EDITORIAL

Salvage Radiosurgery for High Grade Glioma in the Era of Modern Systemic Therapy

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Following the current standard-of-care treatment of maximal surgical resection followed by radiotherapy combined with concurrent and adjuvant temozolomide for glioblastomas and radiotherapy for grade 3 gliomas, local relapse remains the predominant pattern of failure for high grade gliomas. Several studies have reported greater than 70% of recurrences occurring within 2 cm of the original gadolinium-enhanced mass after concurrent radiation and temozolomide.[1,2] Given the high incidence of local recurrence within the region of prior high-dose radiotherapy, there have been a number of studies investigating the role of radiosurgery for recurrent high grade glioma. These include studies of radiosurgery using gamma knife, linac and cyberknife technology.[3-7]

This paper reports a retrospective single institution experience of 33 patients treated with Gamma Knife radiosurgery for focally recurrent, high grade gliomas.[8] Studies evaluating the role of radiosurgery for focally recurrent glioblastoma have demonstrated longer survival than studies evaluating other salvage treatments but this is likely due to patient selection bias. A recent pooled analysis of 300 patients accrued to the European Organization for Research and Treatment of Cancer (EORTC) Brain Tumor Group phase I or II trials for recurrent glioblastoma explored prognostic factors associated with overall and progression-free survival. The following prognostic factors were associated with overall survival (OS) and progressive-free survival (PFS): World Health Organization (WHO) performance status ($p < 0.0001$), presence of neurological deficits ($p = 0.0002$), baseline administration of steroids ($p < 0.0001$), number of target lesions ($p < 0.0001$), tumour size (largest tumour diameter, $p < 0.0001$), and frontal tumour location ($p = 0.02$).[9] Considering these factors, patients who are eligible for radiosurgery at the time of their glioblastoma multiforme (GBM) recurrence generally have good performance status, single or few small tumours that do not require corticosteroids to manage symptoms. These are all recognized prognostic factors in patients with recurrent GBM.

There have also been reports of prognostic factors specifically associated with improved outcomes after salvage radiation. These include younger age, higher Karnofsky performance status (KPS) and better recursive partitioning analysis (RPA) class and lack of steroid dependence, smaller and unifocal tumour targets, use of higher radiation prescription dose, the extent of pre-radiosurgery tumour resection, and use of concurrent chemotherapy. Increased time to tumour recurrence has also been associated with better outcomes.[10-16] Considering all these factors, the patients included in this study had particular favorable prognostic factors with a high average KPS of 85.2 prior to radiosurgery, small average tumour volume of only 4.4 cm^3 (range: 1.1 - 15.7 cm^3) and long duration between initial treatment and the diagnosis of focally recurrent tumour at 43.0 months (range: 1 - 180 months) overall and 24.3 months for patients with GBM.

Prior studies have reported outcomes following combined salvage treatment with various systemic therapies administered before, concurrently and after radiation. The most common systemic agent that has been used in conjunction with radiosurgery and radiotherapy is temozolomide. Although the present study emphasizes the outcomes and responses in relation to radiosurgery, all patients received chemotherapy, either immediately before or after radiosurgery. The chemotherapeutic regimens utilized in this cohort represent many of the agents that have previously been reported including temozolomide (20), thioguanine/procarbazine/lomustine/hydroxyurea (5), carboplatin (2), procarbazine, lomustine, and vincristine (PCV) (1), and lomustine (1). Therefore, the outcomes reported in this retrospective experience reflect that of single fraction radiosurgery in combination with many of the common systemic therapies that may be utilized at the time of tumour recurrence. Despite multiple prior studies exploring multimodality salvage therapy with re-resection, systemic therapy and re-irradiation, the true benefit of these interventions are difficult to evaluate independently due to the highly selected patient populations included in these prior reports.

Although tumour control outcomes are difficult to interpret, it has been recognized that patients treated with concurrent temozolomide and re-irradiation are at higher risk of radiation toxicity including radionecrosis. Evaluating the common factors that can contribute to radionecrosis including the dose, fractionation and volume of re-irradiation, this study utilized a higher mean dose prescribed to the 50% isodose line of 17.5 Gy (range: 12 - 24 Gy) in a single fraction compared with prior studies that range from 13 Gy in a single fraction up to 37.5 Gy in 15 fractions.[5,16-18] However, this study generally treated smaller volume tumours with a mean tumour volume of 4.8 cm^3 (range: 1.3 – 18.2 cm^3) compared to other studies that included tumour volumes up to 30 cm^3.[5,10] In this retrospective series, the rate of adverse radiation effects (ARE) was high, occurring in 26 of 29 patients (89.7%). This may reflect the higher dose, single fraction delivery but may also reflect the definition of ARE used in this evaluation, which may have higher sensitivity that criteria used in prior studies. In this study, 48.3% of patients were dependent on dexamethasone due to symptoms in comparison to 83% of patients treated with a mean dose of 20 Gy in two fractions with temozolomide requiring ongoing dexamethasone following treatment.[3] As demonstrated by these variable results, there is a great need for consistent criteria for reporting ARE events to facilitate meaningful comparison of toxicities associated with different radiation regimens and techniques across studies.

There is growing evidence that bevacizumab may reduce the risk of radionecrosis in patients with recurrent and progressive GBM who are being considered for re-irradiation.[17] Gutin et al reported safety and efficacy in combining hypofractionated radiosurgery of 30 Gy delivered in five daily fractions with bevacizumab 10 mg/kg IV every two weeks until tumour progression. This treatment resulted in median overall survival of 12.5 months with 3 of 25 patients experiencing significant toxicity associated with bevacizumab with one case of intratumoral hemorrhage, one wound dehiscence and one bowel perforation.[19] However, further multi-instituional studies are ongoing to determine the efficacy and toxicity associated with this approach.

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