with 1-4 lesions, and systemic approaches with or without ablative treatments, is increasing[2,9] in part due to the toxicity associated with WBRT. In this review, we discuss strategies to mitigate the effects of WBRT on neurocognitive function in patients with BM.

Whole-brain Radiation Therapy (WBRT)

Since its inception in the 1950s, WBRT has been the primary treatment option for patients with BM.[10] For decades, this treatment was considered the gold standard for patients with BM as it was easy to deliver, readily available, and effective at palliating neurologic signs and symptoms. Multiple phase III studies were conducted to determine the optimal dose and fractionation scheme of WBRT, with median survivals ranging 3 to 6 months.[11-14]

The results of the Quality of Life after Treatment for Brain Metastases (QUARTZ) trial have brought into question the use of WBRT for poor performance status patients with BM.[15] In this study, patients with BM from nonsmall cell lung cancer were randomized to optimal supportive care vs. WBRT. The use of WBRT did not improve quality of life, overall survival, or decrease steroid use compared to best supportive care. However, the trial has been criticized because of poor survival in both arms (8-9 weeks), an unplanned early evaluation that biased results, and the high rate of steroid use in both arms (98% received at least 8 mg of daily dexamethasone), which may have impacted the EuroQol EQFD-3L quality of life metric used in the trial.

Neurocognitive Decline from WBRT

For years, toxicities from WBRT, including neurocognitive decline, were largely ignored given the poor outcomes associated with BM. A wide spectrum of WBRT-associated neurological impairments have been described,[16-18] many of which are believed to have multifacto-

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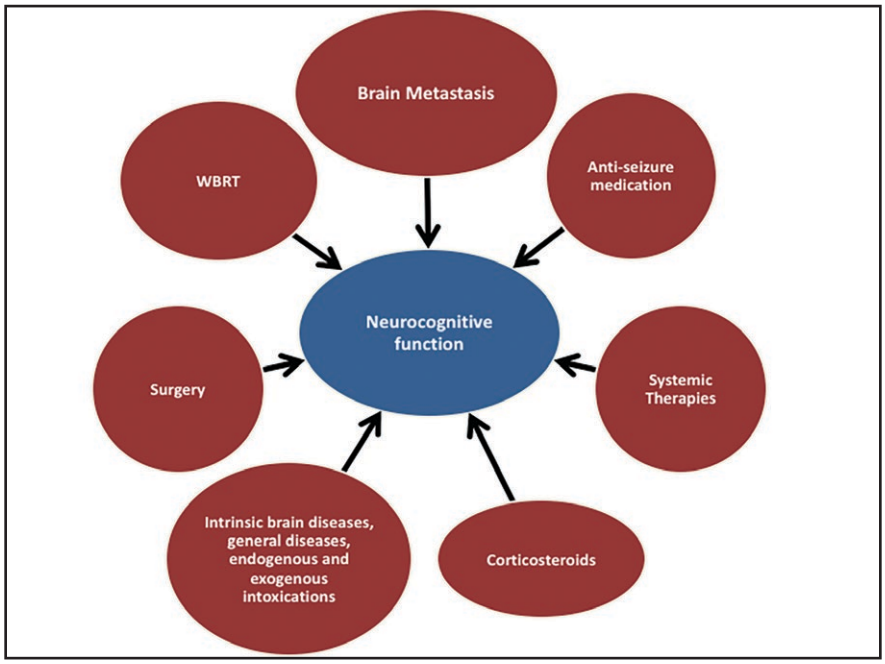

FIGURE 1. *Multifactorial influences of neurocognitive function in patients with brain metastases.*

rial causes, including radiation-induced injury, effects from tumors, and chemotherapy (**Figure 1**).

A phase III trial of WBRT vs. WBRT plus motexafin gadolinium, a radiation sensitizer, provided the first comprehensive assessment of neurocognitive changes in patients undergoing WBRT.[19,20] Assessment was performed using the Hopkins Verbal Learning Test (HVLT) for immediate recall, delayed recall, and recognition; Controlled Oral Word Association (COWA) for verbal fluency; Trailmaking Test A for visual-motor scanning speed; Trailmaking Test B for executive function; and pegboard dominant hand and pegboard nondominant hand for fine motor skills. Of 401 enrolled patients, 90.5% had neurocognitive impairment prior to WBRT initiation. The addition of motexafin gadolinium did not result in a significant reduction in cognitive decline compared to WBRT alone; however, a subgroup analysis suggested that patients with NSCLC benefited from the standpoint of time to neurocognitive progression. Based on its design, the study was not able to identify neurocognitive changes attributable to WBRT;[20] however, regression of brain metastases after WBRT was associated with improved survival and preserved neurocognitive function.[21]

Given concern for the effect of WBRT on neurocognitive function, the use of stereotactic radiosurgery (SRS) as a primary modality for BM treatment has increased. A phase III study performed at the University of Texas MD Anderson Cancer Center, Houston, reported by Chang and colleagues randomized patients to SRS plus WBRT compared to SRS alone and demonstrated greater decline in memory (as demonstrated by the Hopkins Verbal Learning Test-Revised [HVLT-R]) at 4 months) in patients who received WBRT.[22] Other studies have demonstrated that the addition of WBRT to SRS in selected patients does not improve survival but does decrease distant brain failures, at the cost of decreased cognitive function and quality of life at 3 months.[23-25] Despite these results, it is important to remember that a systematic review of neurocognitive effects of WBRT for newly diagnosed brain metastases reported that neurocognitive decline is predominant at 4 months, mild in severity (only 8% ≥ grade 2 on the SOMA-LENR scale), strongly dependent on brain metastases control, and partially resolved at a later time.[26]

Given increasing concern regarding the effect of WBRT on neurocognitive function, strategies to mitigate the effects of WBRT are an unmet need and are being actively explored. This article reviews approaches and rationale for avoiding or limiting damage to healthy brain, small and medium blood vessels, the hippocampus, and white matter.

Strategies to Mitigate WBRT Effects

The following strategies have shown promise for preventing neurocognitive decline: hippocampal avoidance (HA)-WBRT, the NMDA receptors antagonist memantine, renin angiotensin-aldosterone system (RAAS) blockers, donepezil / lithium, peroxisomal proliferator-activated receptor agonists, and use of SRS alone (the latter not addressed in this review). It is important to recognize that SRS alone is not appropriate in every case of BM, such as patients with multiple metastases (> 5 lesions), leptomeningeal disease, and small cell lung cancer histology; hence, strategies to mitigate effects of WBRT are essential.

Hippocampal avoidance (HA)-WBRT

The hippocampus plays an integral role in memory formation. Neural stem cells in the subgranular zone of the hippocampus are susceptible to radiation damage, which usually compromises memory function.[27,28]

The rationale of HA-WBRT arose from the observation that cognitive function deficits following WBRT correlated with hippocampal-related functions of memory, learning, and spatial processing. Based on this observation, two studies sought to determine if hippocampal sparing was feasible from the

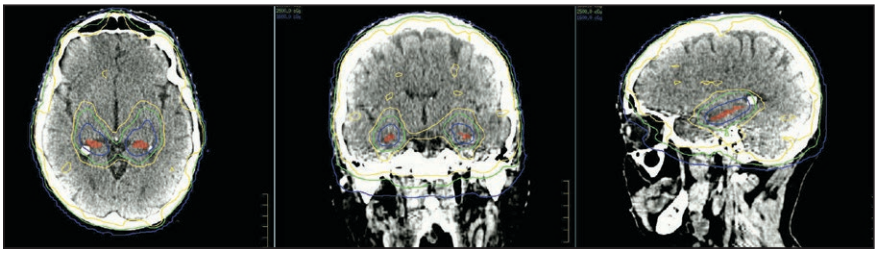

FIGURE 2. *Hippocampal avoidance (HA) whole-brain radiotherapy (WBRT) using linear accelerator-based intensity-modulated radiation therapy (IMRT). The images show the hippocampi (red), the 30 Gy isodose line (yellow), 25 Gy isodose line (green), and 16 Gy isodose line (blue) - (D max (0.03 cc) hippocampus </= 16 Gy). HA-WBRT with IMRT achieves significant dose reduction (hippocampus), while delivering 30 Gy to the rest of the brain.*

standpoint of hippocampal involvement by metastasis. Wan et al showed a 1.1% involvement rate (of more than 2,270 metastases) in hippocampal regions.[29] In an analysis of 371 BM patients with a total of 1,133 tumors, Gondi et al found no hippocampal lesions; however, 9% of patients had tumors within 5 mm of the hippocampal regions.[30]

RTOG 0933, a phase II trial, analyzed the impact of HA-WBRT on declarative memory and used specific contouring guidelines for the subgranular zones of the hippocampi with a 5-mm expansion.[31] Dose to 100% of the hippocampus was limited to 9 Gy with a maximum dose limited to 16 Gy. The remaining brain parenchyma received a dose of 30 Gy in 10 fractions. In this study, 42 patients showed a mean decline from baseline in HVLT delayed recall (HVLT-DR) of 7% at 4 months compared to 30% observed in a historical control treated with traditional WBRT ($p = 0.0003$). Of note, 8% is what one might expect for immediate memory deterioration with SRS alone. No decline on QoL was reported nor was ≤ grade 4 toxicity.[31] **Figure 2** shows HA-WBRT using linear accelerator-based intensity-modulated radiation therapy (IMRT). Currently, two randomized trials, NRG CC001 and CC003, described later, are ongoing to confirm the results of RTOG 0933.

NMDA Receptor Antagonist (Memantine)

N-methyl-D-aspartate (NMDA) receptors in the hippocampus are activated by glutamate and play a role in learning and memory. Radiation therapy to the brain can overexcite these receptors, which alters the ratio of NMDA to GABA receptors, translating to possible neuronal cell death (excitotoxicity). Memantine is a noncompetitive NMDA receptor antagonist with proven efficacy to prevent receptor remodeling and preserve long-term potentiation in animal models and in vascular and Alzheimer's dementia.[32,33]

The role of memantine was assessed by RTOG 0614, a phase III trial comparing WBRT (37.5 Gy in 15 fractions) plus memantine vs. WBRT plus placebo.[34] This trial enrolled 554 patients with memantine administered within 3 days of starting WBRT and for the following 24 weeks, escalating to a final dose of 10 mg BID. At 24 weeks, a decline in delayed recall (HVLT-DR) was appreciated in patients receiving memantine. Unfortunately, the study was underpowered (35%), as only 149 patients were analyzable at 24 weeks due to early deaths in both arms, and this result was not statistically significant ($p = 0.059$). The addition of memantine did, however, demonstrate a longer time to cognitive decline with a probability of cognitive function failure at 24 weeks of 53.8% vs. 64.9% ($p = 0.01$).[34] The authors of the study advocate for the routine use of memantine in patients receiving WBRT given the low toxicity and longer time to cognitive decline, despite not meeting the primary HVLT-DR endpoint. As part of the trial, a significant number of patients also enrolled on the translational section of the study in which apoE (Alzheimer's gene) and inflammatory markers were measured. Results and correlation to outcome are expected later this year.

Renin Angiotensin System (RAS) Blockers

The Renin Angiotensin System (RAS) is known for having marked effects within organs as well as a systemic role in fluid balance. The local brain RAS is complex and involves maintenance of the blood-brain barrier, learning, memory spectrums, behaviors, and emotions.[35] Preclinical models have demonstrated that the RAS may be involved in radiation-induced damage. The blockade of the RAS in irradiated rats has been shown to prevent radiation effects in lung and kidney tissues.[36,37]

Kim et al administered ramipril for 6 months to rats treated with brain RT (30 Gy), reporting a significant reduction in the demyelination of optic nerves and reduced severity of visual injury with the addition of Ramipril.[38] Similarly, the administration of an angiotensin receptor blocker, L-158,809, to rats prior to and after 40 Gy WBRT prevented radiation-induced cognitive impairment.[39]

While RAS blockers have proven activity in modulating radiation-induced brain injury, their mechanism of action in the brain is poorly understood. However, based on their safety profile, widespread use, and potential benefits to neurocognitive function, they should be considered in future studies for patients receiving WBRT.[40]

Donepezil

Donepezil, an acetylcholinesterase inhibitor, is used to treat mild to moderate dementia in Alzheimer's disease (AD). This drug enhances cholinergic neurotransmission by delaying breakdown of acetylcholine in synaptic clefts, a mechanism associated with memory.

In this context, improved cognitive function, mood and QoL were reported when donepezil was administrated for

24 weeks in a group of patients with primary brain tumors who had post-RT survival ≥ 6 months.[41] Following these results, a randomized, double-blinded, placebo-controlled trial of donepezil and partial or WBRT was performed.[42]

Rapp et al reported on 198 adult brain tumor survivors ≥ 6 months who received central nervous system (CNS) irradiation (WBRT or partial) to ≥ 30 Gy and were randomly assigned to receive 24 weeks of donepezil 5-10 mg per day or a placebo. Cognitive functioning was evaluated at baseline, 12 weeks, and 24 weeks with a battery of neuropsychological tests (cognitive composite score), which was completed by 74% of the participants. Treatment with donepezil did not significantly improve the overall composite score, but the donepezil group performed better than placebo on memory (recognition, $p = .027$; discrimination, $p = .007$), and motor speed and dexterity tests ($p = .016$). Significant interactions between pretreatment cognitive function and treatment were found for cognitive composite ($p = .01$), immediate recall ($p = .05$), delayed recall ($p = .004$), attention ($p = .01$), visual-motor skills ($p = .02$), and motor speed and dexterity ($p < .001$).[42]

While it appears donepezil has a role in treating cognitive impairment associated with brain cancer and its treatments, more studies are necessary to prove the value of this drug in this selected population.

Peroxisomal Proliferator-activated Receptor Agonists (PPAR)

Chronic inflammation has been implicated in the development and progression of radiation-induced late effects.[43] This provides a rationale for the application of anti-inflammatory interventions to reduce radiation-induced brain injury. Peroxisomal proliferator-activated receptors (PPAR) α, β (δ), and γ are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors that regulate gene expression.[44] PPAR activation can affect anti-proliferative and anti-inflammatory cellular physiology. These effects are observed in many cell types, including brain glial cells and blood lymphocytes, cells whose activation contributes to the initiation and progression of damage occurring in neurological diseases such as AD and multiple sclerosis (MS).[45]

Animal models have demonstrated the impact of PPAR agonists to reduce radiation-therapy-related late cognitive effects. For example, administration of the anti-inflammatory peroxisomal proliferator-activated receptor γ (PPARγ) agonist, pioglitazone, to adult male rats was proven to substantially reduce radiation-induced cognitive impairment and similar results have been shown for the PPAR alpha agonist, fenofibrate.[46,47] Furthermore, fenofibrate preserves hippocampal neurogenesis and inhibits microglial activation after WBRT, and protects cortical neurons from inflammatory mediators.[48,49]

Similar anti-inflammatory properties have been demonstrated with the PPARγ agonist, pioglitazone.[50] Data shows promise for mitigating cognitive changes related to brain radiation therapy, and a phase 1 trial (NCT01151670) studying the side effects and optimal dose of pioglitazone hydrochloride in preventing radiation-induced cognitive dysfunction for both patients with BM and primary brain tumors was recently completed.

Ongoing Studies

The NRG has two ongoing studies to corroborate the results of RTOG 0614 and RTOG 0933. NRG-CC003 is a randomized phase II/III trial of prophylactic cranial irradiation (PCI) comparing WBRT to HA-WBRT in patients with extensive and limited-stage small-cell lung cancer who achieve a complete or partial response to chemotherapy. The randomized phase II trial is a noninferiority trial to determine whether the 12-month brain relapse rate following HA-PCI is noninferior compared to the rate after PCI. The phase III trial tests whether HA-PCI reduces the likelihood of a 6-month decline in HVLT-R delayed recall compared to PCI. Patients will be stratified by memantine use, stage (limited vs. extensive), and age (< 60 vs. ≥ 60 years old).

NRG-CC001 is a randomized phase III trial of HA-WBRT plus memantine vs. WBRT (30 Gy in 10 fractions) plus memantine for patients with histologically or cytologically proven diagnosis of solid tumor malignancy within 5 years prior. This trial will determine whether use of HA-WBRT increases time to neurocognitive failure at months 2, 4, 6 and 12 as measured by neurocognitive decline on a battery of tests compared to WBRT. Prior therapy for brain metastasis, including radiosurgery and surgical resection, is allowed.

Conclusion

Treatments affecting neurocognitive function are of major concern for patients, their families, and physicians. It is, therefore, of paramount importance that treatment strategies for BM balance tumor control and survival with preservation of cognitive function, which impacts quality of life. The etiology of neurocognitive decline in cancer patients with BM is multifactorial and includes the tumors themselves, systemic agents, and the effects of WBRT.

Current approaches to reduce the effects of WBRT on neurocognitive function in patients with BM include avoidance of WBRT, implementation of HA-WBRT, and prophylactic use of the NMDA receptor antagonist memantine. Both HA-WBRT and memantine use are being investigated in ongoing NRG studies. Other promising strategies include RAS blockers, acetylcholinesterase inhibitors, and peroxisomal proliferator-activated receptor agonists.

We strongly encourage enrollment in ongoing and future trials that investigate strategies to mitigate the effects of WBRT on neurocognitive function in patients with BM.

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Optimization of stereotactic radiosurgery for the treatment of brain metastases

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Brain metastases (BM) are the most common intracranial neoplasm occurring in up to 20% to 40% of patients with cancer.[1,2] The incidence of BM is increasing due to the longer survival of patients with cancer in the setting of modern treatment modalities, improved imaging techniques, and increased cancer screening.[2] The prognosis for the majority of patients with BM remains quite poor. In fact, in a study of 1,953 consecutive patients with BM treated at the Cleveland Clinic, the 1-year survival was 30% and the 5-year survival was 3%.[3] These patients commonly have a high burden of neurologic symptoms and often mortality due to their intracranial disease.[4]

Treatment options for patients with BM can include surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or a combination of these modalities. Treatment recommendations depend on the disease histology, burden of intracranial disease, extracranial disease status, and the patient's performance status.[5]

Several landmark trials have informed our modern day practices including the first Patchell study, which demonstrated the importance of surgical resection in patients with single brain metastasis; the second Patchell study, which established the role for adjuvant WBRT after surgical resection in patients with a single brain metastasis; and the Aoyama study, which proved the feasibility of SRS alone.[6-8] Through the years, SRS has continued to gain popularity as it offers a technique for radiation dose-intensification while minimizing dose to normal brain tissue through its use of high doses of radiation in 1-5 fractions delivered via a highly conformal technique. This review aims to discuss methods of optimizing the use of SRS in the treatment of brain metastasis with the goal of improving local control, decreasing toxicity, and ultimately improving survival. Topics include the use of targeted agents, treatment planning strategies, toxicity prognostication and reduction strategies; and prognostication and response assessment using imaging characteristics.

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Targeted Agents

SRS is now being studied alongside the development of targeted therapies.[9] Traditionally, systemic therapies have had a limited role in treating BM due to their inability to penetrate the blood-brain barrier and the relative chemoresistance of tumor cells.[2,10] Targeted agents differ from cytotoxic chemotherapy in that they act against specific aberrant cellular processes rather than halting uncontrolled cell proliferation. Johnson et al analyzed patients who received upfront SRS with or without targeted agents and found that the use of targeted agents improved 1-year outcomes including survival (65% vs. 30%, $p < 0.0001$), distant failure-free survival (32% vs. 18%, $p = 0.0001$) and freedom from WBRT (88% vs. 77%, $p = 0.03$) across all histologies.[11] These results, along with several retrospective studies,

highlight the increased therapeutic effect of targeted agents and SRS.[10,12-14] The use of targeted agents has an increasing role in the management of BM from breast cancer, renal cell carcinoma and melanoma, among other malignancies.

Breast cancers with human epidermal growth factor receptor 2 (HER2) mutation have been found to have an increased propensity for BM.[2] Classic targeted therapies used in the definitive setting (eg, trastuzumab, a monoclonal antibody) have not been proven useful after the development of BM due to relatively large size (> 150 kDa). A newer targeted agent, lapatinib, which is a small-molecule inhibitor (< 800 Da) against HER2, has been shown to be tumoricidal with an ability to penetrate the blood-brain barrier. Its utility for BM without combined SRS has been confirmed by multiple studies including the LANDSCAPE trial[15,16] as well as a study led by Yomo et al. In the latter study, the administration of lapatinib with SRS increased 1-year local control rates (86% vs. 69%, $p < 0.001$).[17] Similarly, data from the Cleveland Clinic has demonstrated that the use of concurrent lapatinib with SRS reduced the risk for local failure in HER2-amplified patients from 15.1% to 5.7% ($p < 0.001$).[18] As this remains an ongoing area of investigation, an ongoing phase II trial is examining WBRT or SRS in the setting of lapatinib (NCT01622868).

Renal cell carcinoma (RCC) is another commonly studied malignancy with the potential to improve response to radiation therapy with the use of targeted therapies. Established targeted therapies in this patient population include multiple tyrosine-kinase inhibitors (eg, sunitinib, sorafenib), mTOR inhibitors (eg, temsirolimus), and anti-VEGF agents (bevacizumab).[12] While sunitinib has demonstrated intracranial tumoricidal activity, studies investigating sorafenib, temsirolimus and bevacizumab have only shown safety and lack of neurologic adverse events.[9] Cochran et al analyzed 61 patients who received SRS with or without sunitinib, sorafenib, or temsirolimus. Patients receiving targeted agents demonstrated improved survival from 7.2 to 16.6 months ($p = 0.04$) and increased local control from 60% to 93% ($p = 0.01$).[12] Targeted agents for RCC have modest intracranial tumoricidal activity and are generally combined with other agents for extracranial metastatic disease. The evidence of synergistic activity when combined with SRS suggests these agents act as radiosensitizers for BM.

Malignant melanoma has the highest propensity to metastasize to the brain. In addition, because of its conceived radioresistance, it is an area requiring further research. A significant proportion of melanomas are associated with a *BRAF* mutation, for which the targeted agents dabrafenib, vemurafenib and trametinib have been shown to be efficacious.[19] Long et al conducted a multicenter phase II trial studying dabrafenib in patients with *BRAF*-mutant melanoma BM and significant intracranial activity.[20] However, safety of this agent remains a concern given the associated risks of intratumoral hemorrhage and increased risk of radiation necrosis (RN) when combined with SRS, as reported by Ly et al.[21,22] Others have also demonstrated that the timing of the *BRAF*-directed therapy when given with SRS is important to reducing the risk of local failure.[23] A current prospective phase II trial aims to determine the effect of dabrafenib combined with SRS on distant and local control and toxicity (NCT01721603). For patients with BM from *BRAF*-wild type melanoma, immunotherapy (eg, ipilimumab) has demonstrated central nervous system (CNS) penetration and potential benefit.[2] In a study by Kiess et al involving 46 patients with 113 total BM lesions, ipilimumab administered prior to or concurrently with SRS was associated with an improved 1-year distant intracranial local control when compared to the patient cohort receiving ipilimumab after SRS (69% vs. 64% vs. 92%, $p = 0.003$).[14] Further investigation is warranted to establish optimal therapy sequencing in the appropriate patient population.

Treatment Planning Strategies

Strategies in radiation therapy planning to optimize SRS delivery include modifying the radiation dose, prescribing to different isodose lines, and changing tumor volume expansions. Dosing schemes for treating BM with SRS were established by the Radiation Therapy Oncology Group (RTOG) 90-05 clinical trial. Based on maximum tumor diameter, tumors < 2 cm, 2.1 to 3 cm, and 3.1 to 4 cm were recommended to receive 24 Gy, 18 Gy, and 15 Gy, respectively.[24] However, these dosing regimens are not strictly followed, and many studies evaluating SRS outcomes have median doses less than RTOG 90-05 protocol.[25] There is evidence correlating radiation dose and different local control rates of BM despite the use of RTOG 90-05 dosing schemes. In an analysis of 375 BM undergoing SRS, Vogelbaum et al demonstrated BM < 2 cm prescribed to 24 Gy to the tumor margin had better local control than larger BM receiving 15 Gy or 18 Gy (85% vs. 49% vs. 45%; $p = 0.0005$).[25] Mohammadi et al reported results of an updated study including 3,034 BM ≤ 2 cm. They demonstrated BM < 1 cm were associated with a lower risk of local progression (HR 2.32; $p < 0.001$) and RN (HR 2.13; $p < 0.001$) as compared to larger lesions.[26] Collectively, these results provide evidence that treating BM ≤ 2 cm with 24 Gy maximizes local control with no increased risk of radiation-induced toxicities.

The goal of treatment planning for SRS is to maximize peripheral tumor dose, while achieving a steep dose gradient just beyond the tumor margin. Differing prescription isodose lines (IDL) can alter dose distributions to the

Table 1. Measures of Dose Conformality

Conformality Indices	Equation	Variable definition	Definition
Conformality index (CI)	*PIV / TV*	PIV: prescription isodose volume TV: target volume	How well the distribution of radiation conforms to the shape of the radiosurgical target.
Heterogeneity index (HI)	*MD / PD*	MD: maximum dose PD: prescription dose	Defines the uniformity of dose distribution in the target volume. The inverse of isodose lines.
Gradient index (GI)	PIV_{half}/PIV	PIV_{half}: volume of half the prescription isodose PIV: prescription isodose volume	Quantification of dose falloff outside the planning target volume.

target volume, and RTOG 90-05 suggests IDL ≥ 50% to minimize normal tissue toxicity.[24,27] In an investigation of SRS efficacy of differing IDLs and conformality indices (**Table 1**), Shiue et al analyzed 496 BM treated with SRS and expectedly demonstrated that tumor size predicted for local control (HR 1.696, $p < 0.001$). However, differing heterogeneity and conformality indices, and higher IDLs did not significantly affect local control or RN.[27] In a similar analysis, Jani et al also found no significant difference in local control with IDLs > 50%.[28] These results suggest that prescribing to higher IDLs can reduce treatment time without increasing the risk for RN or local failure. Romano et al analyzed IDLs as a continuous variable in 374 BM treated with SRS. They demonstrated that prescribing to a higher IDL and maximum tumor dose improved local control ($p < 0.001$ and $p = 0.07$, respectively) with no effect on radiation-related toxicities ($p = 0.53$ and $p = 0.86$, respectively).[29] Collectively, these results suggest that a tumoricidal dose outside of tumor margins afforded by higher IDLs, rather than a maximum dose at the center, improves local control.[27-29] Microscopic invasion beyond the visible tumor margins is supported from data by Nöel et al, who demonstrated that adding a 1-mm margin to the gross tumor volume (GTV) significantly improves local control without an increased risk of toxicity.[30] To further define the optimal planning target volume (PTV), Kirkpatrick et al randomized patients to SRS with either a 1 mm or 3 mm margin. Local progression free survival was equally high in both groups, as the median time to failure was not met. However, patients who received SRS with a 3 mm margin trended toward higher toxicity, as the volume receiving 12 Gy ($V12_{Gy}$) was significantly higher ($p < 0.01$), which independently has shown to be a risk factor for developing RN.[31,32]

For optimizing the treatment of larger, unresectable BM, multifraction and dose-staged SRS takes advantage of the radiobiological therapeutic index of fractionating radiation therapy, while maintaining highly conformal dose distributions.[33] In a comparison of single-fraction vs. multifraction (9 Gy x 3) SRS for BM > 2 cm, Minniti et al demonstrated that 27 Gy in 3 daily fractions compared to single fraction SRS, improved local control ($p = 0.01$) while reducing the risk of RN ($p = 0.03$).[32] Another novel technique for large BM, called dose-staged SRS: two sessions of SRS in 2-4 week intervals, with each subsequent stage treating a smaller tumor that is responding to treatment.[34] Similar to multifraction SRS, dose-staged takes advantage of dose-buildup while reducing the risk of RN. Preliminary studies show durable local control and acceptable toxicity, but long-term data is limited.[34]

Toxicity

Radiation necrosis, though uncommon, remains a limiting toxicity to radiation dose-intensification and has been treated with dexamethasone. Traditionally, RN has been estimated to occur at rates of 5% to 10% (**Figure 1**).[24] Symptomatic RN may cause significant neurologic deterioration and may become the cause of death. It often mimics tumor progression, and standard MRI techniques have shown to be insufficient in distinguishing the two.[35] Major risk factors that predict for RN include lesion size, maximum dose, the volume irradiated and BM histology.[24,35] RTOG 90-05 established that as the tumor volume increases the dose that can be safely delivered to a tumor decreases. In terms of RN, multivariate analyses demonstrated maximum dose/prescription dose (dose homogeneity) > 2, and prescription isodose volume/tumor volume (dose conformality) > 2 are predictors.[24,35] The volume of normal brain tissue receiving 10 Gy ($V10_{Gy}$) and 12 Gy ($V12_{Gy}$) has also been associated with RN. In an analysis of 173 BM, Blonigen et al demonstrated RN risk up to 68.8% for $V10_{Gy} > 14.5\ cm^3$ and $V12_{Gy} > 10.8\ cm^3$ ($p < 0.001$).[36] In an analysis of RN associated with BM histology, Miller et al found that BM from renal cell carcinomas, *HER2*-amplified breast cancer, *ALK*+ lung cancers, and *BRAF* V600 wild-type melanomas are all associated with increased risk of RN.[37]

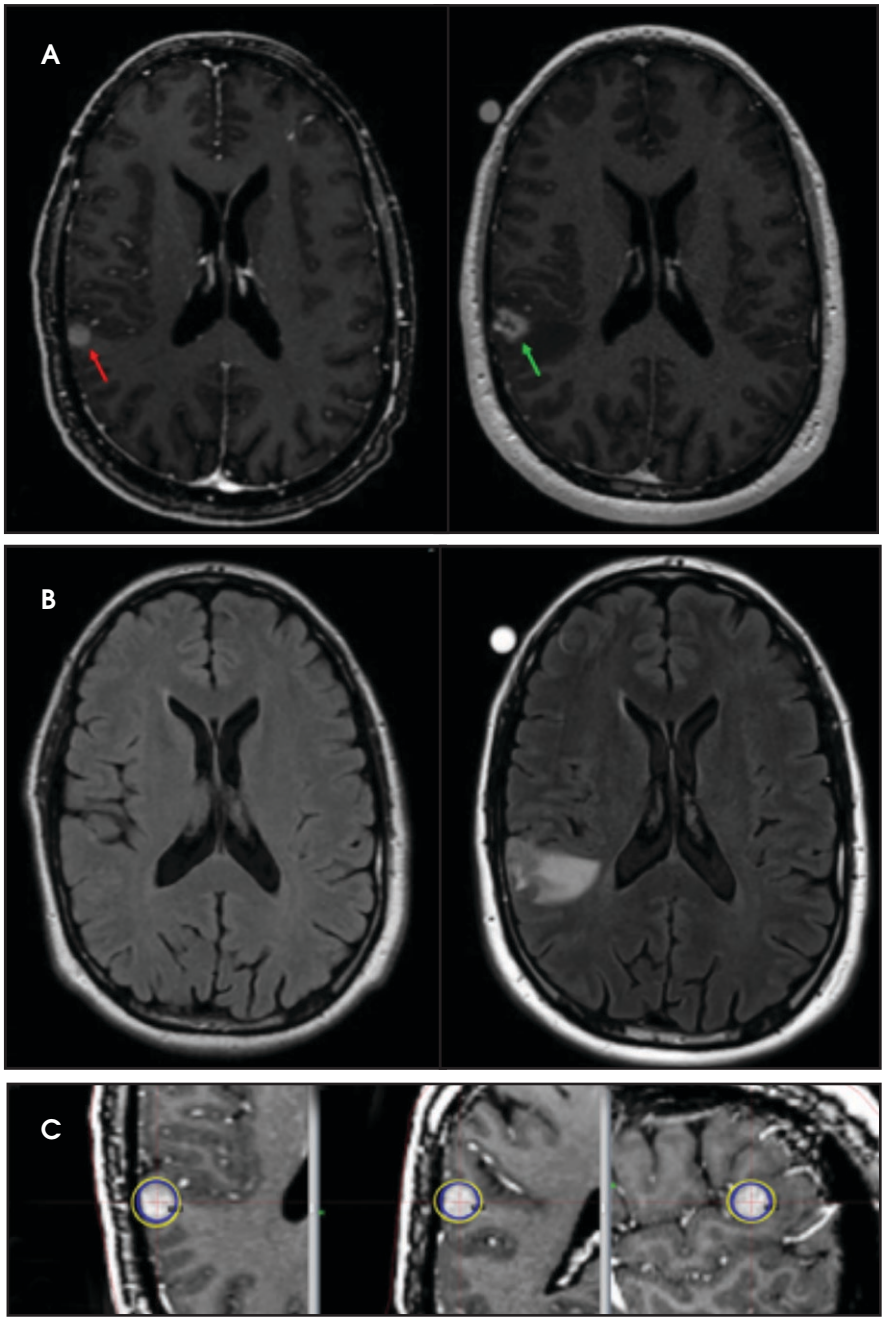

FIGURE 1. *(A) Axial T1-weighted postcontrast pretreatment MRI (left) demonstrates an enhancing brain metastasis in the right parietal lobe measuring 9 mm in maximum diameter (red arrow). Axial T1-weighted postcontrast MRI 18 months post-treatment (right) demonstrates that the enhancing lesion has increased, measuring 1.6 cm in maximum dimension consistent with radiation necrosis (green arrow). (B) Axial T2-weighted FLAIR (fluid attenuation inversion recovery) pretreatment MRI (left) demonstrates lack of FLAIR changes surrounding the right parietal brain metastasis. Axial T2-weighted FLAIR MRI 18 months post-treatment (right) demonstrates increased vasogenic edema consistent with radiation necrosis. (C) Representative images from the stereotactic radiosurgery plan (left to right: axial, coronal, and sagittal). The blue contour represents the brain metastasis. The yellow line correlates to 24 Gy prescription isodose line.*

Compared to the evidence that exists for the detection and management of RN, data on therapeutic interventions to prevent and reduce the risk of RN is limited.[35] Aside from optimizing SRS planning, there is preliminary data on the use of hyperbaric oxygen and administration of pentoxifylline and vitamin E as prophylaxis for RN. Ohguri et al studied hyperbaric oxygen therapy one week after SRS in 32 patients as prophylaxis against RN demonstrating decreased incidence of RN in patients receiving prophylaxis from 20% to 11% ($p = 0.05$).[38] The use of pentoxifylline and vitamin E has been established as a treatment for RN, and has been shown to reduce radiation-induced damage in extracranial disease sites.[39,40] For its role in the brain, an ongoing phase II trial is evaluating the combination for prophylaxis of RN (NCT01508221). With the increased use of SRS for definitive treatment, future research for RN should include improved detection of RN, groups at risk for RN, and techniques to prevent RN in high-risk groups.

Imaging Characteristics

Imaging characteristics may have value in predicting outcomes of SRS and overall prognosis.[41] Goodman et al investigated patterns of enhancement on day-of-treatment imaging as a prognostic indicator for local failure. They characterized lesions as homogenously enhancing, heterogeneously enhancing, or ring-enhancing and found local control at 1 year was 90%, 76% and 57%, respectively ($p = 0.019$).[42] Necrotic-appearance of BM on MRI has been suggested as a negative prognostic factor with the hypothesis that the necrotic region correlates to hypoxic tumor cells, which may demonstrate relative radioresistance.[42,43] Similarly, Xu et al analyzed 147 women with BM from breast cancer treated with SRS, stratified by tumor necrosis on pretreatment MRI, revealing the non-necrotic cohort had better neurologic survival compared

Table 2. Comparison of Brain Tumor Response Criteria

	RECIST 1.1	RANO-BM[45]	$_{VC}$ (Follwell et al.)[46]	$_{V3d}$ (Follwell et al.)[46]
Complete response (CR)	100% decrease	100% decrease	100% decrease	100% decrease
Partial response (PD)	≥ 30% decrease	≥ 30% decrease	≥ 65% decrease	≥ 58.5% decrease
Stable disease (SD)	< 30% decrease or < 20% increase	< 30% decrease or < 20% increase	< 65% decrease or < 75% increase	< 58.5% decrease or < 71.5% increase
Progressive disease (PD)	≥ 20% increase	≥ 20% increase	≥ 75% increase	≥ 71.5% increase
Measurement techniques	Uni-dimensional	Uni-dimensional	3-dimensional	3-dimensional
Imaging modality	MRI or CT	MRI or CT	MRI	MRI
Neurologic status	Not included	Included	Not included	Not included
Corticosteroids	Not included	Included	Not included	Not included
Extracranial disease	Included	Not applicable	Not applicable	Not applicable

Abbreviations: RECIST (Response Evaluation Criteria in Solid Tumors); RANO-BM (Response Assessment in Neuro-Oncology - Brain Metastases); $_{VC}$ (calculated volume); $_{V3d}$ (3-dimensional volume using MRI segmentation); MRI (magnetic resonance imaging); CT (computed tomography).

to the necrotic cohort (25 vs. 17 months, $p = 0.006$).[44] Local control for necrotic BM may be improved by combining SRS with hypoxic cell sensitizers (eg, nimorazole, nicotinamide, carbogen), or fractionating SRS to improve central oxygenation.[42] Other techniques of optimizing SRS for necrotic-appearing BM include the use of previously established radiosensitizers (eg, capecitabine, bevacizumab), or increasing the relative dose to the central necrotic regions by prescribing to lower isodose lines.[42,44]

To evaluate response to treatment, Response Evaluation Criteria in Solid Tumors (RECIST) has been commonly implemented. However, in the age of modern systemic therapies, the Response Assessment in Neuro-oncology - Brain Metastases (RANO-BM) response criteria (**Table 2**) offers a more objective and reproducible method of interpreting response to treatment. RANO-BM includes radiographic assessment of target (based on changes in linear dimensions) and nontarget lesions, as well as assessment of clinical status and corticosteroid use.[45] For small-volume BM with complex geometries, these criteria may be unfit to accurately assess treatment response.[46] Follwell et al analyzed 178 brain metastases treated with SRS with MRI segmentation software to derive a 3-dimensional volume-based response criteria that is approximately based on the RECIST criteria.[46] Multivariate analysis identified BM with a baseline diameter > 3 cm or a 3-dimensional volume > 6 cm^3 are at increased risk of local failure.[46] The response assessment systems are summarized in **Table 2**.

Conclusion

The use of SRS for the management of BM has evolved from a targeted-boost to the lesion to definitive upfront treatment. The advent of targeted therapies and immunotherapies has created a new tumor microenvironment within the brain and provides opportunities to investigate their combination with SRS. Several retrospective series have shown a synergistic effect in local control of SRS combined with lapatinib for HER2-positive BM, sunitinib, sorafenib and temsirolimus for RCC BM, and dabrafenib and ipilimumab for BRAF-mutated and wild-type melanoma BM. However, the retrospective nature of these analyses and subanalyses should only guide future prospective studies and no conclusive recommendations can be made without further hypothesis-driven evidence.

As more patient groups are being defined that are best suited for SRS, there is an increased interest in optimizing treatment planning. Dose-escalation to 24 Gy for small (< 2 cm) lesions has shown to improve local control without increasing toxicity, and alterations in fractionation schemes may improve the therapeutic window for larger metastases. Advances in imaging have allowed for improved differentiation between tumor progression and radiation-induced toxicities, and are characterized as BM by radiographic differences (eg, non-necrotic vs. necrotic centers and homogenous vs. heterogeneous lesions). Future investigations should focus on taking advantage of imaging characteristics to improve the efficacy of SRS as well as discovering therapeutic options in preventing toxicities. The influx of retrospective data for SRS in recent years needs to be validated by randomized controlled trials. Although prospective analysis of BM has been a major challenge, contributions from the RANO group will help guide the creation of clinical trials that will offer more personalized treatments for patients with BM.

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Stereotactic radiosurgery for cerebellar metastases and the risk of obstructive hydrocephalus

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Abstract

Purpose: Cerebellar location has been reported as a poor prognostic factor among patients with brain metastases. Stereotactic radiosurgery (SRS) is commonly utilized in patients with brain metastases, but the role of SRS in cerebellar metastases is less clear. It is believed that SRS could result in obstructive hydrocephalus with tumor edema or progression, and resection could minimize that risk. Our purpose was to report our institution's clinical experience treating such patients to investigate this concern.

Methods: Patients with brain metastases treated with SRS to cerebellar disease at their first SRS session at our institution from 1997 to 2014 were included in the analysis. Patient and tumor characteristics, dosimetry, toxicity, and survival following SRS were collected and analyzed for factors associated with obstructive hydrocephalus and SRS toxicity.

Results: One hundred patients with 155 cerebellar metastases met inclusion criteria. The median Karnofsky performance score (KPS) was 90 and median number of cerebellar metastases was 1 (range: 1 to 7). Prior cerebellar tumor resection was performed in 9.7% (n = 15) of tumors, and whole-brain irradiation in 30% (n = 30) of patients. Patients received a median SRS prescription of 20 Gy to the 50% isodose line. Median overall survival was 15.9 months, and 4 patients (4%) developed obstructive hydrocephalus and/or received a shunt following their first SRS. On multivariate analysis, after controlling for tumor volume and proximity to the 4th ventricle, the only factor associated with probability of developing hydrocephalus and/or shunt placement after SRS was previous resection ($p = 0.02$).

Conclusion: Our series demonstrates that SRS to cerebellar metastasis is generally safe and effective. Resection prior to SRS may increase the long-term risk for subsequent obstruction. While cerebellar tumor location may be associated with poor prognosis, SRS-related toxicity is uncommon.

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Intracranial metastases are a sign of systemic progression in patients with a malignancy and have a dismal prognosis if left untreated.[1] While limited brain metastases have been traditionally managed with open neurosurgical resection,[2] in recent years stereotactic radiosurgery (SRS) has emerged as a widely accepted therapeutic option for patients with limited brain metastases.[3-7] Unless extirpation is indicated for immediate relief from mass effect symptoms or for histopathologic diagnosis, SRS is less invasive and preferred when treating multiple, small metastases, especially when eloquent or deep-seated areas are involved.

While most metastases occur in the supratentorium, the posterior fossa accounts for about 15% to 20% of tumors.[8,9] Compared to supratentorial location, metastasis to the cerebellum has been reported as a negative prognostic factor for survival.[10,11] One potential explanation is that, by virtue of its location, patients with cerebellar metastases are at risk for obstructive hydrocephalus and brainstem compression.[8,12-14] However, only a few series in the literature evaluate the outcomes of SRS specific to cerebellar metastases.[14,15] Although survival outcomes have been reported, there were limited data to determine rates of toxicity following treatment with SRS.

The purpose of this investigation was to evaluate our institution's experience in treating patients with cerebellar metastases with SRS, including the efficacy and toxicity outcomes of cerebellar SRS, with the goal of addressing the theoretical concern that SRS to the cerebellum can result in post-SRS obstructive hydrocephalus.

Table 1. Clinical Characteristics of 155 Cerebellar Metastatic Tumors in 100 Patients

Characteristics	Value	Percentage or range
Sex (Male: Female)*	46:54	
Age (median, y/o)*	60.5	33.5-87.2
KPS (median)*	90	60-100
Extracranial metastases*	48	48%
Tumor histology†		
NSCLC	53	34.2%
Breast cancer	39	25.2%
Melanoma/Renal cell carcinoma	16	10.3%
Others	47	30.3%
Prior cerebellar tumor resection†	15	9.7%
Prior WBRT*	30	30.0%
Prior chemotherapy*	54	54.0%
Cerebellar tumor diameter (median, mm)†	8	0.1-50.0
Intracranial metastases (median)*	3	1-18
Cerebellar metastases (median)*	1	1-7
Distance from tumor to 4th ventricle (median, mm)	19	0-46
SRS†		
Treatment volume (median, ml)	0.80	0.02-22.9
Margin dose (median, Gy)	20	12-24
Isodose level (median, %)	50	30-97
Maximum dose (median, Gy)	36	18.6-60.0
Median image follow-up (months)*	14.8	0-118.9
Median survival (months)*	15.9	0.1-118.9

Abbreviations: KPS: Karnofsky performance score, SRS: Stereotactic radiosurgery, NSCLC: nonsmall cell lung cancer, y/o: years old, WBRT: whole brain radiotherapy, Gy: Gray. *Reported on a per-patient basis, n = 100. †Reported as median values for each cerebellar metastasis, n = 155.

Methods

Patient Population

Data were obtained through a prospectively collected, IRB-approved database of patients treated with SRS at our institution. All patients received SRS for cerebellar metastases between 1997 and 2014 on a Leksell Gamma Knife radiosurgery platform (Elekta, Stockholm, Sweden). Patients receiving cerebellar surgical resection, whole-body radiation therapy (WBRT), and/or chemotherapy prior to receiving SRS were included, although patients who underwent SRS to other lesions and later received cerebellar SRS were excluded. Clinical characteristics for each patient were collected including gender, age, Karnofsky performance score (KPS), tumor histology, maximal cerebellar tumor diameter, cerebellar tumor volume, intracranial and extracranial disease burden, prior therapies, and overall survival. Distance to the 4th ventricle was calculated by measuring the shortest linear distance (mm) from the tumor to the 4th ventricle on an axial-oriented MRI (T1 gadolinium-enhanced sequence). SRS dosimetric parameters including margin dose, isodose, and maximum dose were additionally collected through review of the treatment planning software.

Stereotactic Radiosurgery

Our institution's SRS technique has been described previously.[16,17] In brief, patients are treated with a Leksell Gamma Knife radiosurgery unit in a single fraction. Three Gamma Knife models were used during this

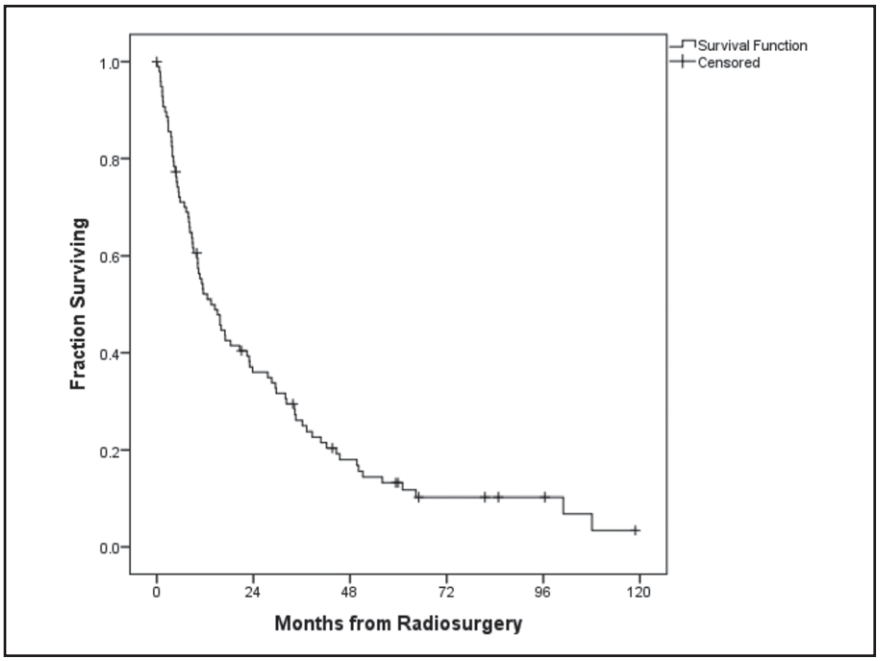

FIGURE 1. *Overall survival of patients with cerebellar metastases following stereotactic radiosurgery.*

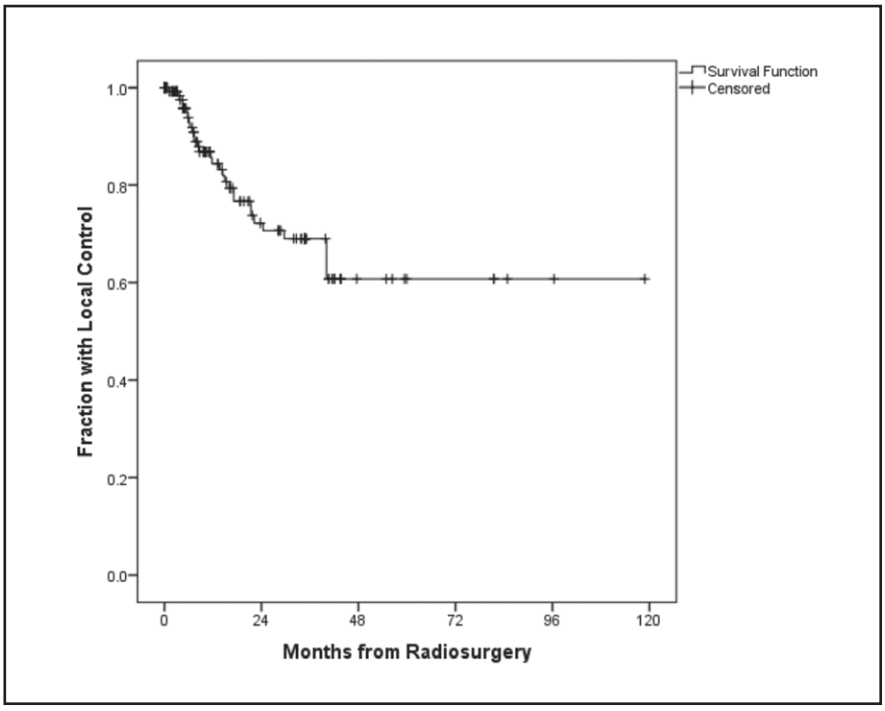

FIGURE 2. *Local cerebellar metastasis control following stereotactic radiosurgery.*

period: the model U (1992-2001), the model C (2001-2007), and the Perfexion (2007-present). After stereotactic head frame placement and neuroimaging (MRI and/or CT if MRI is medically contraindicated), the images were loaded to the radiosurgical planning software and coregistered in 3-dimensional space to the SRS treatment platform. Prior to treatment initiation, all radiosurgical plans were reviewed and approved by a neurosurgeon, radiation oncologist, and medical physicist. Utilizing ^{60}Co sources, the prescribed dose was delivered via one or more isocenters to the isodose line encompassing the periphery of the tumor defined by neuroimaging (without margin). In the postoperative setting, our general practice is to target the postoperative cavity as defined by MRI and prescribe coverage that extends 1mm into the adjacent tissue. We also cover any enhancing tumor at the operative bed. Of note, we typically wait 1 to 2 weeks between resection and SRS for dynamic changes at the tumor resection cavity to be largely stabilized.[18]

Follow-up

Patients typically underwent imaging follow-up at approximately 3-month intervals after SRS. All images were reviewed by treating clinicians and a neuroradiologist. These images were reviewed and compared to images obtained at the time of SRS for changes in tumor volume (increase, decrease, or stable) and brain edema (increase, decrease, or stable). Tumor volume growth >10% during follow-up were considered evidence of local failure.[19] Patients had regular clinical follow-up after SRS to monitor for clinical toxicity and/or progressive disease. These medical records were reviewed for evidence of new or worsening cerebellar mass effects (imbalance, ataxia, nausea, and vomiting), hydrocephalus, shunt insertion after SRS, new cranial nerve deficits, and adverse effects from treatment (ie, SRS-induced edema requiring steroids) graded by the Common Terminology Criteria for Adverse Events version 4.[20] Patients who underwent ultimate resection of the cerebellar metastasis after SRS were also recorded. Overall survival (OS) was measured from the data of SRS to the date of death or last follow-up.

Table 2. Stereotactic Radiosurgery Outcomes of 155 Cerebellar Metastases

Characteristics	Resection followed by SRS (%)	SRS alone (%)
n	15	140
New or worsening hydrocephalus	2 (13%)	2 (1.4%)
Insertion of a shunt after SRS	2(13%)	1 (0.7%)
New or worsening SRS-related edema	0	10 (7.1%)
New or worsening symptoms of cerebellar mass effect following SRS		
None	6 (40%)	118 (84%)
Imbalance and ataxia	7 (47%)	21 (15%)
Nausea and vomiting	0	0
Both	2 (13%)	1 (0.7%)
New or worsening cranial nerve function	2 (13%)	4 (2.9%)
Ultimate resection of cerebellar tumor following SRS	na	6 (4.3%)

Abbreviations: SRS: Stereotactic radiosurgery, na: not applicable.

Statistical Analyses

Potential prognostic variables (eg, age, gender, laterality, histology, KPS, total number of brain and cerebellar metastases, tumor volume, distance to the 4th ventricle, margin dose, isodose, maximum dose, and pre-SRS interventions) were evaluated using logistic regression models for an association with hydrocephalus and/or shunt placement following cerebellar SRS. Overall survival (OS) and local control (LC) were analyzed using the Kaplan-Meier method. All statistical analyses in this study were performed using statistical software (SPSS, version 20.0; SPSS Inc., Chicago, Illinois).

Results

Clinical Outcomes

We identified 100 patients with 155 cerebellar metastases treated with SRS at our institution. The clinical characteristics of the cohort are summarized in **Table 1**. The median KPS at the time of SRS was 90 (range: 60 to 100). Cerebellar tumor resection was performed prior to SRS in 15 patients (9.7%). The number of cerebellar metastases ranged from 1 to 7 (median: 1 cerebellar tumor). The cerebellar metastases had a median diameter of 8 mm (range: 0.1 - 50.0 mm) and the median distance to the 4th ventricle was 19 mm (range: 0 - 46 mm). The typical SRS prescription delivered 20 Gy into the 50% isodose line. Most "other" tumor histologies were of gastrointestinal origin (38 tumors, 24.5%).

Overall Survival and Local Control

In this series, median imaging follow-up and OS were 14.8 months and 15.9 months, respectively. **Figure 1** illustrates the OS for all patients, with a median OS of 15.9 months. In terms of local control, **Figure 2** demonstrates the fraction of patients with local control during follow-up. Local control following SRS was 99%, 93%, and 84% at 3, 6, and 12 months, respectively.

Clinical Outcomes

Table 2 summarizes the clinical outcomes of patients in this series, stratified by whether they underwent pre-SRS resection or SRS alone. As demonstrated in **Table 2**, new or worsening hydrocephalus occurred more frequently in the pre-SRS resection cohort (13% vs. 1.4%). Onset of new/worsening cerebellar mass effect symptoms was also more frequent in the pre-SRS resection cohort, as was the relative rate of cranial nerve deficits (**Table 2**). Interestingly, SRS-related edema was not observed with the pre-SRS resection cohort (vs. 10 % in the SRS alone cohort).

Figure 3 depicts the relationship between cerebellar tumor size and subsequent hydrocephalus and/or shunt. **Table 3** displays the prognostic factors associated with hydrocephalus and/or shunt placement following cerebellar SRS by both univariate and multivariate analyses. Of the investigated variables, only resection prior to SRS was associated with a significantly increased risk of hydrocephalus and/or shunt placement status after SRS (*HR* 35.8, 95%*CI* 1.6 - 784.13, $p = 0.023$). Cerebellar tumor volume, cerebellar tumor number, distance to the 4th ventricle, margin dose, isodose, and prior WBRT failed to demonstrate an association with the ultimate development of obstructive hydrocephalus.

Discussion

Cerebellar metastases are unique due to the reported risk of obstructive hydrocephalus and intracranial hypertension,[8,12-14] and their reported association with inferior survival outcomes.[10,11]

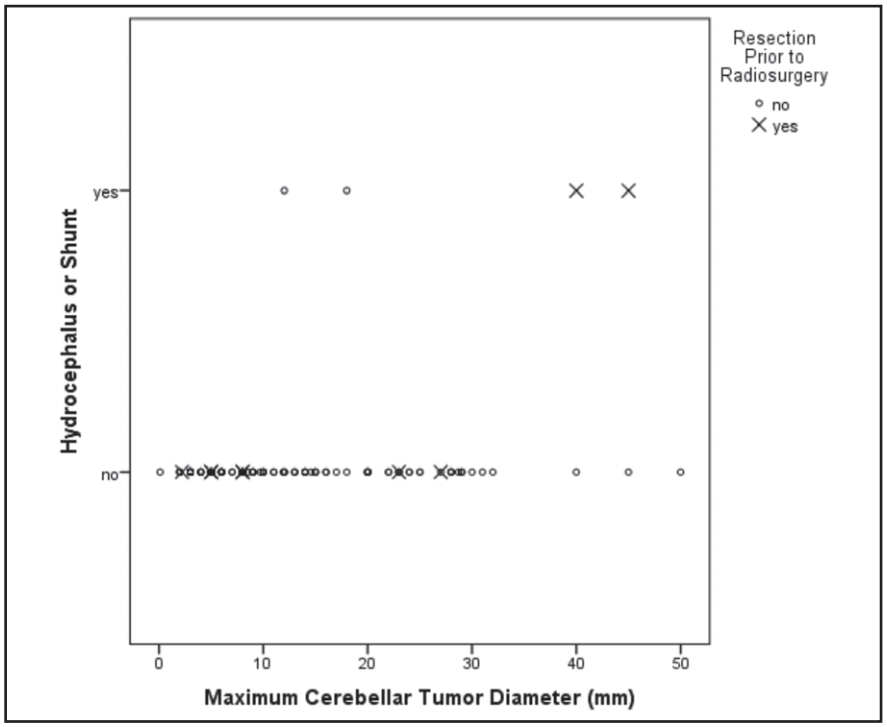

FIGURE 3. *Incidence of obstructive hydrocephalus and/or shunt following stereotactic radiosurgery based on tumor location, stratified by resection prior to radiosurgery.*

However, limited data exist regarding treatment outcomes after radiation therapy for cerebellar metastases, with only a few published series to date.[14,15,21] Our study demonstrates that SRS can be safely used for cerebellar metastases and, interestingly, that resection prior to SRS could be associated with a higher risk of toxicity following SRS. As the paradigm has shifted from WBRT to SRS for limited intracranial disease, further understanding of the contribution of less-studied clinical factors for SRS such as tumor location is critical for therapeutic decision-making.

This analysis has a unique position within the context of the existing literature. In an analysis by Javalkar et al of 35 patients with solitary, small cerebellar metastases, 24 were treated with resection and adjuvant WBRT and 11 had SRS alone.[14] Local failure, distant failure, and overall survival were not statistically significantly different between patients treated with resection and those

Table 3. Prognostic Factors Associated with Hydrocephalus and/or Shunt Placement Following Cerebellar SRS (Among All Patients, n =100)

Factors	Univariate	Multivariate		
	p-value	*p-value*	*HR*	*95% CI*
Age	0.090	0.086	0.882	0.763-1.018
Gender†	0.870			
Laterality†	0.947			
Histology†	0.871			
KPS	0.587			
Total brain metastases	0.256			
Total cerebellar metastases	0.997			
Distance from tumor to 4th ventricle*	0.727			
Largest cerebellar tumor volume	**0.027**	0.772	1.033	0.831-1.283
Margin Dose	0.883			
Isodose	0.959			
Maximum Dose	0.430			
Prior WBRT†	0.998			
Prior Resection†	**0.018**	**0.023**	**35.773**	**1.632-784.128**
Prior Chemotherapy†	0.406			

Abbreviations: CI: confidence interval, SRS: Stereotactic radiosurgery, HR: hazard ratio, KPS: Karnofsky performance score, WBRT: whole brain radiotherapy. Bolded if p-value < 0.05.
*Closest cerebellar tumor to the 4th ventricle per patient. †Analyzed as a categorical variable; otherwise analyzed as a continuous variable.

not.[14] In contrast, Ampil et al found that median OS was higher in patients receiving surgery and adjuvant WBRT (15 months) compared to WBRT alone (3 months).[21] However, this could have been confounded by the difference in the number of brain metastases between groups (15% of the WBRT alone group had solitary cerebellar metastasis compared to 73% in the group receiving resection first, $p = 0.001$).[21] A larger series of 109 patients found that survival outcomes were best after surgery and adjuvant RT, including WBRT or SRS, (35.5 months) compared to resection alone (20.5 months), WBRT alone (6.5 months), or SRS alone (9.1 months).[15] The results from this study are difficult to interpret as baseline prognostic features were reported based on the entire series not on a cohort-by-cohort basis. Fadul et al determined that WBRT and resection yielded a median OS of 6 months compared to 5.5 months for WBRT alone, although the sample size was relatively small (n = 21).[13]

Our series is unique in that it is the first to report on treatment toxicity rates following SRS for metastatic disease to the cerebellum and, in addition, identifies significant prognostic factors. As a historical barometer, RTOG 90-05, a phase I dose escalation trial, evaluated SRS dose tolerance limits in previously irradiated tumors and determined that SRS has an acceptable safety profile, although only among patients with gross disease.[22] The results of our series support this conclusion in our patient cohort, as the overall incidence of toxicity following SRS was low. When subjected to multivariate analyses, the only factor significantly associated with post-SRS hydrocephalus and/or shunt placement was previous surgical resection. Of note, other factors such as total cerebellar metastases, largest tumor volume, and even distance to the 4th ventricle failed to demonstrate a relationship. A reasonable assumption is that patients initially treated with surgery prior to receiving SRS had larger tumors with impending ventricular obstruction, although we could not identify that association. It is also possible that previously resected tumors have more risk of debris (eg, hemorrhage or cells from piecemeal resection of the tumor), which could cause unintended consequences of cerebrospinal fluid (CSF) outflow obstruction over time.

In light of our study results, perhaps a more plausible explanation is that SRS induces inflammation and this is compounded with changes already brought about by surgery, precipitating extensive peritumoral edema that can compress the adjacent ventricles. In contrast, we failed to identify SRS-induced edema in the pre-SRS resection cohort, a finding that could be related to the difficulty interpreting postoperative and post-SRS parenchymal changes radiographically. Patel et al reviewed MRI sequences of 516 brain metastases treated with SRS and determined that 32% of lesions increased in volume following SRS with a delayed onset often emerging 6 weeks following treatment and lasting as long as 15 months post-SRS.[23] They concluded that post-SRS growth was not always due to tumor recurrence but can be a sign of an inflammatory response. Hypothetically, cellular damage and the release of inflammatory toxins could lead to a pronounced inflammatory reaction, increased vasogenic edema, and a breakdown of the blood-brain barrier. Furthermore, studies on intracranial meningomas have reported on the importance of the tumor-brain contact interface area and how disruption of the interface is a prognostic factor for peritumoral edema.[24] One can extrapolate this data to suggest that extensive neural damage caused by resection and radiosurgery combined can also create architectural changes that predispose a patient to similar outcomes. In addition, brain metastases are already at an increased risk of intracranial edema due to disruption of the blood-brain barrier and increased permeability of tumor vessels.[25-27] Although distance to the 4th ventricle was not a significant prognostic factor, it bears considering that cerebellar metastases likely have a higher inherent risk for hydrocephalus given the proximity to the ventricular system compared to their supratentorial counterparts.[8,12-14] The combination of these factors – location, inherent predisposition to inflammation, and combined modality therapy – could produce a cascade of events increasing the risk for a mass effect on the ventricular system following treatment with SRS.

The limitations of this study relate to this being a retrospective analysis of a single institution's experience with the utilization of radiosurgery for cerebellar metastases. However, the size of the cohort makes this study a significant contribution to the literature. It is not certain that these results are generalizable to other radiation techniques, such as fractionated stereotactic radiation therapy.[28] In this series, 30% of patients had prior WBRT and 9.7% of patients had prior resection, so we could not isolate complications solely due to SRS. However, the current series reflects the multimodality treatment now commonly employed to treat brain metastases. Although we attempted to control for factors associated with the risk of hydrocephalus, the factors associated with the decision for neurosurgical tumor resection are complicated and could not be completely controlled for our analysis. In the future, similar analyses incorporating conformality indices will be critical in defining the drivers of toxicity in these patients.

Conclusion

In the first study to describe treatment toxicity rates following the use of radiosurgery for metastatic disease in the cerebellum, prior intervention with resection was associated with an increased rate of toxicity following

SRS. However, the overall incidence of treatment toxicity was low, demonstrating that SRS is a safe treatment option for cerebellar metastases even following surgical resection. Although further studies are needed to compare outcomes with different treatment modalities, our survival rates with SRS are encouraging. These data suggest that radiosurgery monotherapy (without resection) has the potential to result in acceptable toxicity, local control, and favorable survival rates in the cerebellum in properly selected patients. Future studies on radiosurgery for brain metastases should consider intracranial tumor location in clinical factor stratification due to the potential of location-specific mortality and morbidity effects.

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The expanding role of stereotactic radiosurgery in the treatment of brain metastases

Mary Beth Massat

Stereotactic radiosurgery (SRS), introduced in 1951 by Swedish neurosurgeon, Lars Leksell, MD, continues to advance the treatment of brain metastases. Historically, SRS has been performed in a single session using the Leksell Gamma Knife (Elekta, Stockholm, Sweden), developed by Dr. Leksell in 1968.[1] However, as linear accelerator technology progressed with sophisticated beam-shaping technology, advanced treatment planning systems and image-guidance tools, new linac-based SRS solutions entered the market, including the CyberKnife (Accuray, Sunnyvale, California), Novalis Radiosurgery (Brainlab, Munich, Germany) and the Edge (Varian Medical Systems, Palo Alto, California).

"SRS has revolutionized the management of brain metastases, and more or less replaced whole-brain radiation therapy (WBRT) for patients who have limited disease," says Gene H. Barnett, MD, MBA, a neurosurgeon and director of Cleveland Clinic's Brain Tumor and Neuro-Oncology Center, Cleveland, Ohio. Dr. Barnett is also vice chairman of the Department of Neurological Surgery, and director of the Cleveland Clinic Health System Gamma Knife Center.

***Ms. Massat** is a freelance healthcare writer based in Crystal Lake, IL.*

"Now that we can treat the individual spots that we see in the brain, we can spare exposing much of [a patient's] normal brain tissue to radiation," adds Lawrence Richard Kleinberg, MD, associate professor of Radiation Oncology and Molecular Radiation Sciences at Johns Hopkins Medicine, Baltimore, Maryland. Dr. Kleinberg uses the Cyberknife system (**Figure 1**).

In general, two types of SRS systems are available: a dedicated, frame-based system such as the Gamma Knife, and linac-based systems such as the CyberKnife, Novalis and Edge. The Gamma Knife involves a high-dose, single-fraction treatment while the linac-based solutions typically involve multiple fractions at lower doses.

"More recently, there has been enthusiasm for multisession treatments," says Samuel T. Chao, MD, a radiation oncologist at the Cleveland Clinic and associate professor at the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Cleveland, Ohio.

In particular, a study by Minniti et al concluded that multifraction SRS at a dose of 27 Gy in 3 daily fractions for brain metastases > 2 cm was associated with better local control and reduced risk of radiation necrosis compared to a single-fraction SRS treatment.[2] "We know that in brain metastases much greater than 2 to 2.5 cm, local control would decrease and toxicity would increase if we use a single fraction," says Scott G. Soltys, MD, radiation oncologist and assistant professor, Stanford University Cancer Center, Stanford, California. "The normal control rate in brain metastases < 2 cm is 85% to 90%, but that drops to 60% to 70% with larger-sized metastases."

The Minniti study also found that the most significant difference in local control was for lesions > 3 cm, with single-fraction SRS treatment having a local control of 54% at 1 year vs. 73% with multifraction SRS.[2] Dr. Barnett and colleagues have been using single-fraction SRS on patients with larger-sized brain metastases who traditionally would not have achieved the desired local control with a staged treatment. In these cases, the patient would return in a month for another treatment to achieve the necessary therapeutic dose, thus reducing the need for surgery, he says.

While surgery has an important role in treating brain metastases, the focus has shifted to the timing of SRS in conjunction with surgery to further

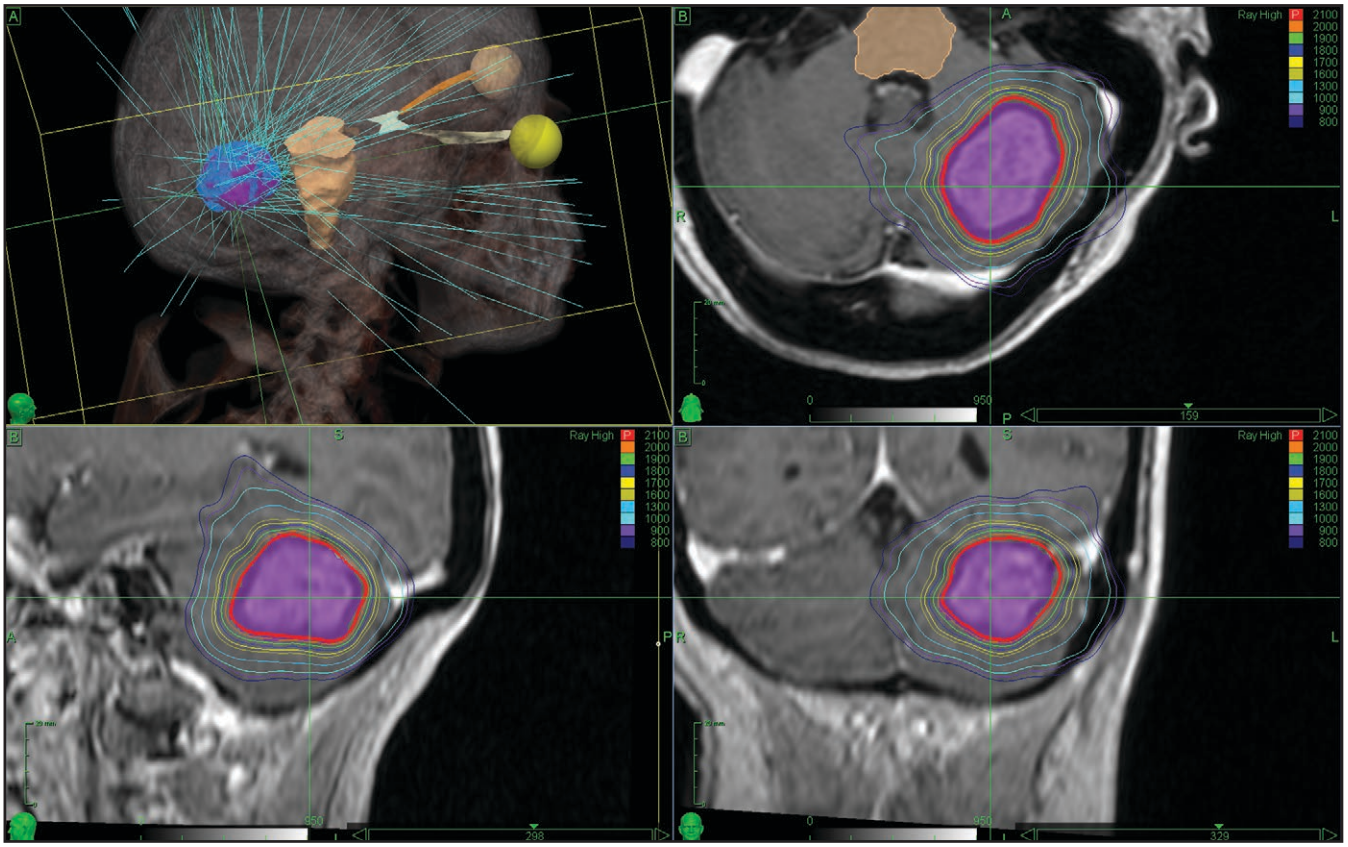

FIGURE 1. *Cyberknife (Accuray, Sunnyvale, California) brain metastases treatment plan.*

maximize control, adds Dr. Chao. The recurrence rate is 50% with surgery alone compared to > 70 % with surgery followed by SRS, he says.

WBRT or SRS?

In addition to offering better control with larger-sized metastases, SRS is being used more often for cases with multiple brain metastases. More studies report that the total intracranial tumor volume correlates with survival rather than the number of tumors.[3-5]

Ideal WBRT candidates include patients with leptomeningeal disease in which the tumor cells spread to the membranes surrounding the spinal cord and brain, and those with multiple radiosensitive lesions, says Dr. Barnett. Modern linacs capable of volumetric-modulated arc therapy (VMAT)/intensity-modulated radiation therapy (IMRT) or tomotherapy can help avoid the hippocampi, which may lessen the risk of cognitive side effects, adds Dr. Soltys.

Brown et al studied the effects on cognitive function in patients with 1 to 3 metastases who either received treatment using SRS alone or SRS in conjunction with WBRT. In the 213 randomized participants, the study found less cognitive deterioration at 3 months with SRS alone compared to when SRS was used with WBRT.[6] Based on this study and others, the American Society for Radiation Oncology (ASTRO) issued recommendations in 2014, which were updated in 2016, that oncologists should not routinely add adjuvant WBRT to SRS in patients with limited brain metastases, with good performance status and brain metastases from solid tumors.

The Yamamoto study was the first clinical trial to prospectively omit WBRT in patients with up to 10 brain metastases.[7] "When comparing 2 to 4 or 5 to 10 brain metastases, Yamamoto et al found there was no detriment to survival when using SRS rather than WBRT," says Dr. Chao. Now, he and Cleveland Clinic colleagues still consider SRS for patients with up to 8 or even more brain metastases, and consider delivering hypofractionated or multiple session SRS treatments more frequently.

"The Yamamoto study provides prospective data to justify SRS alone for up to 10 brain metastases," says Dr. Soltys. "Whether this principle can be extended to > 10 metastases is unknown."

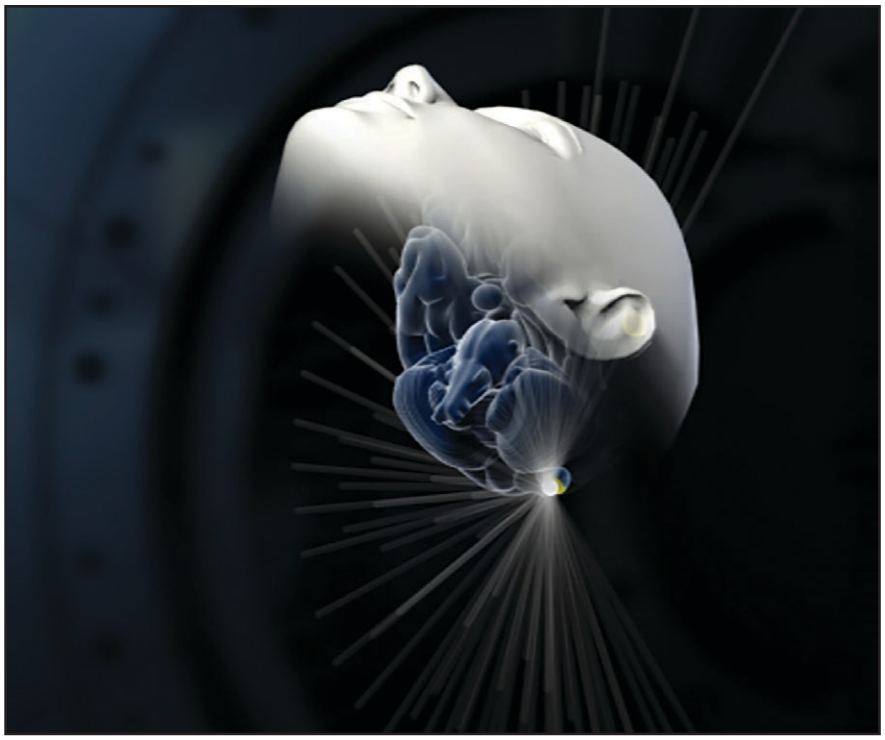

FIGURE 2. *A planning image for Gamma Knife (Elekta, Stockholm, Sweden) illustrating the delivery of a prescribed dose to a target area via multiple converging beams of radiation.*

Clinicians also need to consider patients with poor prognosis who may be best served with palliative or supportive care, he says. The Quality of Life after Treatment for Brain Metastases (QUARTZ) trial compared WBRT to optimal supportive care (OSC) and found no difference in overall survival between the two groups, and a small difference in quality of life for the OSC group. The author suggested that in this patient group—nonsmall cell lung cancer with brain metastases unsuitable for resection or stereotactic radiation therapy—WBRT "provides little additional clinical significant benefit."[8]

Chemotherapy, Systemic Therapy

With SRS, patients also can continue chemotherapy during treatments. Dr. Kleinberg explains that a combined toxicity occurs when using WBRT and chemotherapy. Blood circulates through the brain and, after WBRT, blood counts and immune cells both drop; chemotherapy has the same effect.

"We have learned that SRS … can be done in the midst of chemotherapy depending on the type [of systemic drug] the patient is receiving," Dr. Kleinberg says. "We try to use SRS in the weeks the patient does not receive chemotherapy treatments, and it has been very safe."

Although not commercially available, systemic therapies involving targeted agents and immunotherapy are also being investigated for their therapeutic role with SRS. "Now with a better understanding of biomarkers and genetics, we need to think about the variety of ways we can manage a patient with brain metastases—how we can utilize that systemic therapy to improve the ability to control disease in the brain," says Dr. Chao.

Radiation Necrosis

Despite advances in SRS, an unfortunate and serious side effect remains: radiation necrosis, which can resemble tumor recurrence on MR imaging, says Dr. Kleinberg. "Beyond necrosis, a patient can also get edema after radiation exposure," he adds, "and we have no means to differentiate necrosis from swelling and tumor re-growth."

Dr. Kleinberg says that some investigations of MR spectroscopy and MR protein transfer, as well as other potential imaging techniques involving fluorothymidine F 18 (FLT) PET, may help distinguish these conditions in the future. In addition to continued development of sequences and tracers, a blood biomarker could help distinguish between necrosis, swelling, and tumor regrowth, says Dr. Soltys.

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RADIATION ONCOLOGY CASE

Long-term outcome after two-stage low-dose Gamma Knife radiosurgery for large recurrent petroclival meningioma

Federico Ampil, MD; Moiz Vora, MD; Mardjohan Hardjasudarma, MD; and Anil Nanda, MD

CASE SUMMARY

A 60-year-old woman presented in September 2001 with a large (21 cm^3) petroclival tumor involving both cavernous sinuses and the sellar floor without displacement of the brainstem. Physical examination was unremarkable for neurological dysfunction. About 8 years prior, she had undergone resection of a skull base meningioma. The large recurrent skull base neoplasm was treated with low-dose two-stage Gamma Knife (Elekta, Stockholm, Sweden) radiosurgery (GKRS). The treatment stages were 5 months apart, and the tumor volumes for the first and second parts of the treatment plan were 16 cm^3 and 5 cm^3, respectively. A margin dose of 11 Gy was applied to each portion of the target neoplasm. The patient did not develop acute ill effects and lived with the unchanged tumor for a long time following therapy.

IMAGING FINDINGS

MRI shows the margin dose of 11 Gy prescribed at the 50% isodose line and demonstrates the petroclival tumor in contact with only a small portion of the brain including part of the radiation falling off into the bone, sphenoid sinus and infratemporal region (**Figure 1**).

Dr. Ampil *is a professor and Gamma Knife radiosurgery radiation oncologist;* ***Dr. Vora*** *is a fellow in the Department of Pathology;* ***Dr. Hardjasudarma,*** *is a professor in the Department of Radiology;* ***Dr. Nanda,*** *is a professor and chair of the Department of Neurosurgery, Louisiana State University Health Sciences Center, Shreveport, LA.*

DIAGNOSIS

Recurrent petroclival meningioma (PCM)

DISCUSSION

Meningiomas are considered particularly suitable for stereotactic radiosurgery because they are well-encapsulated, easily defined using contrast-enhanced MRI/computed tomography and responsive to radiation. GKRS is a preferred treatment for meningiomas that have a maximum diameter of 3 cm; a distinct margin and minimal to no surrounding edema on imaging; and a sufficient distance from critical normal tissue to allow for accepted normal tissue dose restriction.

Benign neoplasms of the skull base pose unique challenges in radiosurgical treatment because of their irregular shapes, proximity to critical structures, and variable tumor volumes. Additionally, PCMs can be even more challenging because of their propensity to engulf nerves and blood vessels, invade the cavernous sinus, and extend to multiple cranial fossae and foramina.

The goals in GKRS for large meningiomas, similar to those for smaller lesions, are preventing tumor progression and preserving neurological function. With intracranial benign tumor, which involves both the target volume and surrounding normal structures, late-responding tissues are of concern.[1] Fractionated radiation therapy (FRT) relies on a tumor with hypoxic cells. It re-establishes oxygenated states, which results in such cells becoming sensitive to radiation. However, due to the slow-growing nature of meningiomas, these late-responding tissues may not gain additional benefit from FRT.[2] From a clinical standpoint, large neoplasms are precluded from receiving an optimal prescription dose to the tumor margin because the fall-off in radiation dose into the surrounding brain tissues is not as steep. Management options for locally extensive meningiomas include cytoreductive microsurgery, as feasible, followed by stereotactic radiosurgery, hypofractionated radiosurgery or staged GKRS. Currently, there is a paucity of information about the long-term effects of staged, low-dose GKRS performed in these patients.

Our patient's large neoplasm was treated using the two-stage low-dose GKRS technique.[3-7] Factors that influenced our decision for a staged treatment approach were: First, the tolerance of brain tissue for single dose GKRS set a maximum target volume limit of approximately 20 cm^3.[5] Second, tumors > 10 cm^3 and applied margin doses of > 16 Gy have been associated with a greater risk of permanent radiation-related complications.

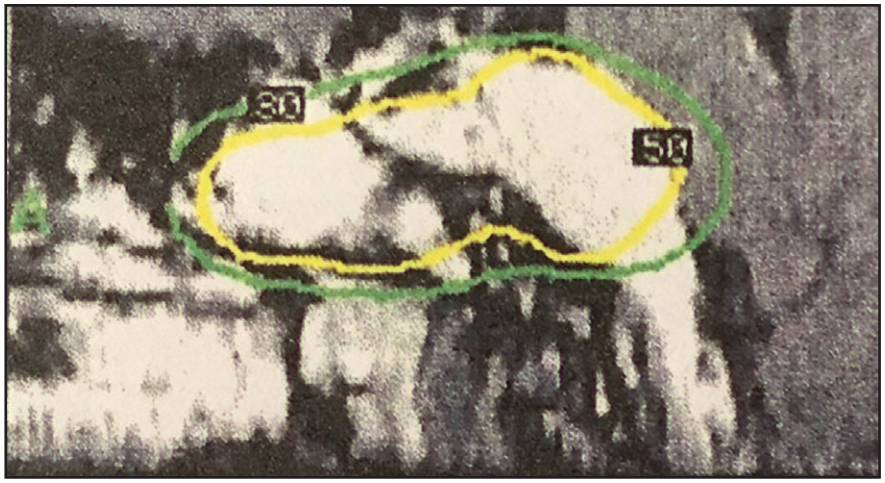

FIGURE 1. *MRI shows the margin dose of 11 Gy prescribed at the 50% isodose line and demonstrates the petroclival tumor in contact with only a small portion of the brain, including part of the radiation falling off into the bone, sphenoid sinus and infratemporal region.*

Third, the proximity of the PCM to the optic pathway and other cranial nerves in the cavernous sinuses generally imposes dose limits to critical structures (eg, 8 Gy to the optic apparatus; 12 Gy to the brainstem). Fourth, no symptoms were related to mass effect and there was no significant displacement of the brainstem on MRI. The speculated marginal dose needed to stop the growth of the meningioma was within 12 Gy to 15 Gy.[8] We preferred a lower dose (≤ 12 Gy) for two reasons: 1) Earlier published work has found this efficacious in preventing progression of these large-sized neoplasms;[9] 2) The only consistent correlation pertaining to the occurrence of adverse radiation effects is the volume of brain receiving ≥ 12 Gy.[10]

The treatment plan (**Table 1**[11]) was divided into volumetric stages with attempts to minimize dose overlap between tumor segments, especially outside the target. The plan design was to deliver a marginal dose of 11 Gy to cover the lesion (**Figure 1**) and 8 Gy to the adjacent optic nerve and chiasm. To safeguard visual function,[12] the "suboptimal" treatment plan called for a deliberate reduction (to 8 Gy) in the margin dose to the part of the tumor that obscured the optic apparatus. Multiple isocenters were employed for both parts of the treatment scheme.

A July 2011 MRI compared with a July 2009 MRI showed stable disease. At last follow-up (October 2012, 134 months after completion of GKRS), the patient was functional, requiring minimal assistance. However, she complained of diplopia and had occasional syncopal episodes. On clinical examination, upward gaze paralysis was noted but there was no apparent deterioration of vision.

Although reported response rates after radiosurgery have ranged from 25% to 46%,[3-5,12] local control of voluminous meningiomas is more difficult to achieve.[13] Despite the large size of the PCM, we believe that the prolonged absence of tumor progression in our patient could be understood through a few concepts. First, the apparent cessation of tumor growth may be attributed to the extended follow-up and the reduced presence of hormonal activity on account of the patient's postmenopausal status. Second, theoretically, superior dose-neoplasm congruity in the scheme should promote local tumor control and reduce the incidence of complications. Radiosurgical treatment of meningiomas frequently necessitates compromise between irradiating the tumor and risking damage to adjacent structures.[14] Covering the entire tumor with the prescription dose remains the ideal radiosurgery strategy but, in practice, is not always safe or feasible. In our patient, given the tumor's proximity to the optic nerve and chiasm, adjustments in the dose prescription and plan conformity were made, resulting in a plan that was highly conformal to the defined lesion, treated the bulk of the tumor with the prescribed dose, and accepted that part of the tumor was outside of the prescription isodose. Additionally, the radiosurgical treatment planning technology made it possible for the dose gradient to be steeper in the direction of the optic apparatus.

We recognized that the patient's adjusted plan was "suboptimal." Skeie et al[10] studied the long-term outcome of 100 patients with cavernous sinus meningioma. The lesions that received a less than optimal dose to a small part of the neoplasm due to proximity to critical structures, regardless of percentage of coverage, had an associated higher recurrence rate of 39% compared to the 8% rate observed in lesions receiving an optimal dose (p = .001). Suboptimal radiation dose coverage occurred more frequently in growing tumors compared to nongrowing meningiomas, 60% and 17%, respectively (p = .001). Also of note is that the location of local recurrences is mainly outfield, eg, commonly in regions receiving < 90% of the prescribed dose. However, vision deterioration or tumor growth after using a suboptimal GKRS plan[12] (unlike the outcome in this case) has not been frequently reported. Moreover, the treatment approach seemed justified considering that "an optimal dose-plan should not be allowed to place persisting useful vision at risk."[12] We maintained the marginal dose at 11 Gy (a dose that has been efficacious for tumor control with minimal morbidity).[6,7]

Table 1: Staged Gamma Knife Radiosurgery (GKRS) Summary for Large Petroclival Recurrent Meningioma

GKRS[a] stage	Tumor volume	Margin dose[b]	No. isocenters used	Dose to optic pathway	Dose to brainstem	Tumor to brainstem relationship[c]
First	16 cm^3	11 Gy	13	6.6 Gy	6.6 Gy	Grade 1
Second	5 cm^3	11 Gy	8	6.6 Gy	< 6.6 Gy	Grade 0

[a]Interval between the treatments in the two-stage GKRS method was 5 months.
[b]The margin dose was at the 50% isodose line.
[c]Grade 0 (Nakaya et al[11] grading system) indicating tumor reaching without indentation of the brainstem surface or effect on the fourth ventricle; Grade 1 meant tumor indenting the brainstem with no effect on the fourth ventricle.

With respect to treatment toxicity, the minor[15] neurological deficit observed during follow-up emphasizes the lower frequency of postradiosurgery complications in patients with skull-based benign tumors compared to people with convexity or falx-tentorial meningiomas (unfavorable events are attributed to more of the brain surface irradiated in the latter cases). We hypothesize that the oculomotor neuropathy was possibly due to the use of multiple isocenters considering that the tumor was large, irregular and complex in shape. The use of multiple isocenters to treat a neoplasm produces regions in which the dose may be 2 to 3 times that of the dose delivered from the use of a single isocenter.[16]

After reviewing the literature about the use of staged, low-dose GKRS[3-7] for mostly skull-based meningiomas with maximum tumor volumes ranging from 28.9 cm^3 to 90.3 cm^3, we found 2 other patients who experienced long-term progression-free survival up to 120 and 182 months.[3] The noted sustained effect suggests that recurrent petroclival meningiomas should be treated as aggressively as possible. This was highlighted in a recent report by Li and associates[17] regarding 39 patients. Those individuals rejecting treatment suffered a significantly poorer overall survival (7%) and shorter survival duration (42 months), while patients who were treated exhibited better corresponding outcomes of 67% survival, lasting 86.9 months.

Our positive result notwithstanding, we recognize limitations associated with this report. For example, it is inappropriate to judge treatment efficacy from a retrospective viewpoint and based on a single case. Also, patient follow-up in this presentation may not be long enough, as recurrences can occassionally surface 20 years later.[10]

CONCLUSION

Given that benign meningiomas are characterized by slow growth, accounts of successful long-term outcome achieved with radiosurgery are important to document. This report described a case of extended progression-free survival observed after staged low-dose GKRS for a sizable recurrent petroclival meningioma. The critical location of the meningiomas underscores the importance of utilizing improved neuroimaging, radiosurgical 3-dimensional conformal treatment planning and technical expertise. Staged low-dose GKRS for large skull-based meningiomas appears to have balanced treatment success with adverse radiation-related effects.

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RADIATION ONCOLOGY CASE

Paraganglioma of the skull base treated with intensity-modulated radiation therapy

Zhe Ma, BS; Shireen Parsai, MD; Senthilkumar Gandhidasan, MD; and John H. Suh, MD, FASTRO

CASE SUMMARY

A healthy 56-year-old Vietnamese woman presented in January 2009 with a 1-year history of left-sided hearing loss and tinnitus, intermittent dizziness, and hoarseness. Audiometry evaluation revealed bilateral low-frequency hearing loss that was more severe on the left. Office nasopharyngoscopy showed a slightly hypomobile left vocal cord. An MRI of the brain with contrast revealed a 2.2 × 1.8 × 6.0-cm heterogeneously enhancing left skull base mass in the transverse (TV), anteroposterior (AP), and cranial-caudal (CC) dimensions, respectively (**Figure 1A**). Somatostatin receptor scintigraphy confirmed increased radiotracer uptake in the skull base lesion. The patient was clinically diagnosed with a paraganglioma of the left skull base.

Mr. Ma *is a fourth-year medical student, University of Central Florida College of Medicine, Orlando, FL;* ***Dr. Parsai*** *is a resident physician,* ***Dr. Gandhidasan*** *is a fellow, and* ***Dr. Suh*** *is chairman, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH.*

Conflicts of interest: Dr. Suh: consultant for Varian Medical Systems, Palo Alto, CA; speaker for Philips Medical Systems, Amsterdam, The Netherlands; travel and lodging by Elekta, Stockholm, Sweden.

The tumor was treated definitively using intensity-modulated radiation therapy (IMRT) to a total dose of 4500 cGy in 25 fractions using 6 MV photons prescribed to the 100% isodose line between March and May of 2009, and was delivered using Novalis Tx (BrainLab, Westchester, Illinois) (**Figure 2**). Gross tumor volume (GTV) was defined as the index lesion as identified on CT/MRI fusion imaging. Planning target volume (PTV) was defined as an isovolumetric expansion of 7 mm on the GTV. The patient completed treatment with only grade 1 toxicities, including alopecia, fatigue and nausea.

The patient was seen for follow-up in November 2009, 6 months after completing therapy. At that time, her tinnitus improved without any radiographic changes. She did not report any grade 2 or higher toxicity.

The patient was evaluated annually for follow-up until November 2013 when that changed to biennially, with her last follow-up in November 2015, 6 years after completing therapy. Throughout this period, the index lesion exhibited partial radiographic response per 2009 RECIST (*Response Evaluation Criteria in Solid Tumors*) criteria, with significant improvement in the cranial-caudal axis (**Figure 1B**). Clinically, left-sided hearing loss progressively improved over the 6 years of follow-up.

DISCUSSION

Paragangliomas are rare, benign neuroendocrine tumors arising from extra-adrenal autonomic paraganglia. Generally, parasympathetic paragangliomas are found in the neck and skull base and are nonsecretory. They are commonly found along cranial nerve IX and X, the middle ear, the jugular vein, and the carotid bodies.

The natural growth of paragangliomas has been reported to be 0.8 mm per year with a doubling time of 14 years.[1] Although these tumors have an indolent course, paragangliomas can be locally invasive and cause mass effect on nearby neck structures, especially the cranial nerves, which can present as dysphagia, hoarseness, pulsatile tinnitus, and hearing loss. Larger lesions can be palpated as a rubbery, nontender mass in the lateral neck and may cause a bruit if there is mass effect on the carotid vessels. Jugulotympanic lesions can result in a bluish pulsating mass behind the tympanic membrane.

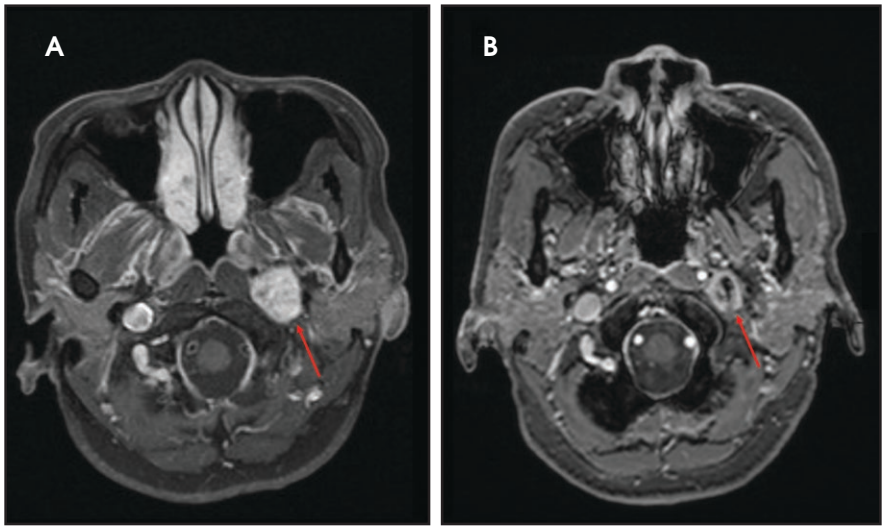

FIGURE 1. *(A) Pre-treatment axial T1 post-contrast fat-saturated MRI of the brain revealing a heterogeneously enhancing lobulated mass (red arrow) measuring 2.2 x 1.8 x 6 cm in the transverse (TV), anteroposterior (AP), and cranial-caudal (CC) dimensions, respectively. (B) Four-year post-treatment axial T1-post-contrast MRI of the brain reveals reduction in size of the enhancing mass (red arrow) now measuring 1.3 x 2.0 x 3.0 cm (TV x AP x CC), indicating response to therapy.*

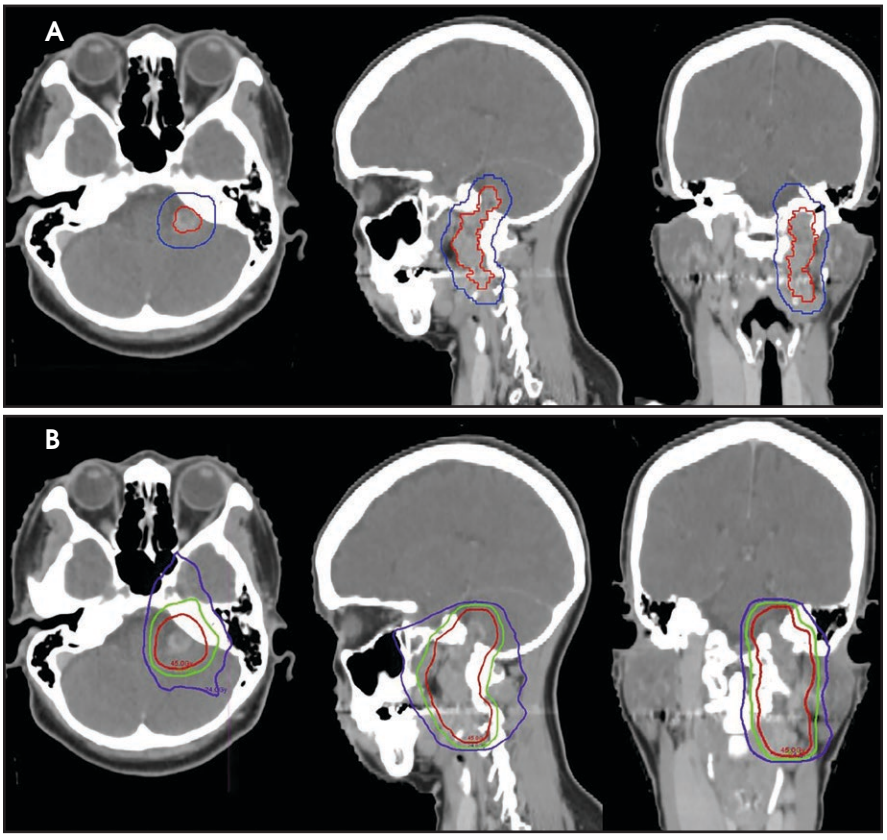

FIGURE 2. *(A) Radiation plan in axial, sagittal, and coronal views: Red is gross tumor volume (GTV) and blue is planning target volume (PTV). (B) Isodose lines in axial, sagittal, and coronal views: Red is 45 Gy, green is 36 Gy, and purple is 24 Gy.*

A variety of other pathologies can be considered with presentation of a head and neck mass: aneurysms of the carotid artery, lymphadenopathy, head and neck malignancies, branchial cleft cysts, meningiomas, schwannomas, and thyroid nodules.

Diagnosis typically consists of biochemical and/or imaging modalities. Characteristic findings on computed tomography imaging include homogeneous mass with intense contrast enhancement. Characteristic findings on MRI include intense hypervascular appearance and classic "salt and pepper" representing hemorrhage and flow voids, respectively, on T2-weighted sequences. Somatostatin receptor scintigraphy utilizes indium-111 labeled pentetreotide, a somatostatin analog, which binds avidly in neuroendocrine tumors and can be detected with single-photon emission computed tomography imaging. Although tissue diagnosis is definitive, many of these lesions are not biopsied prior to resection either due to large size or active secretion. Thus, somatostatin scintigraphy can be used to localize and differentiate neuroendocrine tumors from other more common head and neck malignancies.

The treatment goal for a paraganglioma consists of achieving cure as defined by durable radiographic or clinical stability with avoidance of critical neurovascular structures and absence of local disease progression. Management options include observation, surgery or radiation therapy.

Observation is ideal for patients who are asymptomatic or have smaller lesions (< 2-3 cm), taking advantage of the disease's indolent natural history. Surgical resection is used as definitive treatment for complete removal of paragangliomas. General indications for surgery include any lesions below the neck, or large skull base/neck tumors (> 3 cm), secreting or symptomatic. Surgical cure rates have been reported up to 89% to 100%, but with

a significant presence of cranial nerve neuropathy.[2,3] Pooled estimates have shown toxicity in CN XI/IX to be more common (40% and 38%, respectively), and less common in CN X/XII (26% and 18%, respectively).[4]

In the last few decades, radiation therapy has come to the forefront of managing paragangliomas with the goal of maximizing local control and minimizing damage to neurovascular structures. To date, published data on the use of radiation therapy consists of retrospective data or single institution experiences utilizing different radiation techniques. Durable radiographic or clinical stability is reported > 90% for conventional radiation therapy with similar biological effective dose, as in our case (45 Gy in 25 fractions). This is essentially equivalent to surgical local control rates with good long-term follow-up and no severe complications.[3,5]

Modern, highly conformal radiation techniques such as IMRT, stereotactic radiation therapy (SRT), and stereotactic radiosurgery (SRS) allow for less normal tissue toxicity and have proven to be just as efficacious, with pooled estimates showing local control rates > 90% with concomitant symptom control.[4,6,7] Combs et al recently reported a single institution experience treating 39 patients with fractionated SRT, SRS, or IMRT at 18 Gy in single fraction treatment or median total dose of 57.6 Gy (at 1.8 or 2 Gy per fraction) with median follow-up of 127 months. Actuarial 10-year local control was reported at 97% with no severe long-term side effects or secondary malignancies.[6]

With SRS via linear accelerator, Gamma Knife (Elekta, Stockholm, Sweden), or CyberKnife (Accuray, Sunnyvale, California) modalities, there is a potential risk for damage to nearby structures secondary to large single-dose radiation; however, it has been shown that the rate of cranial nerve morbidity is vastly improved at < 12% vs. 18% to 40% after gross total resection in pooled estimates.[4] Typical single-fraction dose has been quoted to be 13-20 Gy in the literature.[6]

Overall, radiation therapy and SRS provide equivalent local control compared to surgery, with the benefit of decreased morbidity.[4,6] Selection of treatment options is often based on institutional bias and clinical preference. Nonsurgical candidates or those with high potential for neurovascular morbidity may benefit from radiation therapy, typically IMRT. SRS is usually reserved for smaller lesions (< 3 cm) given the risk of a marginal miss or for those who cannot tolerate a fractionated course. Although a randomized controlled trial would allow for an objective comparison of surgery vs. radiation therapy/SRS as primary treatment, this is unlikely given the low incidence of this condition and strong opinions regarding best management.

CONCLUSION

A 56-year-old woman presented with a 1-year history of hearing loss/tinnitus, intermittent dizziness and hoarseness. MRI of the brain revealed a $2.2 \times 1.8 \times 6.0$-cm heterogeneous mass in the infratemporal region below the skull base within the jugular foramen. With positive uptake on somatostatin receptor scintigraphy, the presumed diagnosis was a paraganglioma of the skull base. She was treated with IMRT to 4500 cGy in 25 fractions using 6 MV photons. The patient reported only grade 1 side effects at the end of therapy. She was last seen at a 6-year follow-up when she was nearly asymptomatic, and a previous MRI at a 4-year follow-up, which showed a progressively smaller $1.3 \times 2.0 \times 3.0$-cm mass.

Historically, surgery was the gold standard in definitive treatment for skull base/neck paragangliomas. Although cure rates were excellent, there was a significant rate of cranial nerve morbidity, especially with skull base/neck structures. Here we report a case of a skull base/neck paraganglioma that was treated with IMRT and achieved local control with 6 years of follow-up.

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