Original Article: Case Series

Who gains from repeat radiosurgery for progressive previously treated brain metastases?—a case series

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Background: Characterization of potential beneficiaries from repeat radiosurgery (RRS) for progressive previously treated brain metastases (PPT-BRM) has not received much attention, perhaps because many patients with BRM die following salvage radiosurgery. These individuals remain at risk for neurological deterioration when BRMs are left untreated.

Methods: We attempted to study the advantaged people from our four patients and 531 patients identified in a literature search who were treated with RRS for PPT-BRMs.

Results: The 2% incidence rate of PPT-BRM from our institution was lower than rates in previous reports (range, 4–25%). The overall efficacy and minimal morbidty associated with RRS have consistently been demonstrated. Even though RRS for PPT-BRM is believed to be essential in patients with good functional status, descriptions of people who benefitted from RRS are poorly documented.

Conclusions: RRS for PPT-BRM, generally efficacious, is associated with a low toxicity profile. It is vital that there is careful patient selection for RRS of PPT-BRM given the overall dismal outlook and the potential serious effect of neglected beneficial treatment as well as the intervention-related radionecrosis on the quality of remaining life. Based on the available evidence, we advocate the continued but cautious use of salvage RRS in these people. More research is needed about the patients gaining benefit from the re-irradiation.

Keywords: Stereotactic radiosurgery; brain metastases (BRM); repeat radiosurgery (RRS); case series

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Introduction

The proportion of patients with brain metastases (BRM) that are retreated will increase with the longer duration of follow-up (1). It has been reported that when BRMs are left untreated, neurological deterioration culminating in death occurred in nearly half of the patients (2). The frequency of progressive previously treated (PPT) BRM after stereotactic radiosurgery is in the range of 4% to 25% (3-10). The clear expressions of benefit from repeat radiosurgery (RRS) have recently been described (11). The question, "Who among these treated people might benefit from RRS for PPT-BRM?", prompted this retrospective audit. We analyzed our four patients and 531 patients identified from the literature to determine which individuals would be better served. We

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Table 1 Clinical summary of repeat stereotactic radiosurgery treatment for progressive previously treated brain metastases—a case series

Case Number	Age (years)/gender	Primary tumor[§]	Number of RRS sessions	Clinical follow-up after last SRS
1*	62/male	Kidney	5	Alive and well at 13 months with stable BRMs
2*	60/male	Lung	4	Died at 4 months of respiratory failure with stable BRMs
3	60/female	Lung	3	Died 23 months with brain RN
4*	70/male	Lung	3	Died 22 months with systemic disease progression and enlarged PPT-BRM

*, in cases 1 and 2, another concurrent, new BRM was treated at the time of RRS for PPT-BRM; in case 4, progression of extracranial metastatic disease occurred after re-irradiation. §, primary tumor stages at the time of RRS were TxNxM1, T3N1M1, T1N0M1 and T2N0M1 for case 1, 2, 3 and 4, respectively; the serial tumor growths of the three PPT-BRMs in case 1 were 0.4, 1.8 and 2.5 cm^3; the growths of the two PPT-BRMs in case 2 were 5.8 and 1.1 cm^3; the growths of the two PPT-BRMs in case 3 were 0.5 and 0.3 cm^3, and the growth of the PPT-BRM was 1.2 cm^3 in case 4. RRS, repeat radiosurgery; SRS, stereotactic radiosurgery; BRM, brain metastases; RN, radionecrosis; PPT-BRM, progressive previously treated brain metastases.

present the following article in accordance with the AME Case Series reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-21-41/rc).

Methods

Between October 2014 and June 2020, 207 patients were treated for BRM with gamma knife radiosurgery (GKRS). Four consecutive symptom-free individuals (2%) underwent repeat GKRS of the same BRM site for progressive/recurrent disease (*Table 1*). This retrospective case series is an institutional review board approved outcome study (No. 1824). The study participants from a single institution were treated at the Louisiana State University Health Sciences Center in Shreveport. Patients were included in the study if: (I) PPT-BRM was detected on follow-up magnetic resonance imaging (MRI), (II) RRS was applied for the recurrent BRM, and (III) follow-up information was available. Patients were excluded when RRS was administered for non-PPT-BRM. The decision to treat was jointly made by the staff neurosurgeon and radiation oncologist in consultation with the neuroradiologist. In our four patients, RRS use was deemed advisable because of the need to preserve neurological function. PPT-BRM, was defined as either a histologically proven recurrence or a serial increase in contrast-enhancement at the same treated site on follow-up MRI. No study participant had a history of whole brain radiotherapy; one patient underwent craniotomy with PPT-BRM resection prior to RRS because of mass effect and increased intracranial pressure. The median interval between prior radiosurgery and RRS was 11.5 months (range, 1–23 months). The median applied margin dose was 18 Gy (range, 12–24 Gy), and the median tumor volume was 2.9 cm^3 (range, 0.2–5.4 cm^3). Toxicities and compliance were documented after chart and radiological reviews. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Louisiana State University Health Sciences Center-Shreveport institutional review board (for outcome investigation No. 1824), and written informed consent was not obtained from the patients because anonymized, de-identified information was used for the report.

Results

The mean age was 63 years, and the origin of PPT-BRM was from cancer of the lung (three patients) and kidney (one patient). The PPT-BRMs were all located in the supratentorial compartment of the brain. It is interesting to note that our patient with BRM progression in the medulla was asymptomatic and functional at 13 months follow-up after RRS. Because the potential for morbidity from RRS is likely to be heightened by the increase in volume of recurrent tumor, we treated only the growing part of the medullary BRM with a margin dose of 12 Gy. All patients completed the single-session RRS without interruptions and did not experience acute side-effects. At last contact, the primary malignant neoplasms in this study cohort were stable, and local control of the treated PPT-BRM was noted in two patients (50%). Radionecrosis (RN), defined by the decreased level of N-acetyl-aspartate (12) noted on magnetic resonance spectroscopy (MRS), was detected in a symptom-free patient (*Table 1*, third case). The time to RN development was seven months from the last radiosurgery

Table 2 Effects of repeat radiosurgery for progressive previously treated brain metastases—literature review[¶]

Features	Observed rates
Local tumor control rates	1-year 61–81%; 2-year 60–85%; 5-year 54%
Prognosis	Median survival: range 8–36 months; 1-year survival rate: 32–70%; 2-year survival rate: 20–49%
Radionecrosis[§]	Range: 2–24%

[¶], references (3-10,13-16); [§], references (3,4,6-10,13-16), radionecrosis (asymptomatic or symptomatic in some cases).

session; the applied marginal doses to different tumor volumes in the same parietal lobe-situated BRM were 24 Gy (2.3 cm^3), 15 Gy (0.40 cm^3), and 12 Gy (0.70 cm^3) in the first, second, and third treatment sessions, respectively. Causes of death were from progressive systemic disease with BRM growth (one patient), from neurological deterioration with imaging-declared RN (one patient; 25%), and from cause unrelated to PPT-BRM (one patient); the remaining individual was alive with stable BRM on follow-up radio-imaging. The overall crude 1-year survival rate was 75%, and the median survival was 17.5 months.

Discussion

Four patients underwent RRS for PPT-BRMs at a median interval of 11.5 months between treatments. The absence of symptoms and neurologic deficit were unchanged following salvage therapy in all cases. Control of tumor growth was achieved in half of the participants at a mean follow-up of 14.7 (range, 3–22 months) months. There were no acute ill-effects experienced by the patients, and RN was diagnosed in one case. To examine the broader experience of treating these people, we reviewed published studies about RRS-PPT-BRM with described outcomes (3-10,13-16). The determination revealed similarities in several clinical findings: (I) the patients, in the fifth to the sixth decades of life, were asymptomatic when they presented with small tumor volumes; and (II) lung cancer was the more common origin of the PPT-BRMs. In the largest 179 patient experience of Koiso *et al.* (5), multivariate analysis failed to show a clear characterization of which patients might derive worth from salvage RRS. In the meta-analysis report about RRS for progressive BRM, Ammirati *et al.* (17) did not describe the population subset more apt to be advantaged by the application of retreatment. Kwon *et al.* (6) noticed that recursive partitioning analysis (RPA) prognostic model class I–II patients experienced prolonged survival. The outcomes from the present case series appear in accord with those found in previous investigations (*Table 2*) (3-10,13-16). The acceptable median survival in our patient cohort should be viewed with the reality that most of these people die following salvage treatment (3,9,10). Death could be attributed to progression of systemic disease [observed in 55% to 66% of cases (6,8,9)], from progression of intracranial metastatic disease [seen in 26% to 37% of patients (8,9)], or from a decline in neurological status [documented in 7% to 67% of individuals with PPT-BRM (3,5,7,14)]. The finding of PPT-BRM in the medulla led us to assess the literature about GKRS use in patients with brainstem metastases and local recurrences after treatment. Fuentes *et al.* (18) in 2006 retrospectively evaluated outcomes after GKRS of brainstem metastases in 28 patients. Two individuals (7%) underwent RRS for local recurrence. Survival was short (≤5 months) for both subjects; the effect of salvage treatment on the recurrent tumor was not declared. In 2008, Kased *et al.* (19) examined the outcomes of 42 consecutive patients treated with GKRS for brainstem metastases at the University of California San Francisco. RRS was performed for tumor progression in the same brainstem site in two individuals; both patients with follow-up periods of 14.8 and 23.4 months were deceased, and tumor status was not described. In 2012, Kawabe *et al.* (20), focusing on how long patients can survive without neurological deterioration following GKRS for brainstem metastases, studied 200 people treated at their institution during a 13-year period. Local recurrence occurred in 22 study participants (17%). Among those 13 patients treated with RRS, follow-up imaging studies available in eight individuals revealed controlled BRM in five participants and uncontrolled lesions in three patients. Even though patient longevity was not stated, the comment made was that "smaller tumor volume tended to contribute to tumor control". Although the present account of four cases may not add to the findings already documented in the literature, for such BRM recurrences, potentially beneficial salvage therapy should not summarily be dismissed because it presents an opportunity for averting what may otherwise be a detrimental effect of PPT-BRM on quality of life and

extending existence.

RRS places the individual at a higher chance of RN compared to single-session radiosurgery (21). It is important to differentiate tumor growth from RN through magnetic resonance perfusion imaging and MRS because these can mitigate the risk associated with repeat irradiation. The reported incidence of RN following radiosurgery has ranged from 2% to 24% (3,4,6-10,13-16). The known risk factors involved in its development have included large BRM volumes and the application of higher RRS margin doses (7,9,15). Although the impact of RN on the quality of life remains poorly documented, this unwanted RN complication, in the Cleveland Clinic experience of 59 patients (22), was not especially associated with significant decline in the quality of remaining life.

We recognize the limitations of this report (i.e., the retrospective design, small patient sample and selection bias involving patients thought to be fit enough to undergo RRS). In the absence of a control untreated patient cohort, we do not have sufficiently strong evidence to support the contention that repeated treatment contributed to patient longevity. We failed to identify the select people who might benefit from retreatment of PPT-BRM. Nevertheless, it permits us to emphasize that RRS is advisable [as has been consistently suggested (23-26)] when patients with PPT-BRM exhibit high (>70–80 Karnofsky) functional scores. We agree with the assertion that "for a treatment option to be considered worthwhile, the observed survival duration should be at least 4–6 months longer than that expected for untreated cases" (27).

Because of continuing relevance and the potential for extended survival, the practical implication that may be acquired from this report is that GKRS management of PPT-BRM is still a cornerstone of salvage therapy due to the technological advantage that it offers (the rapid fall-off in dose distribution to tissues surrounding the recurrent brain tumors). RRS for recurrent BRM should not be abandoned, and a more considered approach needs to be adopted.

Conclusions

Until a fully defined characterization of the particular beneficiaries from reirradiation is available, we think that higher RPA class patients may gain from RRS for progressive same site treated BRMs. Our failed attempt supports the need for continued determinations of the select individuals who may obtain favorable outcomes following RRS for PPT-BRMs.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://tro.amegroups.com/article/view/10.21037/tro-21-41/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-21-41/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Louisiana State University Health Sciences Center-Shreveport institutional review board (for outcome investigation No. 1824), and written informed consent was not obtained from the patients because anonymized, de-identified information was used for the report.

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