Advances in Radiation Oncology (2024) 9, 101349

advances in radiation oncology

www.advancesradonc.org

Teaching Case

A Novel Multimodal Approach to Refractory Brain Metastases: A Case Report

Kalman A. Katlowitz, MD, PhD,[a,b] Thomas H. Beckham, MD, PhD,[c] Rajat J. Kudchadker, PhD,[f] Jeffrey Wefel, PhD,[d] Yasir Y. Elamin, MD,[e] and Jeffrey S. Weinberg, MD[b,*]

[a]Department of Neurosurgery, Baylor College of Medicine, Houston, Texas; [b]Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, Texas; [c]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [d]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [e]Thoracic-Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and [f]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas

Received 19 April 2023; accepted 31 July 2023

Introduction

Control of metastatic disease within the brain often requires multidisciplinary care, with each type of therapy offering unique advantages. It has long been established that surgery is an important part of the standard of care for larger lesions in patients with brain metastases, particularly those causing symptoms through mass effect and local edema.[1,2] However, surgery is unable to control microscopic disease even when gross total resection is achieved. Approximately 40% to 50% of patients with brain metastases experience local recurrence despite maximal medical treatment.[3,4] The incidence of surgical site recurrence can be reduced by adjuvant radiation treatments such as whole brain radiation therapy,[5] stereotactic radiosurgery (SRS), or fractionated stereotactic radiation therapy.[6,7] However, depending on the modality, these treatments can have significant local or systemic side effects, such as cognitive deficits in whole brain radiation therapy and radiation necrosis in SRS.[6,8,9] Finding the correct balance between maximizing postoperative oncological control and minimizing side effects is still an unsolved problem, and significant variation exists across individual cases.

SRS has been used since the 1950s[10] and provides a steep dose gradient at the margins. This allows for a high dose inside the planning target volume and a low dose in the surrounding healthy brain.[6] SRS is now used routinely after initial surgical resection of brain metastases.[7] However, this technique still has significant disadvantages. There is typically a delay after surgery before the initiation of SRS treatment, potentially limiting its efficacy.[11] Early radiation risks include scalp wound breakdown, which, in patients with metastatic cancer, can delay re-initiation of systemic therapy.[12] Additionally, even highly focused SRS carries significant risk to local tissue associated with cavity margin expansion due to target delineation uncertainty.[11] Radiation necrosis can be challenging to manage and causes adverse effects on patient quality of life.[9,13] Some studies have sought to avoid these caveats by employing preoperative radiation.[14] This approach may have the added benefit of lowering rates of leptomeningeal disease and radiation necrosis but has not been shown to have superior rates of recurrence.[15] Whichever approach is taken, control of brain metastases poses a significant and unsolved clinical problem, as retrospective series have

Sources of support: This work had no specific funding.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Jeffrey S. Weinberg, MD; E-mail: jweinberg@mdanderson.org

https://doi.org/10.1016/j.adro.2023.101349

demonstrated that the risk of recurrence in the surgical cavity after failure of SRS is high (up to 40%),[7,16] suggesting the need for new solutions. Unfortunately, currently there is no agreed-upon standard approach for adjuvant radiation therapy for previously irradiated tumors, due to concerns from exposing normal brain tissue to repeat radiosurgical doses.[12]

Brachytherapy is one option for immediate focal treatment after surgery that has become a therapeutic option for a variety of cancers, including cervical, endometrial, breast, and prostate cancer.[17] The first report of central nervous system brachytherapy using radon for an intrasellar tumor was published in 1936.[18] Since that time, other options, such as ^{192}Ir and ^{198}Au, have also been used. Beginning in the 1990s, ^{125}I was used either as directly implanted seeds[19] or delivered as an aqueous solution via devices such as GliaSite and MammoSite, though the latter did require further procedures for explantation.[20] GammaTile (GT) is a newly United States Food and Drug Administration (FDA)−approved device that incorporates ^{131}Cs into an absorbable wafer. This isotope has a much shorter half-life (eg, approximately 10 days vs 60 days for ^{125}I) and a higher dose rate than other isotopes. Arranging radioactive sources within a collagen matrix minimizes source migration and helps to avoid overdosing the underlying brain parenchyma. This is an advance over prior attempts at central nervous system brachytherapy, which in some cases placed seeds directly on brain tissue, resulting in unacceptably high rates of radionecrosis.[21] GT allows dosimetric spacing with delivery of physical doses of 120 to 150 Gy at the surface and about 60 Gy at 5 mm depth due to tissue attenuation and absorption,[22] which is greater than the typical postoperative prescription dose to the tumor bed across other modalities.[23]

GTs were cleared by the FDA in 2018, and further work to investigate their role in the treatment of brain tumors is ongoing. The benefits and appropriate indication for GT placement is still an active area of research. Over the past 6 years, a few case series have investigated the safety and benefits of GT placement in both brain metastases and primary brain tumors.[24-28] Although side effects such as cerebral spine fluid leaks, hematomas, infections, radiation necrosis, and seizures have been reported, a favorable risk/benefit ratio of GTs was demonstrated across multiple clinical settings and types of tumors.[29] In fact, GTs may even have significant advantages over standard of care. For example, in one published case series of patients with previously untreated brain metastases, the rate of recurrence during the first year after surgery and GT placement was 0%.[30] Here we discuss a single patient with metastatic lung cancer who underwent surgical resection, GT placement, and salvage radiation therapy after 3 of more than 20 brain lesions proved refractory to radiosurgery and systemic treatment.

Case

The patient is a 52-year-old right-handed man with a 40-pack per year smoking history who received a diagnosis of lung adenocarcinoma in 2019 after a left lower lobe lesion was discovered on a routine screening physical. The tumor exhibited *KRAS G12C, TP53*, and *LKB1* mutations. PD-L1 tumor proportional score was 10%. Brain imaging at that time was negative for metastatic disease. He was treated with cisplatin and pemetrexed chemotherapy for 1 month, after which a biopsied suprapubic mass demonstrated metastatic disease and pembrolizumab was added to his treatment regimen.

A screening magnetic resonance imaging (MRI) performed 4 months after the original diagnosis demonstrated 4 small subcentimeter intracranial lesions. A repeat scan 1 month later showed resolution of all lesions (likely a response to systemic therapy) except for a right frontal lesion which demonstrated interval growth. The patient was treated with Gamma Knife (GK) radiosurgery. Serial imaging identified further intracranial metastases, and the patient again underwent GK radiosurgery for 8 supratentorial lesions, the largest of which was 1.4 cm. Three months later, the patient had his third session of GK for 7 new lesions. He was also switched to ipilimumab and nivolumab at this time. Repeat MRI 1 month later demonstrated 3 new lesions, for which he underwent another round of GK. MRI also demonstrated sizable recurrence of 3 lesions that had already been irradiated (Fig. 1a), and the decision was made to proceed with surgical resection supplemented by GT.

These 3 lesions were resected through 2 separate craniotomies (Fig. 1b). GTs were implanted in each resection cavity. One and a half GTs were placed in the posterior cavity, 3 were placed in the temporal cavity, and 2.5 were placed in the frontal cavity with an effort to cover the dura in an area where dural involvement was confirmed by direct observation. Postoperative MRI demonstrated gross total resection of the intraparenchymal lesions (Fig. 1b). A thin-cut computed tomography scan was acquired to assess tile locations to use for dosimetry calculation (Fig. 1c-e). The patient recovered well with only minor postoperative word-finding difficulties that resolved by his 2-week post operative clinic visit.

The patient presented to the emergency room 2 months after surgery after a 5-minute generalized seizure. Imaging demonstrated no evidence of recurrence at prior resection cavities, although 2 new lesions had developed. The patient returned to baseline and underwent a fourth GK session for the 2 new lesions.

Next, the patient's systemic therapy was changed to sotorasib. He returned 1 month later following another episode of seizures. A repeat MRI at 4.5 months after surgery demonstrated good control at 2 of the resection sites, although the patient did develop dural thickening in the left frontal cavity, concerning for dural recurrence

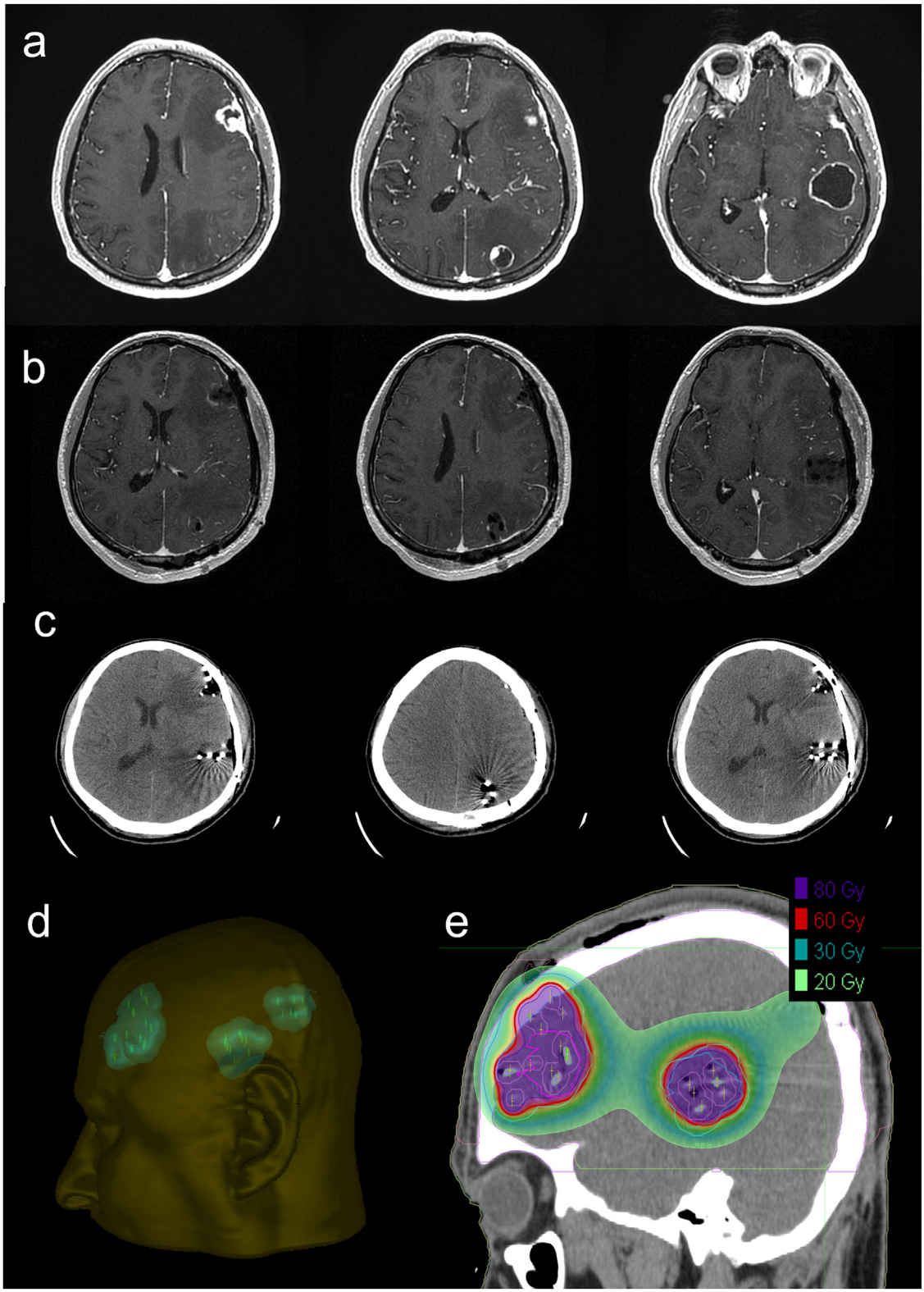

Figure 1 Simultaneous resection and GammaTile placement for 3 intracranial lesions that failed GK treatment. Magnetic resonance imaging T1+C of the left frontal (left), parietal (middle), and temporal (right) lesions immediately before (a) and after (b) surgery. (c) Noncontrasted computed tomography immediately postoperative. (d) Representation of the distribution of the cavities (green cloud) and ^{131}Cs seeds (green bars). (e) Dose clouds from GammaTile on a representative sagittal image.

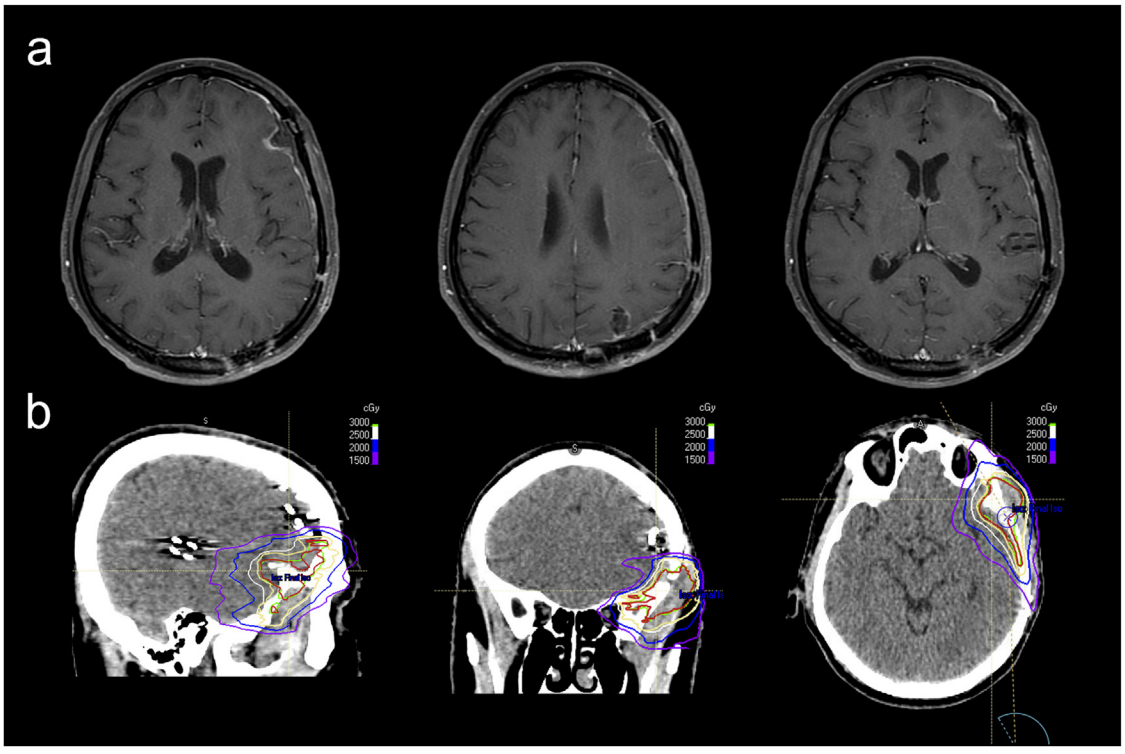

Figure 2 Left frontal dural recurrent and salvage stereotactic body radiation therapy. (a) Magnetic resonance imaging T1 +C 4.5 months postoperative demonstrating dural recurrence of the frontal lesion (left) with appropriate control at parietal (middle) and temporal (right) locations. (b) Sagittal (left) coronal (middle) and axial (right) noncontrasted computed tomography scans demonstrating salvage stereotactic body radiation therapy after marginal failure at the left frontal dura. This was treated in 5 fractions with 30 Gy prescribed to the gross tumor volume (red) and 25 Gy to a clinical target volume along the dura (yellow).

(Fig. 2a). Of note, this area was out of the range of the GTs that were implanted in the subdural space (Figs. 1c-e, 2). The patient received salvage SRS with 30 Gy in 5 fractions to this region (Fig. 2b).

Although local control was obtained in the dura covered in the SRS plan (Fig. 2b), he unfortunately developed new out-of-field dural based lesions (Fig. 3a, left). These lesions caused uncontrolled edema and seizures, leading to a dependence on steroids which would interfere with his immunotherapy. Therefore, he underwent a redo left frontal craniotomy 7 months after his original surgery. The prior resection cavity was densely necrotic with surrounding edematous and nonpulsatile brain as well as multiple subdural membranes. Interestingly, pathology analysis confirmed tumor not only within the parenchyma but within the subarachnoid space and dura as well, consistent with the focal leptomeningeal involvement findings noted on the preoperative MRI. Intraoperative findings were also notable for reabsorption of the collagen matrix, with the metal GT seeds left behind. Though standard treatment does not require the removal of seeds as they are bio-inert at this timepoint, all seeds were removed. There was no obvious damage or focal necrosis at the site of the GT placement. Postoperative MRI showed good resection of the intraparenchymal lesion (Fig. 3a, middle). The patient then underwent a 10-fraction course of intensity modulated radiation therapy 1 month later (Fig. 3b). He was transitioned to ramucirumab plus docetaxel due to hepatotoxicity from his sotorasib. The latest MRI 15 months after his second surgery shows stable left frontal enhancement (Fig. 3a, right).

Notably, the patient maintained an excellent Karnofsky Performance status throughout his treatment course. Apart from seizures associated with poor antiepileptic drug compliance, he maintained a good quality of life. He remained cognitively normal with full strength, cared for himself, and remained independent. He had a low systemic burden of disease, with lesions in his adrenal and parotid glands and mild lymphadenopathy. His most recent clinic visit before publication was at 22 months after his first surgery. He continues to live at home, remains independent, and performs all activities of daily living. His most recent brain MRI shows no evidence of recurrence at the 3 surgical sites.

Discussion

Difficulties in local control have been one of the key problems for both primary brain tumors and brain

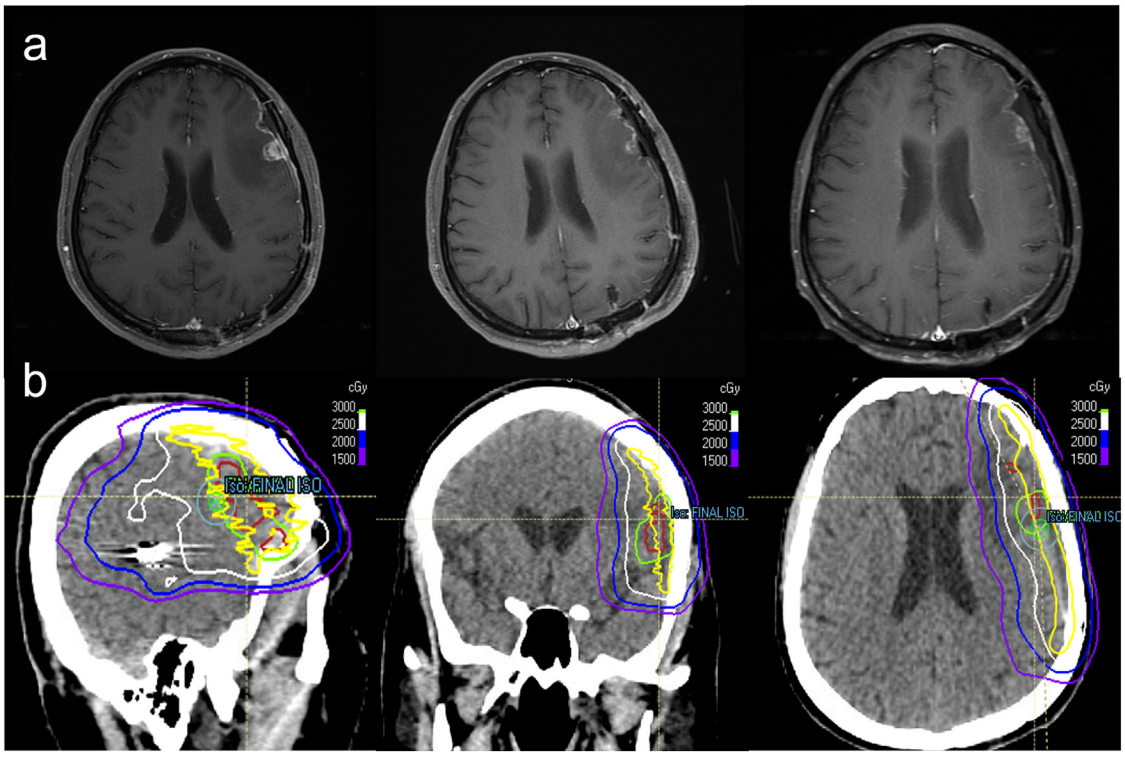

Figure 3 Redo left frontal craniotomy and salvage external beam radiation therapy. (a) Contrasted magnetic resonance imaging from preoperative and 7 months postoperative original surgery (left), immediately postoperative (middle), and 15 months postoperative (right) of redo left frontal craniotomy. (b) Sagittal (left) coronal (middle) and axial (right) noncontrasted computed tomography scans demonstrating salvage external beam radiation for a multifocal marginal recurrence. The gross tumor volume (red) was treated with 30 Gy, and the clinical target volume (yellow) was treated with 25 Gy in 10 fractions.

metastases. Maximizing local control must always be carefully balanced with minimizing side effects. Lesions which fail radiosurgery are generally not amenable to repeat radiosurgery due to concern for increased risk of radiation necrosis. This is further complicated by the fact that radiation necrosis is a poorly understood process. Its development may be related to radiation-induced vascular injury, glial damage, or some combination of the two factors.[31] Risk factors include larger tumor volumes (eg, >2 cm diameter), as well as higher doses (eg, >18 Gy in the case of SRS, or 50 Gy in fractionated treatments) and volume of brain within the radiation fields, though there are no guidelines on absolute contraindictions.[12] Risk of radiation necrosis is also significantly increased for patients who are on concurrent chemotherapy.[32] Of note, the majority of cases are diagnosed radiographically, and the rate of biopsy confirmed or clinically symptomatic lesions is much lower.[31,33]

In this case report, we discuss the use of multimodal treatments on a single patient with an impressively high rate of intracranial metastases from lung adenocarcinoma. Although most of his 24 brain metastases were controlled with radiosurgery, there were 3 lesions that required surgical intervention. In 2 of the 3 surgical lesions, GT placement has prevented recurrence up to his most recent clinic visit nearly 2 years later. The third lesion required a reoperation for progression of disease and multiple courses of external beam radiation therapy to attain local control. Notably, the brachytherapy seeds did not fully cover the diseased dura at this site.

This case is important and unique because it represents the first reported case of both multiple GT placement in 3 separate cavities during the same surgery and reoperation after GT placement. Despite all 3 sites being located within the same hemisphere, there was relatively little convergence of the dose clouds over the 20-Gy isodose line. Additionally, despite heavy radiation exposure through multiple modalities, the patient has not experienced symptomatic radiation necrosis.

Our case further demonstrates that, by expanding past standard of care treatments, our patient had a significant increase in not only survival but also quality of life. In most patients, such extensive brain metastases may have been an indication for hospice referral. Therefore, we present this case as a representative of the extent of control that current treatments can provide.

However, in our case GTs were limited as they did not provide any protection against disease progression

beyond 8 mm from placement. Indeed, despite demonstrating excellent focal control, our patient did develop many other metastases after the GTs were implanted and recurrence at 1 site where the tiles were implanted, albeit outside the range of the GTs. Although their short range is an advantage in terms of treating the walls of the resection cavity as well protecting the adjacent, healthy brain, this feature limits GT application to tumors with large residual or cavities with complex shapes precluding appropriate placement.

The persistent recurrence within the left frontal cavity represents a learning experience for our group and highlights the importance of patient and site selection for GT placement. Notably, in this patient, there was extensive dural thickening preoperatively (Fig. 1a) which at the time of resection was realized to be an invasive tumor. The visibly involved dura was resected and reconstructed, and we attempted to place tiles along this dural extension. However, as the pattern of failure demonstrates, there was insufficient dural coverage of the brachytherapy to attain control along the dural extension of this lesion. Lesions with extensive dural invasion may still be suitable for GT placement as demonstrated by the primary series which used GT for recurrent meningiomas.[27,34] However, this needs to be carefully considered before surgery with an appropriate plan for ensuring adequate coverage. This case also highlights the use of radiation therapy as a tertiary and quaternary salvage modality for this same site: initially with 30 Gy in 5 fractions as demonstrated in Fig. 2 and then with 30 Gy in 10 fractions (Fig. 3). With these interventions, the patient has had 8 months of local control. Importantly, despite the extensive exposure through multiple courses of radiation therapy, he has not had issues with radiation necrosis. The exposure of brain parenchyma to this degree of cumulative radiation is not standard. The associated risks were carefully considered and discussed both as a multidisciplinary team and with the patient.

Despite good oncological control, this patient's postoperative course was complicated by seizures. Prior reports have suggested that seizures may be a side effect of GT placement,[28] yet it is difficult to fully assign the cause of the seizures to the GTs. First, the patient had an otherwise high burden of intracranial disease and had a significant amount of parenchymal edema, even after the tumors were resected. Additionally, he had other radiation- and surgery-induced insults to the brain as detailed previously. Lastly, his seizures were largely controlled by medication, and many of his breakthrough seizures were in the context of self-discontinuation of antiepileptic drugs.

Future work needs to focus on appropriate patient selection, cost effectiveness, and the risk/benefit profile of GTs. Although evidence of the safety and efficacy of GTs is still being collected, case series that have been conducted so far have shown significant clinical promise.[35] However, as more patients undergo brachytherapy treatment, further complications can arise and must be closely followed. Additionally, it is unclear how these devices fit into the current model of surgery followed by radiation in the larger context of systemic treatments.[20,36,37] Most importantly, there have been no randomized clinical trials comparing the use of GT versus standard of care. Fortunately, there are ongoing studies that specifically relate to our patient, with Memorial Sloan Kettering Cancer Center accruing patients to a phase 2 study, which randomizes patients with recurrent brain metastases who are undergoing surgical resection to either GT placement or physician choice standard of care (NCT04690348). In a related trial, the phase 3 ROADS study is randomizing patients who are undergoing surgery for previously unirradiated brain metastases to either standard of care SRS or GT (NCT04365374). Recent case reports have highlighted the use of GTs across a spectrum of disease with good results.[35] It remains to be seen how GTs will become a routine option for the treatment of primary and/or metastatic brain tumors.

Conclusion

Postoperative placement of GTs provides a novel and unique opportunity for local control of brain tumors. This study represents the first reported case of simultaneous multicavity GT placement as well as a description of reoperation after GT placement. Further work is needed to characterize the possible side effects and role of GTs in refractory brain metastases.

Disclosures

Thomas Beckham reports a relationship with GT Medical Technologies Inc that includes travel reimbursement. Jeffrey Wefel reports a relationship with GT Medical Technologies Inc that includes a consulting or advisory role. Jeffrey S. Weinberg reports a relationship with GT Medical Technologies Inc that includes travel reimbursement and funding grants.

References

1. Patchell RA. The management of brain metastases. *Cancer Treat Rev*. 2003;29:533-540.
2. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Eng J Med*. 1990;322:494-500.
3. Nieder C, Astner ST, Grosu AL, Andratschke NH, Molls M. The role of postoperative radiotherapy after resection of a single brain metastasis. Combined analysis of 643 patients. *Strahlenther Onkol*. 2007;183:576-580.

4. Patel AJ, Suki D, Hatiboglu MA, et al. Factors influencing the risk of local recurrence after resection of a single brain metastasis. *J Neurosurg*. 2010;113:181-189.
5. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain. *JAMA*. 1998;280:1485-1489.
6. Brown PD, Ballman K V, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): A multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1049-1060.
7. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: A single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1040-1048.
8. Pouget JP, Georgakilas AG, Ravanat JL. Targeted and off-target (bystander and abscopal) effects of radiation therapy: Redox mechanisms and risk/benefit analysis. *Antioxid Redox Signal*. 2018;29:1447-1487.
9. Vellayappan B, Tan CL, Yong C, et al. Diagnosis and management of radiation necrosis in patients with brain metastases. *Front Oncol*. 2018;8:395.
10. Leksell L. The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand*. 1951;102:316-319.
11. Yusuf MB, Amsbaugh MJ, Burton E, et al. Increasing time to postoperative stereotactic radiation therapy for patients with resected brain metastases: Investigating clinical outcomes and identifying predictors associated with time to initiation. *J Neurooncol*. 2018;136:545-553.
12. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys*. 2000;47:291-298.
13. Minniti G, Clarke E, Lanzetta G, et al. Stereotactic radiosurgery for brain metastases: Analysis of outcome and risk of brain radionecrosis. *Radiat Oncol*. 2011;6:48.
14. Prabhu RS, Patel KR, Press RH, et al. Preoperative vs postoperative radiosurgery for resected brain metastases: A review. *Neurosurgery*. 2019;84:19-29.
15. Patel KR, Burri SH, Asher AL, et al. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: A multi-institutional analysis. *Neurosurgery*. 2016;79:279-285.
16. Wilcox JA, Brown S, Reiner AS, et al. Salvage resection of recurrent previously irradiated brain metastases: Tumor control and radiation necrosis dependency on adjuvant re-irradiation. *J Neurooncol*. 2021;155:277-286.
17. Skowronek J. Current status of brachytherapy in cancer treatment — Short overview. *J Contemp Brachytherapy*. 2017;9:581-589.
18. Lodge WO. Treatment of intrasellar tumors by radon. *BMJ*. 1936;2:1257-1258.
19. Petr M, McPherson C, Breneman J, Warnick RE. Management of newly diagnosed single brain metastasis with surgical resection and permanent I-125 seeds without upfront whole brain radiotherapy. *J Neurooncol*. 2009;92:393-400.
20. Waters JD, Rose B, Gonda DD, et al. Immediate post-operative brachytherapy prior to irradiation and temozolomide for newly diagnosed glioblastoma. *J Neuro-Oncol*. 2013;113:467-477.
21. McDermott MW, Sneed PK, Gutin PH. Interstitial brachytherapy for malignant brain tumors. *Semin Surg Oncol*. 1998;14:79-87.
22. Rivard MJ. Brachytherapy dosimetry parameters calculated for a 131Cs source. *Med Phys*. 2007;34:754-762.
23. Minniti G, Niyazi M, Andratschke N, et al. Current status and recent advances in resection cavity irradiation of brain metastases. *Radiat Oncol*. 2021;16:73.
24. Ferreira C, Sterling D, Reynolds M, Dusenbery K, Chen C, Alaei P. First clinical implementation of GammaTile permanent brain implants after FDA clearance. *Brachytherapy*. 2021;20:673-685.
25. McClelland S, Gardner UG, Le Y, Ng SK, Shah M V, Watson GA. Safety and efficacy of GammaTile intracranial brachytherapy implanted during awake craniotomy. *Brachytherapy*. 2021;20:1265-1268.
26. Pham A, Yondorf MZ, Parashar B, et al. Neurocognitive function and quality of life in patients with newly diagnosed brain metastasis after treatment with intra-operative cesium-131 brachytherapy: A prospective trial. *J Neurooncol*. 2016;127:63-71.
27. Brachman D, Youssef E, Dardis C. Resection and permanent intracranial brachytherapy using modular, biocompatible cesium-131 implants: Results in 20 recurrent, previously irradiated meningiomas. *J Neurosurg*. 2018;131:1819-1828.
28. Wernicke A, Smith A, Taube S. Cesium-131 brachytherapy for recurrent brain metastases: Durable salvage treatment for previously irradiated metastatic disease. *J Neurosurg*. 2017;126:1212-1219.
29. Ekhator C, Nwankwo I, Rak E, Homayoonfar A, Fonkem E, Rak R. GammaTile: Comprehensive review of a novel radioactive intraoperative seed-loading device for the treatment of brain tumors. *Cureus*. 2022;14:e29970.
30. Nakaji P, Smith K, Youssef E, et al. Resection and surgically targeted radiation therapy for the treatment of larger recurrent or newly diagnosed brain metastasis: Results from a prospective trial. *Cureus*. 2020;12:e11570.
31. Rahmathulla G, Marko NF, Weil RJ. Cerebral radiation necrosis: A review of the pathobiology, diagnosis and management considerations. *J Clin Neurosci*. 2013;20:485-502.
32. Ruben JD, Dally M, Bailey M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: Incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. *Int J Radiat Oncol Biol Phys*. 2006;65:499-508.
33. Chao ST, Ahluwalia MS, Barnett GH, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys*. 2013;87:449-457.
34. Rogers L, Nakaji P, Youssef E, et al. CTNI-58. A prospective trial of resection and surgically targeted radiation therapy for initial or salvage treatment of aggressive meningioma. *Neuro Oncol*. 2020;22(suppl 2):ii56.
35. Imber BS, Young RJ, Beal K, et al. Salvage resection plus cesium-131 brachytherapy durably controls post-SRS recurrent brain metastases. *J Neuro-Oncol*. 2022;159:609-618.
36. Chen AM, Chang S, Pouliot J, et al. Phase I trial of gross total resection, permanent iodine-125 brachytherapy, and hyperfractionated radiotherapy for newly diagnosed glioblastoma multiforme. *Int J Radiat Oncol Biol Phys*. 2007;69:825-830.
37. Archavlis E, Tselis N, Birn G, Ulrich P, Zamboglou N. Salvage therapy for recurrent glioblastoma multiforme: A multimodal approach combining fluorescence-guided resurgery, interstitial irradiation, and chemotherapy. *Neurol Res*. 2014;36:1047-1055.